Six-Year Review 3 Technical Support Document for Disinfectants/Disinfection Byproducts Rules

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Acronyms

2-CAA	2-Chloroacetaldehyde
AOB	Ammonia Oxidizing Bacteria
ASTM	American Society of Testing and Materials
AWWA	American Water Works Association
BAC	Biological Activated Carbon
BAL	Bromoacetaldehyde
BAT	Best Available Technology
BCAA	Bromochloroacetic acid
BCAL	Bromochloroacetaldehyde
BCAN	Bromochloroacetonitrile
BCC	Basal Cell Carcinoma
BDCAA	Bromodichloroacetic acid
BDCAL	Bromodichloroacetaldehyde
BDCM	Bromodichloromethane
BIAA	Bromoiodoacetic acid
BIF	Bromine Incorporation Factor
BMDL	Benchmark dose level
BMX-2	3-Chloro-4-(Dibromomethyl)-5-Hydroxy-2(5H)-Furanone
BrTHMs	Brominated Trihalomethanes
CAGC	Chloramine Formed from Gaseous Chlorine
CAL	Chloroacetaldehyde
CAOF	Chloramine Formed from Off-Site Hypochlorite
CAON	Chloramine Formed from On-Site Hypochlorite
CCC	Chlorine Chemistry Council
CCL	Contaminant Candidate List
CFR	Code of Federal Regulations
CG	Chorionic Gonadotropin
CHF	Chlorohydroxyfuranones
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CLDO	Chlorine Dioxide
CLGA	Gaseous Chlorine
CLM	Chloramine
CLOF	Off-site Generated Hypochlorite Stored as Liquid
CLON	On-site Generated Hypochlorite with No Storage
CMA	Chemical Manufacturers Association
CNS	Central Nervous System
CNX	Cyanogen Halides
CPE	Cationic Polyelectrolyte
CWS	Community Water System
CYP2E1	Cytochrome P450 2E1
DBAA	Dibromoacetic Acid
DBAL	Dibromochloroacetaldehyde
DBAN	Dibromoacetonitrile

DBCAL	Dibromochloroacetaldehyde
DBCM	Dibromochloromethane
DBP	Disinfectant Byproducts
D/DBPR	Disinfectants and Disinfection Byproducts Rules
DCAA	Dichloroacetic Acid
DCAL	Dichloroacetaldehyde
DCAN	Dichloroacetonitrile
DCP	Dichloropropanone
DHAA	Dihaloacetic Acids
DIAA	Diiodoacetic Acid
DMA	Dimethylnitrosamine
DOC	Dissolved Organic Carbon
DON	Dissolved Organic Nitrogen
Cal DPR	California Department of Pesticide Regulation
EBCT	Empty Bed Contact Time
EPA	United States Environmental Protection Agency
EWG	Environmental Working Group
FBRR	Filter Backwash Recycling Rule
FDA	Food and Drug Administration
GAC	Granular Activated Carbon
GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase
GD	Gestational Day
GSH	Glutathione
GST	Glutathione S-Transferase
GSTM1	Glutathione S-Transferase Mu 1
GSTP1	Glutathione S-Transferase Pi 1
GSTT1	Glutathione S-Transferase Theta 1
GSTZ1	Glutathione Transferase Zeta 1
GU	Ground Water Under Direct Influence of Surface Water
GUP	Purchased Ground Water Under the Direct Influence of Surface Water
GW	Ground Water
GWP	Purchased Ground Water
GWR	Ground Water Rule
GWUDI	Ground Water Under Direct Influence of Surface Water
HAA	Haloacetic Acid
HAA5	Group of five regulated HAAs: monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid and dibromoacetic acid
HAL	Haloacetaldehyde
HAN	Haloacetonitrile
HBQ	Halogenated Benzoquinone
HNM	Halonitromethane
HQ	Haloquinone
HRL	Health Reference Level
IAL	Iodoacetaldehyde
IARC	International Agency for Research on Cancer
ICR	Information Collection Request

ICRTSD	Information Collection Request Treatment Study Database
IDSE	Initial Distribution System Evaluation
IESWTR	Interim Enhanced Surface Water Treatment Rule
IDSE	Initial Distribution System Evaluation
ILSI	International Life Sciences Institute
IRIS	Intigrated Risk Information System
IRR	Incidence Rate Ratios
IUGR	Intrauterine Growth Retardation
LBW	Low Birth Rate
LCMRL	Lowest Concentration Minimum Reporting Level
LH	Luteinizing Hormone
LOAEL	Lowest Observed Adverse Effect Level
LRAA	Locational Running Annual Average
LT1	Long-Term 1 Enhanced Surface Water Treatment Rule
LT2	Long-Term 2 Enhanced Surface Water Treatment Rule
MAC	Maximum Acceptable Concentration
MBAA	Monobromoacetic Acid
MCAA	Monochloroacetic Acid
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDBP	Microbial and Disinfection Byproduct
MDL	Method Detection Limit
MGD	Millions of gallons per day
MIAA	Monoiodoacetic acid
MIEX	Magnetic Ion Exchange
MOA	Modes of Action
MRDL	Maximum Residual Disinfectant Level
MRDLG	Maximum Residual Disinfectant Level Goal
MRL	Minimum Reporting Level
MTBE	Methyl Tert-Butyl Ether
MX	3-Chloro-4(Dichloromethyl)-5-Hydroxy-2(5H)-Furanone
NAT2	N-Acetyltransferase 2
NCI	National Cancer Institute
NDBA	N-Nitrosodi-N-Butylamine
NDEA	N-Nitrosodiethylamine
NDMA	N-Nitrosodimethylamine
NDPA	N-Nitrosodi-N-Propylamine
NEMI	National Environmental Methods Index
NMEA	N-nitrosomethylethylamine
NOAEL	No-Observed-Adverse-Effect-Level
NODA	Notices of Data availability
NODU	No Disinfection
NOM	Natural Organic Matter
NPDWR	National Primary Drinking Water Regulations
NRWA	National Rural Water Association
NTNCWS	Non-Transient Non-Community Water System

NTP	National Toxicology Program
NTU	Nephelometric Turbidity Unit
NPYR	N-Nitrosopyrrolidine
OR	Odds Ratio
OTHD	All Other Types of Disinfectant
OZON	Ozone
PAC	Polyaluminum Chloride
PAR	Population Attributable Risk
PBI	Percentage of Bromide Incorporation
PHG	Public Health Goal
PND	Postnatal Day
PTB	Pulmonary Tuberculosis
PTD	Pre-Term Delivery
PWS	Public Water Systems
QA/QC	Quality Assurance and Quality Control
RAA	Running Annual Average
RIA	Regulatory Impact Analysis
ROS	Reactive Oxygen Species
RSC	Relative Score Contribution
RSD	Relative Standard Deviation
RSSCT	Rapid Small-Scale Column Test
RR	Relative Risk
RTCR	Revised Total Coliform Rule
SAB	Science Advisory Board
SCC	Squamous Cell Carcinoma
SCCS	Scientific Committee on Consumer Safety
SCGE	Single Cell Gel Electrophoresis
SDS	Simulated Distribution System
SDWA	Safe Drinking Water Act
SDWIS	Safe Drinking Water Information System
SGA	Small for Gestational Age
SUVA	Specific Ultraviolet Light Absorbance
SW	Surface Water
SWAT	Surface Water Analytical Tool
SWP	Purchased Surface Water
SWTR	Surface Water Treatment Rule
SYR	Six-Year Review
SYR2	Second Six-Year Review
SYR3	Third Six-Year Review
TAME	Tert-amyl methyl Ether
TBAA	Tribromoacetic Acid
TBAL	Tribromoacetaldehyde
TCAA	Trichloroacetic Acid
TCAL	Trichloroacetaldehyde
TCAN	Trichloroacetonitrile
TCR	Total Coliform Rule

TDI	Tolerable Daily Intake
TDS	Total Dissolved Solids
THAA	Trihaloacetic acids
THM	Trihalomethanes
THM4	Group of four regulated THMs: bromoform, bromodichloromethane, dibromochloromethane and chloroform
THMFP	Trihalomethane Formation Potential
TOC	Total Organic Carbon
TON	Total Organic Nitrogen
TOX	Total Organic Halogens
TT	Treatment Technique
TTHM	Total Trihalomethanes
UCMR	Unregulated Contaminant Monitoring Rule
USGS	United States Geological Survey
UV	Ultraviolet
UVLV	Ultraviolet Light
WEOM	Water-Extractable Organic Matter
WHO	World Health Organization
WRF	Water Research Foundation
WTP	Water Treatment Plants

1 Introduction

The 1996 Safe Drinking Water Act (SDWA) Amendments require the United States Environmental Protection Agency (EPA or the Agency) to periodically review existing national primary drinking water regulations (NPDWRs) and determine which, if any, need to be revised.[1] The purpose of the review, called the Six-Year Review (SYR), is to evaluate current information for regulated contaminants to determine if there is new information on health effects, treatment technologies, analytical methods, occurrence and exposure, implementation and/or other factors that provides a health or technical basis to support a regulatory revision that will improve or strengthen public health protection.

EPA completed and published the results of its first Six-Year Review (SYR1), on July 18, 2003 (USEPA, 2003a) and the second Six-Year Review (SYR2), on March 29, 2010 (USEPA, 2010a), after developing a systematic approach, or protocol, for the review of NPDWRs. During SYR1, EPA identified the Total Coliform Rule (TCR) as a candidate for revision. NPDWRs for four additional contaminants (acrylamide, epichlorohydrin, tetrachloroethylene and trichloroethylene) were identified as candidates for revision during the SYR2.

Under the third Six-Year Review (SYR3), EPA is reviewing the regulated chemical, radiological and microbiological contaminants included in previous reviews, as well as the microbial and disinfection byproducts (MDBP) regulations. Except for the 1989 Total Coliform Rule (TCR), which was reviewed in SYR1, this is the first time EPA is conducting a SYR of the MDBP regulations. This review includes the Stage 1 and Stage 2 Disinfectants/Disinfection Byproducts Rules (D/DBPRs) as well as the following microbial contaminant regulations:

- Surface Water Treatment Rule (SWTR)
- Interim Enhanced Surface Water Treatment Rule (IESWTR)
- Long-Term 1 Enhanced Surface Water Treatment Rule (LT1)
- Long-Term 2 Enhanced Surface Water Treatment Rule (LT2)
- Filter Backwash Recycling Rule (FBRR)
- Ground Water Rule (GWR).

Results from the review of the SWTR, the IESWTR, the LT1, the FBRR and the GWR are discussed in a separate support document (USEPA, 2016a).

EPA is reviewing the LT2 in response to the Executive Order 13563 *Improving Regulation and Regulatory Review* (also known as Retrospective Review) and as part of the SYR3 process.

[1] Under the SDWA, EPA must periodically review existing national primary drinking water regulations (NPDWRs) and, if appropriate, revise them. Section 1412(b)(9) of SDWA states: "The Administrator shall, not less often than every 6 years, review and revise, as appropriate, each national primary drinking water regulation promulgated under this title. Any revision of a national primary drinking water regulation shall be promulgated in accordance with this section, except that each revision shall maintain, or provide for greater, protection of the health of persons."

Results from the review of the LT2 are discussed in a separate support document (USEPA, 2016b).

The remainder of this document provides a summary of available information and data relevant to determining which, if any, of the NPDWRs included in the Stage 1 and Stage 2 D/DBPRs are candidates for revision under the SYR. The information cutoff date for SYR3 was December 2015. That is, information published on or before December 2015 was considered as part of the SYR3. The Agency recognizes that scientists and other stakeholders are continuing to investigate disinfectants and disinfection byproducts (DBPs) and publish information subsequent to this cutoff date. While not considered as part of the SYR3, the Agency anticipates providing consideration for that additional information in subsequent activities.

Chapter 2 of this document provides an overview of the protocol that EPA used in this review. Chapter 3 provides an overview of the specific regulations addressed in this support document, along with historical information about their development. Available information and data relevant to making a determination under the SYR3 are provided in Chapter 4 (health effects), Chapter 5 (analytical methods), Chapter 6 (occurrence and exposure), Chapter 7 (treatment) and Chapter 8 (other regulatory revisions).

2 EPA's Protocol for the Six-Year 3 Review

This chapter provides an overview of the process the Agency used to review the NPDWRs discussed in the SYR3. The protocol document, *EPA Protocol for the Third Review of Existing National Primary Drinking Water Regulations*, contains a detailed description of the process the Agency used to review the NPDWRs (USEPA, 2016c). The foundation of this protocol was developed for the SYR1 based on the recommendations of the National Drinking Water Advisory Committee (NDWAC, 2000). This SYR3 process is very similar to the process implemented during the SYR1 and the SYR2, with some clarifications to the elements related to the review of NPDWRs included in the MDBP rules.

Exhibit 2.1 presents an overview of the SYR protocol and major categories of review outcomes. The protocol is broken down into a series of questions about whether there is new information for a contaminant that suggests it is appropriate to revise one or more of the NPDWRs. The two major outcomes of the detailed review are either:

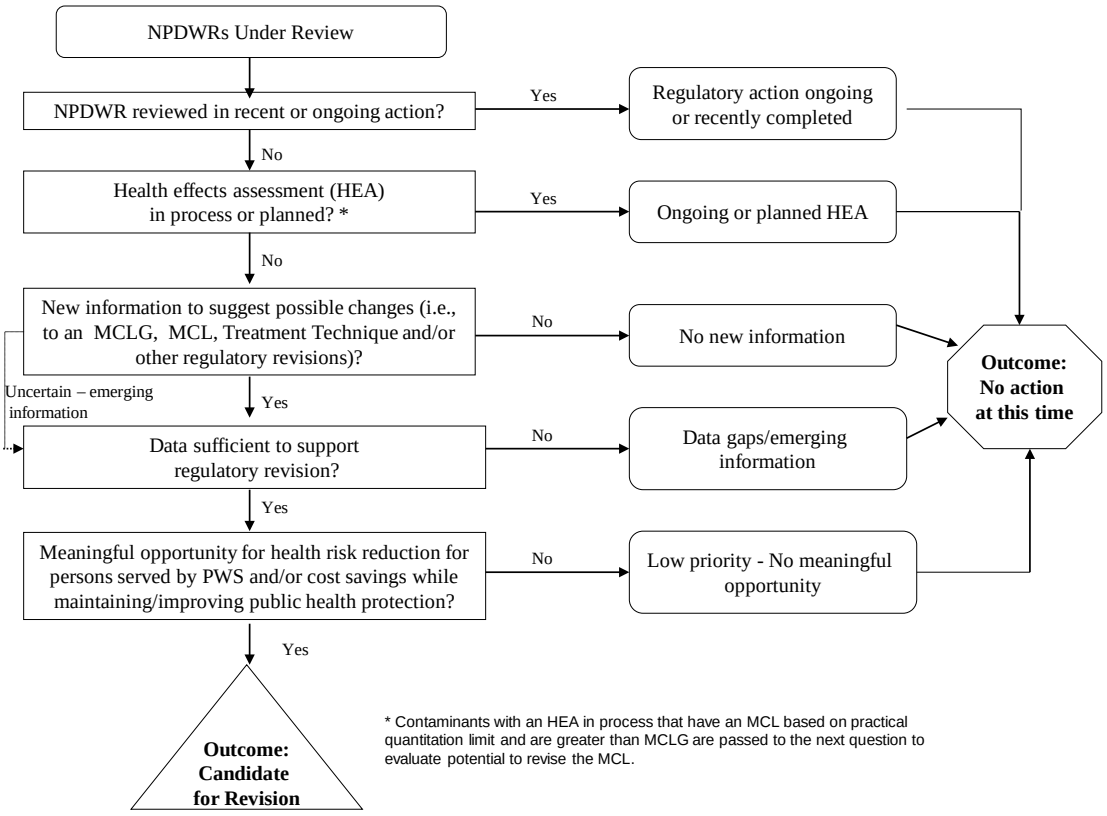
(1) the NPDWR is not appropriate for revision and no action is necessary at this time, or

(2) the NPDWR is a candidate for revision.

Individual regulatory provisions of NPDWRs that are evaluated as part of the SYR are: maximum contaminant level goals (MCLGs), maximum contaminant levels (MCLs), maximum residual disinfectant level goals (MRDLGs), maximum residual disinfectant levels (MRDLs), treatment techniques (TTs), other treatment technologies and regulatory requirements (e.g., monitoring). The MCL provisions are not applicable for evaluation of the microbial contaminants regulations which establish TT requirements in lieu of MCLs. The MRDLG and MRDL provisions are only applicable for evaluation of the Disinfectants and Disinfection Byproducts Rules (D/DBPRs) as part of the SYR.

The review elements that EPA considered for each NPDWR during the SYR3 include the following: initial review, health effects, analytical feasibility, occurrence and exposure, treatment feasibility, risk balancing and other regulatory revisions. Further information about these review elements are described in the protocol document (USEPA, 2016c).

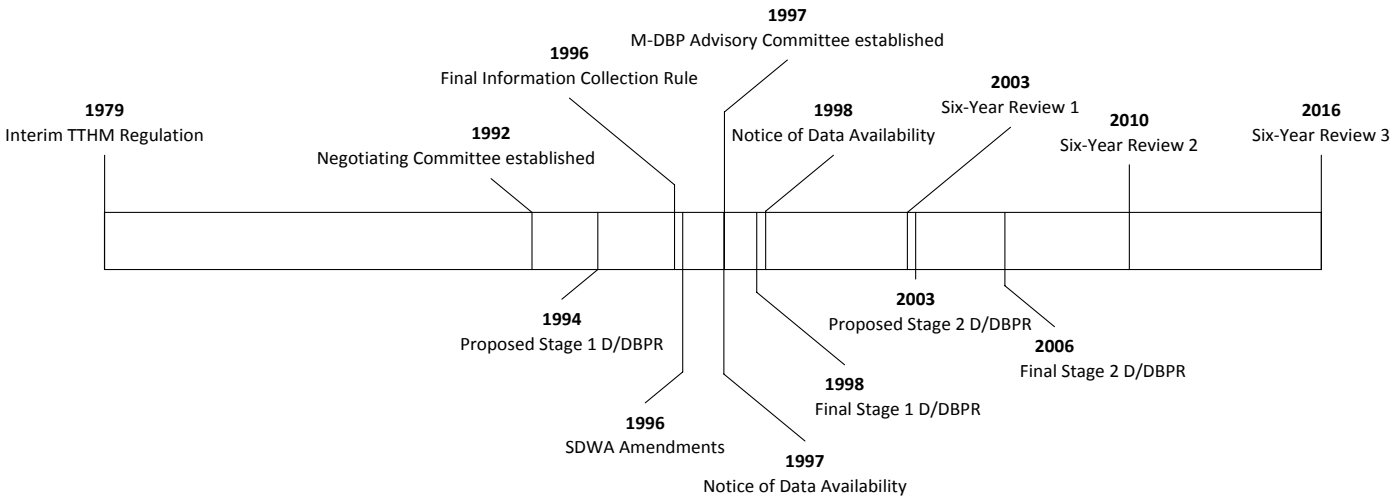
Exhibit 2.1: SYR Protocol Overview and Major Categories of Revise/Take No Action Outcomes



3 History of Disinfectants and Disinfection Byproducts Regulations

This chapter provides a brief history of disinfectants and disinfection byproducts (DBPs) regulations in the United States from 1974 to 2016. A timeline of the regulatory history is shown in Exhibit 3.1. The most recent regulation, the Stage 2 Disinfectants and Disinfection Byproducts Rule (D/DBPR), was promulgated on January 4, 2006 (USEPA, 2006a). As explained in Chapter 2, the Initial Review Branch of the SYR protocol indicates that a regulation that was promulgated or revised more than six years ago is eligible for regulatory review under the SYR process. The Stage 2 D/DBPR meets this criterion and is currently being reviewed. EPA is also reviewing the Stage 1 D/DBPR. Although some parts of the Stage 1 D/DBPR were superseded by requirements under the Stage 2 D/DBPR, much of the Stage 1 D/DBPR is still in effect. EPA did not review the Stage 1 D/DBPR during SYR2 because national primary drinking water regulations (NPDWRs) under Stage 1 were the subject of a recent rulemaking (those under the Stage 2 D/DBPR). Under the Initial Review Branch, NPDWRs for which further review of detailed technical data is premature because the NPDWR is the subject of recent or ongoing rulemaking or an ongoing health effects assessment may be excluded from the SYR. Excluding such NPDWRs from review prevents duplicative Agency efforts.

Exhibit 3.1: Timeline for Selected Regulatory Activities Associated with Disinfectants and Disinfection Byproducts in Drinking Water



As part of the SYR, EPA is also reviewing the regulations addressing microbiological contaminants in drinking water. These are addressed in the technical support document for the microbial contaminant regulations and in a separate technical support document for the Long Term 2 Enhanced Surface Water Treatment Rule (USEPA, 2016a; 2016b).

3.1 Interim Total Trihalomethanes Regulation

In 1974, researchers in the Netherlands and the United States demonstrated that trihalomethanes (THMs) are formed as a result of drinking water chlorination (Bellar et al., 1974; Rook, 1974). There are four common THMs: chloroform, bromoform, bromodichloromethane (BDCM) and

dibromochloromethane (DBCM). EPA subsequently conducted surveys confirming widespread occurrence of THMs in chlorinated water supplies (Symons et al., 1975; USEPA, 1978). During this time toxicological studies became available supporting the contention that chloroform is carcinogenic in at least one strain of rat and one strain of mouse (NCI, 1976).

In November of 1979, EPA set an interim maximum contaminant level (MCL) for the total concentration of the four common THMs, or total THMs (TTHM), of 100 μg/L (0.100 mg/L) as an annual average (USEPA, 1979). This standard was based on the need to balance the requirement for continued disinfection of water to reduce exposure to pathogenic microorganisms with the need to simultaneously lower exposure to animal carcinogens like chloroform. TTHM was also considered a surrogate measure for other chlorination DBPs.

The interim TTHM standard only applied to community water systems (CWSs) serving at least 10,000 people that add a disinfectant (an oxidant) to the drinking water during any part of the treatment process. At the time of promulgation, about 80 percent of the small systems (i.e., those serving fewer than 10,000 people) used ground water sources that were mostly low in THM precursor content (USEPA, 1979), and many of them did not disinfect. Moreover, these small systems were considered more likely to have greater risks of significant microbiological contamination, especially if they were to reduce or eliminate chemical disinfection. Federal rules such as the 1989 Total Coliform and Surface Water Treatment Rules did not yet exist to further protect against microbial contamination. In 1979, the majority of outbreaks attributable to inadequate disinfection occurred in small systems. Further, EPA determined that small systems had limited access to the financial resources and technical expertise needed for TTHM control. Therefore, EPA decided not to require small systems to comply with the TTHM MCL at that time (USEPA, 1994a).

3.2 Stage 1 D/DBPR

3.2.1 Negotiated Rulemaking

EPA was required to develop rules for additional contaminants under the 1986 Amendments to the Safe Drinking Water Act (SDWA). To solicit public comment in developing a rule, EPA released a "strawman" rule (a pre-proposal draft) in October 1989. In this strawman rule, EPA included a primary option of setting maximum contaminant level goals (MCLGs) and MCLs for THMs, haloacetic acids (HAAs), chlorite and chlorate. Compliance with the MCL for HAAs was to be based on total concentrations of five HAAs (HAA5): monochloroacetic, dichloroacetic, trichloroacetic, monobromoacetic and dibromoacetic acids. THM4 and HAAs had shown an association with cancer, and they were also potential indicators of the presence of other byproducts in disinfected water that may also have adverse health effects (USEPA, 1994a). EPA intended to monitor concentrations of TTHM and HAA5 for compliance, but their presence in drinking water was thought to be representative of many other DBPs that may also be present in the water; thus, a reduction in TTHM and HAA5 would indicate a reduction of total DBPs. In addition to DBPs, the primary option in the strawman rule also included limits and health goals for the disinfectants chlorine, chloramines and chlorine dioxide (USEPA, 1994a).

Many system operators who commented on the strawman rule were concerned about the effects of modifying their treatment processes to meet DBP MCLs (USEPA, 1994a). These concerns

included reduced microbiological protection, creation of conditions that favored distribution system microbiological growth (e.g., use of ozone would create biodegradable organics, and use of chloramines would provide a nitrogenous source) and formation of residuals during treatment that would require disposal.

EPA published a status report in June 1991 on DBP regulation development that was designed to reflect the Agency's thinking on the strawman rule (USEPA, 1994a). The status report indicated that EPA was considering extending coverage under the rule to all community and non-transient non-community systems (instead of just CWSs serving at least 10,000 people, as under the 1979 TTHM rule) and was proposing a shorter list of compounds for regulation than were included in the 1989 strawman rule.

In the status report, EPA identified risk-balancing as an issue that needed to be considered as the rule was being developed. EPA wanted to ensure that the new regulation would not introduce new risks. For instance, one issue was the use of alternate disinfectants to limit chlorination byproducts. The Agency recognized that although alternate disinfection schemes (e.g., ozone and chloramines) could greatly reduce chlorination byproducts, little was known about the byproducts of the alternate disinfectants and their associated health risks. EPA did not want to promulgate a standard that encouraged the shift to alternate disinfectants unless the associated risks (including both those from byproducts and differential microbial risks from a change in disinfectants) were adequately understood (USEPA, 1994a).

Another aspect of risk-balancing was integration with other rules, such as the Surface Water Treatment Rule (SWTR), which had been promulgated in 1989. EPA wanted to ensure that compliance with regulations on DBPs would not affect compliance with or protection provided by the SWTR. Although the SWTR only mandated 3-log (99.9 percent) removal or inactivation of *Giardia* and 4-log (99.99 percent) removal or inactivation of viruses, EPA guidance recommended higher levels of treatment for poorer quality source waters. EPA was concerned that systems would reduce microbial protection to levels nearer to the regulatory requirements by reducing disinfection and, as a result, possibly increase microbial risks in an effort to meet DBP MCLs. The Agency wanted to ensure adequate microbial protection while reducing risk from DBPs (USEPA, 1994a).

EPA became interested in pursuing a negotiated rulemaking process for the development of the D/DBPR, in large part, because no clear path for addressing all the major issues identified in the June 1991 status report on the D/DBPR was apparent. A negotiated rule process would help stakeholders understand the complexities of the risk-balancing issue and help reach a consensus on the most appropriate regulation to address concerns on both DBPs and microorganisms. In 1992, EPA established the Negotiating Committee (USEPA, 1994a).

The Committee worked out an "agreement in principle" on a first round of DBP controls at its February 1993 meeting. The "Stage 1" agreement recommended MCLs for TTHM and HAA5 at levels the Committee deemed protective of public health: 80 and 60 μg/L (0.080 and 0.060 mg/L), respectively. To limit DBP precursors, the committee agreed to develop a series of "enhanced coagulation" requirements, to vary according to systems' influent water quality and treatment plant configurations. Members also agreed to reconvene in several years to develop a

second stage of DBP regulations, when the results of more health effects research and water quality monitoring were available (USEPA, 1994a).

For the most part, EPA adopted the recommendations of the Negotiating Committee and the supporting Technical Work Group for the proposed Stage 1 D/DBPR (USEPA, 1994a).

3.2.2 Proposed Stage 1 D/DBPR

The proposed Stage 1 D/DBPR was published in the Federal Register on July 29, 1994. EPA proposed maximum residual disinfectant level goals (MRDLGs) for chlorine, chloramines and chlorine dioxide, and MCLGs for each of the four THMs, two HAAs (dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA)), chloral hydrate, bromate and chlorite. EPA also proposed maximum residual disinfectant levels (MRDLs) for three disinfectants (chlorine, chloramines and chlorine dioxide), and MCLs for TTHM, HAA5 and two inorganic DBPs (chlorite and bromate) (USEPA, 1994a). No MCLG was proposed for chlorate due to insufficient toxicological and epidemiological data. Note that EPA proposed that the MRDL for chlorine dioxide also apply to transient non-community systems because of the concern from short-term exposure health effects; this was the only requirement in the proposal to apply to transient systems. All other proposed requirements applied only to community and non-transient non-community systems adding a chemical disinfectant (as EPA had recommended in its 1991 status report). The proposed MRDLs and MRDLGs were similar in concept to MCLs and MCLGs; however, since disinfectants were a necessary part of the treatment process, they could not be considered contaminants. EPA therefore developed new terms to describe limits for disinfectants. In addition, EPA proposed treatment techniques (TTs) (enhanced coagulation and enhanced softening) to remove DBP precursors in systems using conventional treatment. The proposed regulations also included monitoring, reporting and public notification requirements.

3.2.3 DBP Information Collection Rule

In 1994 EPA also proposed the Information Collection Rule (ICR) (USEPA, 1994b). The monitoring requirements of the ICR were proposed to (1) characterize source water parameters that influence DBP formation, (2) determine the concentrations of DBPs in drinking water, (3) refine models for predicting DBP formation based on treatment and water quality parameters, and (4) establish cost-effective monitoring requirements that are protective of public health. It required systems to monitor for DBPs, along with source water parameters such as total organic carbon (TOC), pH and alkalinity (USEPA, 1994b). The ICR also required source water monitoring for *Cryptosporidium*, *Giardia*, viruses, *Escherichia coli* and total coliform bacteria in surface water systems and systems using ground water under the direct influence of surface water (GWUDI). The specific requirements varied by system size and source water type. The proposed rule also required water systems, unless they met certain exclusionary criteria, to conduct pilot- or bench-scale studies of GAC or membranes to determine the effectiveness of these technologies for DBP removal. The ICR served as one of most important data sources supporting the development of the Stage 2 D/DBPR and is further described in Chapter 6.

3.2.4 The 1996 Safe Drinking Water Act Amendments, Microbial and Disinfectants/Disinfection Byproducts (MDBP) Advisory Committee and Notices of Data Availability

The SDWA amendments of 1996 codified the risk-balancing concept. They allowed EPA to establish an MCL "at a level other than the feasible level, if the technology, TTs and other means used to determine the feasible level would result in an increase in the health risk from drinking water by (i) increasing the concentration of other contaminants in drinking water or (ii) interfering with the efficacy of drinking water TTs or processes that are used to comply with other national primary drinking water regulations" (section 1412(b)(5)(A)). The amendments further required that MCLs or TTs "minimize the overall risk of adverse health effects by balancing the risk from the contaminant and the risk from other contaminants the concentrations of which may be affected by the use of a TT or process that would be employed to attain the maximum contaminant level or levels" (section 1412(b)(5)(B)).

Congress also required EPA to promulgate the D/DBPR in two stages as part of the 1996 SDWA amendments (section 1412(b)(2)(C)). To help meet the statutory deadlines established by Congress in the amendments and to maximize stakeholder participation, the Agency established the Microbial and Disinfectants/Disinfection Byproducts (MDBP) Advisory Committee under the Federal Advisory Committee Act in 1997 to analyze new information and data, as well as to build consensus on the regulatory implications of this new information. The Committee consisted of 17 members representing EPA, state and local public health and regulatory agencies, local elected officials, drinking water suppliers, chemical and equipment manufacturers, and public interest groups (USEPA, 2003b).

The Committee met five times, from March through July 1997, to discuss issues related to the IESWTR and Stage 1 D/DBPR. Technical support for these discussions was provided by a technical work group established by the Committee. The Committee's activities resulted in the collection, development, evaluation and presentation of substantial new data and information related to key elements of both proposed rules (USEPA, 2003b). These data were included in two notices of data availability (NODAs) issued by EPA, as discussed below.

EPA published the two NODAs in 1997 and 1998. The 1997 NODA (USEPA, 1997a) addressed studies on the ability of enhanced coagulation to remove TOC, new epidemiological and toxicological information, and possible changes for the final rule regarding the point of disinfection and disinfection benchmarking. The 1998 NODA (USEPA, 1998a) provided new epidemiological and toxicological information and requested comment on possible changes to some of the MCLGs in the 1994 proposal. It also requested comment on possible issues that might arise from simultaneous compliance with the Stage 1 D/DBPR and the Lead and Copper Rule.

3.2.5 Final Stage 1 D/DBPR

EPA finalized the Stage 1 D/DBPR (USEPA, 1998b) on December 16, 1998 (note that the final IESWTR was also promulgated at this time). The final rule established the MCLGs and MCLs listed in Exhibit 3.2 and the MRDLs and MRDLGs listed in Exhibit 3.3. The final rule did not include an MCLG for chloral hydrate because it was deemed to be adequately protected for by

the other rule requirements. The final rule revised the proposed MCLG for chlorite and the MRDLG for chlorine dioxide based on new toxicological data presented in the 1998 NODA. All other MCLGs and MRDLGs were promulgated as proposed. All MCLs and MRDLs were also promulgated as proposed. The rule required systems to monitor TTHM and HAA5 at locations representing average and/or maximum residence times in the distribution system, with the sampling frequency and number of samples based on the population served and the number of plants a system had. Compliance with the MCLs for TTHM, HAA5 and (for systems using ozone) bromate, as well as with the MRDLs for chlorine and chloramines was determined based on running annual averages (RAAs) of those samples. Compliance with the MCL for chlorite (only for systems using chlorine dioxide) was based on the average of three samples taken in the distribution system. For chlorine dioxide, the rule established two types of MRDL violations—acute and non-acute, based on whether a system exceeds the MRDL at just the entrance to the distribution system or within the distribution system as well. The rule allowed reduced monitoring for TTHM, HAA5, chlorite and bromate under certain conditions. The final rule applied to all community and non-transient non-community water systems (NTNCWSs) that added a disinfectant. Systems that purchased water that had already been disinfected were not subject to the rule.

Exhibit 3.2: Stage 1 and Stage 2 MCLs and MCLGs

DBPs	Stage 1		Stage 2	
	MCLG (mg/L)	MCL (mg/L) as RAA	MCLG (mg/L)	MCL (mg/L) as LRAA[1]
Chloroform	0	NA	0.07	NA
Bromodichloromethane	0	NA	0	NA
Dibromochloromethane	0.06	NA	0.06	NA
Bromoform	0	NA	0	NA
TTHM	NA	0.080	NA	0.080
Monochloracetic acid	NA	NA	0.07	NA
Dichloroacetic acid	0	NA	0	NA
Trichloroacetic acid	0.3	NA	0.02	NA
Monobromoacetic acid	NA	NA	NA	NA
Dibromoacetic acid	NA	NA	NA	NA
HAA5	NA	0.060	NA	0.060
Bromate	0	0.010	0	0.010
Chlorite	0.8	1.0	0.8	1.0

[1] Locational running annual average, discussed in Section 3.3.1.

Exhibit 3.3: Stage 1 and Stage 2 MRDLs and MRDLGs

Disinfectants	Stage 1		Stage 2	
	MRDLG (mg/L)	MRDL (mg/L)	MRDLG (mg/L)	MRDL (mg/L)
Chlorine	4 (as Cl_2)	4 (as Cl_2)	Same as Stage 1	
Chloramines	4 (as Cl_2)	4 (as Cl_2)		
Chlorine Dioxide	0.8 (as ClO_2)	0.8 (as ClO_2)		

Under the Stage 1 D/DBPR, the best available technology (BAT) for complying with the TTHM and HAA5 MCLs was determined to be enhanced coagulation, enhanced softening or GAC with a 10-minute empty-bed contact time. For bromate and chlorite, control of treatment processes was determined to be the BAT (USEPA, 1998b).

The final Stage 1 D/DBPR also established a TT for TOC removal in plants that use conventional treatment (USEPA, 1998b). The required percentage of TOC removal depended on the source water TOC and alkalinity and is shown in Exhibit 3.4 below. Where meeting the removals in the exhibit below was found to be technically infeasible, the system could apply to the state (i.e., primacy agency) for alternative removal criteria determined by laboratory jar testing. The final requirements were similar to the proposed requirements. However, removal requirements in the final rule for plants with source water TOC >2.0 and up to 4.0 mg/L were decreased as a result of studies showing that the proposed removals would be difficult to meet for many systems and would place a significant burden on states, which would have to approve alternative removal criteria. The TT for TOC removal is discussed further in Chapter 7.

Exhibit 3.4: Stage 1 D/DBPR Required Removal of Total Organic Carbon by Enhanced Coagulation and Enhanced Softening for Subpart H Systems Using Conventional Treatment [1,2,3]

Source Water TOC (mg/L)	Percentage Removal Required (Based on Source Water Alkalinity in mg/L)		
	0–60 mg/L	>60–120 mg/L	>120 mg/L
>2.0–4.0	35.0	25.0	15.0
>4.0–8.0	45.0	35.0	25.0
>8.0	50.0	40.0	30.0

[1] Systems meeting at least one of the conditions in Section 141.135(a)(2) (i)–(vi) of the rule are not required to meet the removals in this exhibit.
[2] Softening systems meeting one of the two alternative compliance criteria in Section 141.135(a)(3) of the rule are not required to meet the removals in this exhibit. Chapter 7 provides greater detail.
[3] Systems practicing softening must meet the TOC removal requirements in the last column to the right.

3.3 Stage 2 D/DBPR

The Stage 2 D/DBPR was designed to further reduce the levels of exposure from disinfectants and DBPs without undermining the control of microbial pathogens. The Long Term 2 Enhanced Surface Water Treatment Rule (LT2ESWTR) was proposed at the same time as the Stage 2 D/DBPR to ensure that drinking water was microbiologically safe at the limits set for disinfectants and DBPs. (Note that the Long Term 1 Enhanced Surface Water Treatment Rule,

which pertained to systems serving fewer than 10,000 people, was finalized in 2001, before the effective compliance date for small systems under the Stage 1 D/DBPR.) These regulations established removal/inactivation requirements for *Cryptosporidium*.)

3.3.1 MDBP Advisory Committee and New Information

EPA reconvened the MDBP Advisory Committee in March 1999 to develop recommendations on issues pertaining to the Stage 2 D/DBPR and LT2ESWTR. The Advisory Committee collected and evaluated new information that became available after the Stage 1 D/DBPR was published. The ICR provided new data on DBP occurrence and treatment control (note that although these data were collected prior to the Stage 1 promulgation they did not become available until after that rule became final); it also included new data on occurrence and treatment of pathogens. These data were supplemented by a survey conducted by the National Rural Water Association (NRWA), data provided by various states, data provided by the American Water Works Association and Information Collection Rule Supplemental Surveys (USEPA, 2003b).

Although the Stage 1 D/DBPR was projected to achieve a major reduction in DBP exposure, the ICR data suggested that some customers would receive drinking water with elevated DBP levels even when their distribution systems were meeting the MCLs established by the Stage 1 D/DBPR. That is, sample results at a single monitoring location could exceed 0.080 mg/L TTHM or 0.060 mg/L HAA5, even when the RAAs were below these levels. The ICR results also showed that Stage 1 D/DBPR monitoring sites might not be representative of the highest DBP concentrations that occur in distribution systems (USEPA, 2003b). In addition, the new information indicated that technologies including ultraviolet light (UV) for inactivation of protozoa, in combination with other technologies for control of DBPs such as GAC, could be very effective at lowering DBP levels. GAC was found to be most effective for systems with TOC levels less than 6 mg/L. Of the plants that conducted a GAC pilot- or bench-scale treatment study under the ICR, approximately 70 percent of the surface water plants studied could meet the 0.080 mg/L TTHM and 0.060 mg/L HAA5 RAAs, with a 20 percent safety factor (i.e., 0.064 mg/L and 0.048 mg/L, respectively) using GAC with 10 minutes of empty-bed contact time and a 120-day reactivation frequency, and 78 percent of the plants could meet the MCLs with a 20 percent safety factor using GAC with 20 minutes of empty-bed contact time and a 240-day reactivation frequency. The ICR treatment study results also demonstrated that nanofiltration was a better DBP control technology (as opposed to GAC) for ground water sources with TOC concentrations above approximately 6 mg/L (USEPA, 2003b).

After promulgation of the Stage 1 D/DBPR, new information on health effects also became available that supported the need for the Stage 2 D/DBPR. New epidemiology and toxicology studies evaluating bladder and rectal cancers increased the weight-of-evidence linking these health effects to DBP exposure. The available epidemiology studies on bladder cancer related to consumption of chlorinated drinking water allowed EPA to develop quantitative risk and benefits estimates for that health endpoint, as discussed in greater detail in Chapter 4. Several new reproductive and developmental studies became available, so EPA completed a more extensive analysis of reproductive and developmental effects associated with DBPs. Both human epidemiology studies and animal toxicology studies showed associations between chlorinated drinking water and reproductive and developmental endpoints such as spontaneous abortion,

stillbirth, neural tube defects, pre-term delivery, intrauterine growth retardation and low birth weight, but the data were not consistent enough to support a quantitative benefits analysis (USEPA, 2006a).

Taking into account this new information, in 2000, the MDBP Advisory Committee developed an agreement in principle for the Stage 2 D/DBPR (USEPA, 2000a). In the agreement, the committee recommended maintaining the MCLs for TTHM and HAA5 at 0.080 mg/L and 0.060 mg/L, respectively, but changing the compliance calculation in two phases. The Stage 1 RAA calculations averaged all samples collected within a distribution system over a one-year period. The Stage 2 compliance determination would switch to a calculation based on the RAA at each sampling location in the distribution system (referred to as the "locational" running annual average (LRAA)). In the first phase, systems would continue to comply with the Stage 1 D/DBPR MCLs as RAAs and, at the same time, comply with MCLs of 0.120 mg/L for TTHM and 0.100 mg/L for HAA5 calculated as LRAAs. Systems would also carry out an initial distribution system evaluation (IDSE) to select compliance monitoring sites that accurately reflect higher TTHM and HAA5 levels occurring in the distribution system. The second phase of compliance would require MCLs of 0.080 mg/L for TTHM and 0.060 mg/L for HAA5 calculated as LRAAs at individual monitoring sites identified through the IDSE. The Agreement in Principle also provided recommendations for simultaneous compliance with the LT2ESWTR so that the reduction of potential health hazards of DBPs did not compromise microbial protection (USEPA, 2003b).

3.3.2 Proposed Stage 2 D/DBPR

EPA published the proposed Stage 2 D/DBPR on August 18, 2003. A summary of the key components of the rule is included here.

The proposed rule (USEPA, 2003b) extended the applicability of the rule to include community and non-transient non-community systems that deliver water that has been treated with a primary or residual disinfectant other than UV light (under the Stage 1 D/DBPR, only systems that *added* a disinfectant were subject to the requirements). This change was intended to account for DBPs in consecutive systems, which purchase or otherwise obtain water from other public water systems but do not necessarily add disinfectant themselves. Consecutive systems would be required to comply with the revised MCLs for TTHM and HAA5 as well as the MRDLs for chlorine and chloramines. They would not need to comply with MRDLs for chlorine dioxide or MCLs for bromate and chlorite.

In response to new health information, the proposed Stage 2 D/DBPR revised the MCLGs for chloroform, TCAA and monochloroacetic acid (MCAA).

In addition to the change in compliance calculation described above under the Agreement in Principle, the proposed rule required that, in most cases, the number of TTHM and HAA5 samples collected would be based on the number of plants in a system. However, for consecutive systems that bought all their water from other systems, the number of samples would be based on the population served. Reduced monitoring would be permitted. For DBPs other than TTHM and HAA5 and for disinfectants, non-consecutive systems would continue to comply with the MCLs

and MRDLs and the monitoring requirements specified in the Stage 1 D/DBPR (USEPA, 2003b).

The proposed rule required systems to conduct an IDSE based on one year of TTHM and HAA5 monitoring; specific requirements were based on source water type and system size. Instead of collecting new data, systems also had the option of performing a study based on historical data, distribution system modeling, or other data, and IDSE waivers were available under certain circumstances. Systems were to submit a monitoring plan based on the IDSE results (USEPA, 2003b).

Lastly, the proposed rule required systems to evaluate "significant excursions," where individual TTHM or HAA5 samples exceed a peak level designated by the state (note that the final rule modified this requirement to a peak level defined by EPA). Systems would be required to evaluate their operations to determine opportunities for reducing DBP formation and would submit a report to the state (USEPA, 2003b). EPA proposed nanofiltration and two GAC options as BATs for wholesale systems complying with the proposed revisions to the MCLs. It proposed a separate BAT for consecutive systems.

3.3.3 Final Stage 2 D/DBPR

The final Stage 2 D/DBPR was published January 4, 2006. Most of the elements of the proposed rule were retained as proposed (USEPA, 2006a). However, there were some differences, as described below.

The MCLGs for chloroform and TCAA were finalized as proposed (USEPA, 2006a); however, the MCLG for MCAA was revised. The final MCLGs are shown in Exhibit 3.2.

The final rule eliminated the proposed two-phase implementation period for calculating compliance. The rule required systems to transition directly from calculating compliance as a RAA to calculating it as a LRAA (USEPA, 2006a). The MCL values themselves remained unchanged from the Stage 1 D/DBPR. The final rule also established monitoring requirements based on population served by the system (the proposal had based requirements on number of treatment plants).

The final Stage 2 D/DBPR revised the "significant excursion" requirements (USEPA, 2006a). The rule established a threshold called the "operational evaluation level" that is determined for each monitoring location using compliance monitoring results, above which systems would be required to implement an operational evaluation. The operational evaluation levels for each monitoring location are determined by the sum of the two previous quarters' TTHM (or HAA5) results plus twice the current quarter's TTHM (or HAA5) result, at that location, divided by four to determine an average ((Q1+Q2 +2Q3)/4)). If the average TTHM exceeds 0.080 mg/L at any monitoring location or the average HAA5 exceeds 0.060 mg/L at any monitoring location, the system must conduct an operational evaluation and submit a written report about the operational evaluation to the state.

The operational evaluation includes an examination of system treatment and distribution operational practices, including changes in sources or source water quality, storage tank operations and excess storage capacity that may contribute to high TTHM and HAA5 formation.

Systems must also identify what steps could be considered to minimize future operational evaluation level exceedances (USEPA, 2006a).

The final rule did not modify the Stage 1 TOC precursor removal requirements, except for a minor edit.

The BATs for the final rule are the same as for the proposed rule, except for a minor change for small consecutive systems.

4 Health Effects

This chapter addresses the health effects of disinfectants and disinfection byproducts (D/DBPs). This chapter is organized into multiple sections, each section addressing the health effects associated with various types of DBPs and disinfectants. Section 4.1 focuses on the adverse health effects that are associated with the regulated organic DBPs, specifically, trihalomethanes (THMs) and haloacetic acids (HAAs). The health effects associated with the regulated inorganic DBPs, bromate and chlorite, are addressed in Section 4.2. Section 4.3 addresses the health effects associated with regulated disinfectants. Section 4.4 describes health effects information for several "unregulated" organic DBPs. Section 4.5 presents a summary of the data available about unregulated disinfectants.

Appendix A provides additional information on the health effects of the regulated organic and inorganic DBPs and the regulated disinfectants. It includes additional toxicological and epidemiological information available during the development of the Stage 1 and Stage 2 D/DBPRs, as well as some additional details on the epidemiological information that has become available since the Stage 2 rule. Appendix A is organized in the same manner as Chapter 4.

4.1 Regulated Organic DBPs

Of the 11 DBPs regulated by EPA, 9 are organic chemicals: 4 THMs (collectively called THM4) and 5 HAAs (collectively called HAA5). THM4 is a group of four regulated THMs: bromoform, bromodichloromethane (BDCM), dibromochloromethane (DBCM) and chloroform. HAA5 is a group of five regulated HAAs: monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA) and dibromoacetic acid (DBAA). Under the Stage 1 and Stage 2 D/DBPRs, MCLGs were established for all four THMs listed above and for three of the five HAAs (MCAA, DCAA and TCAA).

Data from animal toxicity studies were used as the basis for establishing the MCLGs, whereas data from the epidemiology studies were used as the basis for estimating risk reduction associated with implementation of the rule, specifically, for the reduction of bladder cancer. Both the animal toxicity and the epidemiology sections of this chapter focus on cancer effects and reproductive/developmental effects. These endpoints were used to evaluate the risks associated with exposure to the DBPs listed above. The intent of the Stage 1 and Stage 2 D/DBPRs was to reduce human exposure not only to these nine substances but also to mixtures of DBPs formed during disinfection of water. Reduction of human exposure to the nine substances and associated mixtures is achieved through compliance with both the MCLs and the treatment technique (TT) component of the Stage 1 D/DBPR. The TT is aimed at reducing precursors, such as total organic carbon (TOC), found in source waters that leads to the formation of a vast array of organic DBPs. This is discussed further in Chapters 6 and 7 of this support document.

4.1.1 Toxicity Studies

The relevant information from animal toxicity studies of the regulated organic DBPs is presented in three main sections addressing: THMs, HAAs; and the mode of action relevant to carcinogenicity.

At the time of the promulgation of the Stage 1 and Stage 2 D/DBPRs, there was a considerable amount of information on carcinogenicity of the regulated THM and HAA DBPs based on animal toxicity studies. Information about the reproductive and developmental effects of the contaminants also featured prominently in the Stage 2 portion of the rule and was to a lesser extent supported by the animal data for some of the DBPs.

EPA's Integrated Risk Information System (IRIS) conducted weight of evidence characterizations of the carcinogenic potential for six of the regulated DBPs: four THMs - bromoform (USEPA, 1991), BDCM (USEPA, 1993a), chloroform (USEPA, 2001a), DBCM (USEPA, 1992a) and two HAAs – DCAA (USEPA, 2003c) and TCAA (USEPA, 2011a). Cancer risk factors were developed for bromoform, BDCM and DBCM in support of the Stage 1 D/DBPR based on EPA's 1986 Guidelines for Carcinogen Risk Assessment (USEPA, 1986). In 2003, the cancer risk factor for DCAA was published. (USEPA, 2003c). The IRIS documents for chloroform and DCAA were not available for the Stage 1 rule but were available for the Stage 2 rule. The TCAA IRIS document was completed after issuance of the Stage 2 rule.

Additional documentation of the carcinogenicity of bromoform, BDCM and DBCM was evaluated for the Stage 2 rule by EPA following the 2005 EPA Guidelines for Carcinogenic Risk Assessment resulting in changes to the information on IRIS (USEPA, 2005a). A cancer risk factor was not derived for chloroform under the Stage 1 or Stage 2 rule based on the data that demonstrated that the mode of action for cancer is nonlinear and the cancer classification is *not likely* for doses below those leading to tissue necrosis and *likely* at doses that cause necrosis. For that contaminant, the protection afforded by the Reference Dose (RfD) based on liver necrosis is considered to also protect for cancer (USEPA, 2001a).

The MCLGs for MCAA and TCAA were supported by Criteria Documents developed by EPA (USEPA, 2005b, 2005c). TCAA was classified as having "*suggestive evidence of carcinogenicity"* supporting use of the RfD as the endpoint that is the basis of the MCLG. MCAA was classified as having insufficient information to assess carcinogenic potential. The most recent IRIS TCAA assessment (USEPA, 2011a) was completed after the Stage 2 rule and replaces the EPA Criteria Document that supported the rule. The IRIS assessment characterizes the evidence for carcinogenicity as *suggestive* and provides a quantitative assessment of risk based on an EPA study that had not been published at the time of the Stage 2 Rule.

4.1.1.1 Trihalomethanes (THMs)

This section describes the basis for the MCLGs for the four regulated THMs that compose THM4, new information that has become available since the development of the Stage 2 D/DBPRs and observations about its relevance within the context of the SYR.

Prior to the Stage 1 and Stage 2 D/DBPRs, the National Toxicology Program (NTP) completed two-year cancer bioassays in rats and mice for chloroform (NCI, 1976), DBCM (NTP, 1985), BDCM (NTP, 1987), and bromoform (NTP, 1989a).

An overview of relevant studies is provided in the following subsections. Additional information on the toxicological background at the time of Stage 1 and Stage 2 regulations for cancer, mutagenicity/genotoxicity and reproductive/developmental effects is provided in Appendix A.

4.1.1.1.1 Bromoform

Basis for the MCLG

In Stage 1 D/DBPR, EPA established an MCLG of zero for bromoform and classified bromoform as a "*probable human carcinogen*" (USEPA, 1991, 1998b) based on a weight of evidence evaluation of both the cancer and noncancer effects. Under the 2005 cancer guidelines it was classified as "*likely to be carcinogenic by all routes of exposure*" (USEPA, 2005d). The MCLG is based on a chronic animal carcinogenicity study that reported uncommon neoplasms of the large intestines in rats (NTP, 1989b). Insufficient evidence exists regarding the mode of carcinogenic action of bromoform, therefore, the low-dose extrapolation approach was used to be protective of public health (USEPA, 1998b). The RfD of 0.02 mg/kg/day is based on a No-Observed-Adverse-Effect-Level (NOAEL) of 25 mg/kg/day from subchronic data for hepatic lesions in male rats (NTP, 1989b) with the application of an uncertainty factor of 1000 (USEPA, 2005d).

New Information Available Since Development of Stage 2 D/DBPR

There is no new, relevant animal toxicity data for bromoform that would change its MCLG, cancer quantification or RfD.

Relevance for SYR

No new data were identified that would change the MCLG of zero for bromoform.

4.1.1.1.2 Bromodichloromethane

Basis for the MCLG

In the Stage 1 D/DBPR, EPA established an MCLG of zero for BDCM and classified BDCM as a "*probable human carcinogen*" (USEPA, 1993a, 1998b) based on a weight of evidence evaluation of both the cancer and noncancer effects. EPA later classified BDCM as "*likely to be carcinogenic by all routes of exposure*" (USEPA, 2005d) following the new cancer guidelines. The MCLG of zero was assigned based on intestine and kidney tumor data from a chronic animal carcinogenicity study (NTP, 1987). The low-dose extrapolation approach was used to estimate cancer risk since there was insufficient evidence regarding the mode of action of BDCM (USEPA, 1998b). The RfD presented on IRIS at the time of the Stage 1 D/DBPR (and which is still currently on IRIS) is 0.02 mg/kg/day, based on a lowest observed adverse effect level (LOAEL) of 17.9 mg/kg/day for renal cytomegaly in male mice (NTP, 1987) with the application of an uncertainty factor of 1000 (USEPA, 1993a). In support of the Stage 2 D/DBPR, a criteria document for brominated THMs was used in which EPA derived an RfD of 0.003 mg/kg/day for BDCM based on degeneration of the liver in a 24-month dietary study in rats (USEPA, 2005d, 2006a). However, for the Stage 2 D/DBPR, EPA determined that there were no new significant health effects data suggesting the need for a change in the categorization of BDCM as a *likely* human carcinogen nor for a change in the MCLG of zero (USEPA, 2003d, 2006a).

New Information Available Since Development of Stage 2 D/DBPR

Cancer

NTP conducted a bioassay of BDCM with 50 F344N male rats and 50 B6C3F1 female mice for each of four dose groups, using drinking water as the exposure route (NTP, 2006). The animals were given water with BDCM concentrations of 0, 175, 350 or 700 mg/L (an estimated average daily doses of 0, 6, 12 and 25 mg/kg respectively in rats and an estimated daily dose of 0, 9, 18 or 36 mg/kg to mice) for two years. The drinking water studies were limited to male rats and female mice because of their sensitivity to develop neoplasms when administered BDCM by gavage in corn oil. In the 1987 earlier gavage study there was clear evidence of cancer for both male and female mice and rats.

Cancers or neoplastic lesions did not occur more frequently in the treated animals as a result of exposure to BDCM in drinking water. No tumors were found in the exposed animals at levels significantly greater than the controls. NTP concluded that BDCM in the drinking water did not cause cancer in male rats or female mice. Toxic effects of BDCM in drinking water for male rats included chronic inflammation. These results differed from those in the earlier corn oil gavage study (NTP, 1987)

In 2006, Health Canada's Guideline for Canadian Drinking Water Quality: Technical Document for THMs was published and included a maximum acceptable concentration (MAC) of 0.016 mg/L for BDCM in drinking water based on a cancer endpoint using a NTP (1987) study as the key study and was designated as a "not-to-exceed" value as a precaution against potential adverse reproductive effects (Health Canada, 2006). Health Canada determined that an approach based on cancer endpoints is likely to be protective of non-cancer effects, including reproductive/developmental effects.

In 2009, Health Canada withdrew its 2006 guideline for BDCM based on an expert panel assessment of the NTP (2006) cancer bioassay. At the time that the expert panel was commissioned by Health Canada, BDCM was classified in Group II: probably carcinogenic to humans with sufficient evidence in animals and inadequate evidence in humans (Health Canada, 1994). The expert panel concluded that *"The evidence from a lifetime study of [BDCM] given to rodents by corn oil gavage is that it is an animal carcinogen. However, the second NTP lifetime study, which tested lower doses of [BDCM] in drinking water does not support this determination. The combined data from the two studies do not support a linear dose response."* (Health Canada, 2008a). The expert panel concluded that the NTP (2006) drinking water study calls into question the weight of evidence that BDCM is "probably" carcinogenic in humans, but Health Canada's approach is to assume there is no safe exposure level. The panel pointed out that, in shorter term studies in which BDCM was administered to rats in drinking water, aberrant crypt foci developed in the rat large intestine and suggests that BDCM may play a role in carcinogenesis. The panel stated that *". . . the possibility that a mutagenic mode of action contributes to the carcinogenic effects of BDCM in the intestine cannot be dismissed. Therefore, the Panel concluded that the NTP (2006) data alone are not sufficient to change the classification to "possibly" carcinogenic in humans."*

The Health Council of the Netherlands also decided that BDCM should be considered carcinogenic to humans and that BDCM acts by a stochastic genotoxic mechanism that is governed by a sequence of random events (Health Council of the Netherlands, 2007). Their recommendation corresponds to the EU classification of Group 2B: possible human carcinogen. The NTP studies of genetic toxicology found positive results in a mouse lymphoma assay and a small increase in sister chromatid exchanges in the presence of S9, but negative results in Ames Salmonella Assays, Chinese Hamster Ovary Cells and for the vivo bone marrow micronuclei assay in mice.

Reproductive/Developmental

Bielmeier et al. (2007) investigated BDCM-induced pregnancy loss in F344 rats using *ex vivo* and *in vitro* techniques. Using *ex vivo* techniques, BDCM-exposed corpora lutea showed increased progesterone secretion compared to controls, perhaps reflecting a rebound effect. *In vitro* exposure to BDCM reduced luteal progesterone secretion in response to stimulation by human chorionic gonadotropin (hCG), an analog of luteinizing hormone (LH). In earlier studies (Bielmeier et al., 2001, 2004, see Appendix A for further elaboration), a LOAEL of 75 mg/kg/day was identified in F344 rats for full litter resorption. The ability of hCG to prevent BDCM-induced pregnancy loss suggests an effect of BDCM on maternal LH secretion, while not ruling out a possible effect of BDCM on luteal responsiveness. These findings suggest that BDCM disrupts pregnancy in F344 rats via two modes: disruption of LH secretion and diminished luteal responsiveness to LH.

The Health Canada BDCM expert panel concluded that adverse reproductive and developmental effects of BDCM were observed only at very high, maternally toxic doses, were not consistent between animal models and varied with method of administration (Health Canada, 2008a). The panel stated that the weight of evidence did not support an association between adverse reproductive and developmental effects and exposure to BDCM at levels found in drinking water. Data are limited on potential mode(s) of action related to BDCM and adverse reproductive and developmental toxicity.

Relevance for SYR

The outcome from the NTP (2006) study, the deliberations of the Health Canada Scientific panel (2008a) and the Health Council of the Netherlands (2007) are relevant to the SYR of the MCLG for BDCM. The findings from the animal studies as well as recent mechanistic data and epidemiology findings each contributed to the review deliberations. In addition, new pharmacokinetic information about BDCM, described in 4.1.1.3 (mode of action information relevant to DBP carcinogenicity), is important when considering the impact of the new data on the whether the current MCLG of zero is appropriate.

4.1.1.1.3 Dibromochloromethane

Basis for the MCLG

In the Stage 1 D/DBPR, an MCLG of 0.06 mg/L for DBCM was established by EPA based on a weight of evidence evaluation of both the cancer and noncancer effects. At that time DBCM was classified as a "possible human carcinogen" (USEPA, 1992a, 1998b). The MCLG was based on the RfD, an adult tap water consumption of 2 liters/day for a 70 kg adult, and an additional risk management factor of 10 to account for possible carcinogenicity. The assumed drinking water contribution to total exposure was 80 percent (USEPA, 1994a). At the time of the Stage 2 Rule an RfD of 0.02 mg/kg/day was derived based on a NOAEL of 30 mg/kg/day (adjusted to 21.4 mg/kg/day for a 5-day/week exposure) for liver effects from the subchronic portion of a NTP (1985) study in rats and an uncertainty factor of 1000 (USEPA, 2005d). EPA used the chronic studies of the NTP (1985) study to determine a classification of "*suggestive evidence for cancer"* (USEPA, 2005d). No evidence of carcinogenicity was reported in rats, but there was equivocal evidence of carcinogenicity in male mice and some evidence of carcinogenicity in female mice based on an increased incidence of liver tumors. The RfD value did not change due to the lack of significant new health effects data. EPA did not revise the MCLG for DBCM in the Stage 2 D/DBPR (USEPA, 2003d, 2006a).

New Information Available Since Development of Stage 2 D/DBPR

No new, relevant animal toxicity information was found for DBCM.

Relevance for SYR

There are no new data relevant to the SYR of the MCLG for DBCM.

4.1.1.1.4 Chloroform

Basis for the MCLG

In the Stage 1 D/DBPR, EPA finalized an MCLG of zero for chloroform based on a weight of evidence evaluation of both the cancer and noncancer effects and classified chloroform as a "likely human carcinogen" (USEPA, 1994a, 1998b). The MCLG was based on linear default extrapolation until EPA completed additional deliberations with the Agency's Science Advisory Board (SAB) on the scientific basis of the mode of action for chloroform (USEPA, 1998b). At the same time the Agency identified 0.07 mg/L as the MCLG in a situation where a non-linear approach was used in the evaluation of the cancer endpoint (USEPA, 1998b). For the Stage 2 D/DBPR, EPA proposed an MCLG for chloroform of 0.07 mg/L and then finalized the MCLG of 0.07 mg/L in 2006 based on the SAB's conclusions that the nonlinear approach is most appropriate for the risk assessment for chloroform (USEPA, 2003d, 2006a). The MCLG is based on an RfD of 0.01 mg/kg/day, derived using a benchmark dose level (BMDL) of 1.2 mg/kg/day for liver necrosis in dogs (Heywood et al., 1979) with an uncertainty factor of 100, adult tap water consumption of 2 liters/day for a 70 kg adult and a relative source contribution of 20 percent for drinking water exposure (USEPA, 2006a). EPA concluded that chloroform is "*likely to be carcinogenic to humans"* only under high exposure conditions that lead to cytotoxicity and

regenerative hyperplasia and that chloroform is "*not likely to be carcinogenic to humans"* under conditions that do not cause cytotoxicity and cell regeneration.

New Information Available Since Development of Stage 2 D/DBPR

There was no new, relevant animal toxicity information found for chloroform.

Relevance for SYR

There are no new data relevant to the SYR for chloroform.

4.1.1.2 Haloacetic acids (HAAs)

This section describes the basis for the MCLGs for the five HAAs that comprise HAA5 (monochloroacetic acid, dichloroacetic acid and trichloroacetic acid plus monobromoacetic acid and dibromoacetic acid). New information that has become available since the development of the Stage 2 D/DBPR is relevant within the context of the SYR and is described below. Available health effects information about four additional HAAs (not part of HAA5) is provided in Section 4.4.

EPA completed a health criteria document for brominated acetic acids (USEPA, 2005d) for the Stage 2 Rule in which monobromoacetic acid (MBAA), bromochloroacetic acid (BCAA, not part of HAA5) and dibromoacetic acid) were all identified as "not classifiable as to human carcinogenicity" under the 1986 Carcinogen Risk Assessment Guidelines and "*inadequate for an assessment of human carcinogenic potential*" under the 1999 Draft Guidelines for Carcinogen Risk Assessment.

An overview of new studies is provided in the following subsections. Additional information on the toxicological background at the time of Stage 1 and Stage 2 regulations for cancer, mutagenicity/genotoxicity and reproductive/developmental effects is provided in Appendix A.

4.1.1.2.1 Monochloroacetic acid

Basis for the MCLG

In the Stage 1 D/DBPR, EPA did not set an MCLG for MCAA due to the lack of available health data (USEPA, 1994a, 1998b). In the Stage 2 D/DBPR, EPA proposed an MCLG of 0.03 mg/L and finalized an MCLG of 0.07 mg/L (USEPA, 2003d, 2005b, 2006a). The final MCLG was based on an RfD of 0.01 mg/kg/day, using a NOAEL of 3.5 mg/kg/day for decreased body weight, kidney, liver and spleen weights in rats (DeAngelo et al., 1997) with an uncertainty factor of 300, adult tap water consumption of 2 liters/day for a 70 kg adult and a relative source contribution of 20 percent for drinking water exposure (USEPA, 2005b, 2006a). The USEPA (2005b) classified MCAA as having inadequate data to support a finding on its carcinogenicity.

New Information Available Since Development of Stage 2 D/DBPR

Cancer

Health Canada (2008b) considers MCAA unlikely to be a carcinogen to humans based on lack of evidence. Health Canada developed a Tolerable Daily Intake (TDI) of 0.0117 mg/kg/day, equivalent to EPA's RfD of 0.01 mg/kg/day for MCAA. The TDI is based on the same study (DeAngelo et al., 1997), the same NOAEL of 3.5 mg/kg/day and the same uncertainty factor of 300 as used by EPA.

Relevance for SYR

There are no new data relevant to the SYR of the MCLG for MCAA.

4.1.1.2.2 Dichloroacetic acid

Basis for the MCLG

In Stage 1 D/DBPR, EPA established an MCLG of zero for DCAA based on a weight of evidence evaluation of both the cancer and noncancer effects and classified DCAA as a "probable or likely human carcinogen" (USEPA, 1994a, 1998b). The MCLG was based on several studies showing liver tumors in mice and rats from lifetime exposure to DCAA in drinking water. Insufficient evidence existed regarding the mode of carcinogenic action of DCAA; the low-dose extrapolation approach was used to be protective of public health (USEPA, 1998b). The RfD of 0.004 mg/kg/day was based on a LOAEL of 12.5 mg/kg/day for effects on the liver, brain and testis in dogs (Cicmanec et al., 1991) with the application of an uncertainty factor of 3000 (USEPA, 1994a, 2003c). EPA did not revise the MCLG for DCAA in Stage 2 D/DBPR (USEPA, 2003d, 2005f, 2006a).

New Information Available Since Development of Stage 2 D/DBPR

Health Canada considers DCAA to be a probable human carcinogen based on the cancer studies which resulted in liver tumors in rats and mice (Health Canada, 2008a). No new, relevant animal toxicity information was found for DCAA that would alter the MCLG of zero.

Relevance for SYR

There are no data to suggest a change in the MCLG for DCAA.

4.1.1.2.3 Trichloroacetic acid

Basis for the MCLG

In the Stage 1 D/DBPR, EPA established an MCLG of 0.3 mg/L for TCAA (USEPA, 1994a, 1998b) based on developmental toxicity and limited evidence of carcinogenicity in animals. In the Stage 2 D/DBPR, EPA proposed and finalized an MCLG of 0.02 mg/L for TCAA (USEPA, 2003d, 2005c, 2006a) derived from an RfD of 0.03 mg/kg/day, using a NOAEL for liver histopathological changes in rats (DeAngelo et al., 1997), an uncertainty factor of 1000, an

additional risk management factor of 10 to adjust for "*suggestive evidence of carcinogenicity*." This MCLG was based on this RfD, using adult tap water consumption of 2 liters/day for a 70 kg adult and a relative source contribution of 20 percent for drinking water exposure (USEPA, 2005c, 2006a).

New Information Available Since Development of Stage 2 D/DBPR

Cancer

EPA's IRIS program completed an assessment for TCAA after the completion of the Stage 2 D/DBPR (USEPA, 2011a). According to EPA's 2005 Guidelines for Carcinogen Risk Assessment, EPA classified TCAA as having "*suggestive evidence of carcinogenic potential*" (USEPA, 2005c). This classification was based on significantly increased incidence of liver tumors in male and female B6C3F1 mice exposed via drinking water (DeAngelo et al., 2008; Bull et al., 1990; Bull, 2002; Pereira, 1996; Herren-Freund et al., 1987) and a lack of treatment-related tumors in male F344/N rats exposed via drinking water (DeAngelo et al., 1997).

As was the case with the EPA assessment, Health Canada (2008b) considers TCAA to be a possible carcinogen based on liver tumors in mice and the lack of tumors in the male rat (DeAngelo et al., 1997).

The USEPA (2011a) assessment established an RfD for TCAA that differs from that used in the Stage 2 rule. The IRIS RfD of 0.02 mg/kg/day is based on a 95 percent lower confidence level on the modeled benchmark dose for a 10 percent decrease ($BMDL_{10}$) in liver necrosis in the treated B6C3F1 mice of 18 mg/kg/day (DeAngelo et al., 2008). The study used a drinking water route of exposure over a 60-week period. The study was published after the Stage 2 Rule.

Reproductive/Developmental

The following reproductive/developmental studies were considered in the IRIS report (USEPA, 2011a) as well as three older studies that are summarized in Appendix A.

Singh et al. (2005a, 2005b, 2006) conducted a reproductive/developmental study on inbred Charles Foster rats that were administered TCAA via gavage on gestational days (GD) 6 through 15 at doses up to 1800 mg/kg-daily. Effects reported included decrease in maternal weight gain, post implantation loss, reduction in mean testes weight and length of the seminiferous tubules, reduced ovary weights, and effects on fetal brain. Maternal NOAELs and LOAELs of 1,000 and 1,200 mg/kg/day, respectively, and a developmental LOAEL of 1,000 mg/kg/day, the lowest dose tested, were determined.

Warren et al. (2006) administered TCAA via gavage to pregnant Sprague-Dawley rats at 300 mg/kg/day on GDs 6 through 15. Mean fetal body weights were significantly reduced at this dose, but, no statistically significant effects were noted on fetal eye development. A developmental LOAEL of 300 mg/kg/day was determined. When Smith et al. (1989b) treated pregnant Long-Evans rats with TCAA on GDs 6 through 15 by oral intubation at doses of 0, 330, 800, 1200 and 1800 mg/kg/day, orbit malformations were significantly increased in fetuses at

doses of 1200 and 1800 mg/kg/day. A significant increase in embryo lethality (resorbed implants) was also observed at doses ≥ 800 mg/kg/day.

Relevance for SYR

The new IRIS RfD and updated quantification for the cancer slope factor have the potential to change the MCLG for TCAA. The MCLG may be derived from the noncancer RfD with consideration of the cancer data in determination of the risk management factor applied to Category C and suggestive carcinogens.

4.1.1.2.4 Monobromoacetic acid

Basis for the MCLG

In Stage 1 and 2 D/DBPRs, EPA did not set an RfD or MCLG for MBAA due to lack of data on the dose-response for relevant health effects (USEPA, 1998b). Accordingly, there is no MCLG.

New Information Available Since Development of Stage 2 D/DBPR

Cancer

Health Canada (1994) considered bromoacetic acid as unclassifiable with respect to carcinogenicity in humans based on inadequate data from animal studies and has retained this finding based on the USEPA (2005e) assessment of "*inadequate for assessment of human carcinogenic potential*" (Health Canada, 2008b).

Relevance for SYR

Bromoacetic acid currently lacks an MCLG because that data were considered inadequate to support development of an RfD or cancer classification. No new animal toxicity data were identified under the SYR that would change this finding.

4.1.1.2.5 Dibromoacetic acid

Basis for the MCLG

In Stage 1 and 2 D/DBPRs, EPA did not set an RfD or MCLG for DBAA due to lack of appropriate data on the dose-response for relevant health effects (USEPA, 1998b, 2005e).

New Information Available Since Development of Stage 2 D/DBPR

Cancer

NTP administered DBAA in drinking water to male and female F344/N rats and B6C3F1 mice at daily doses up to 40 and 45 mg/kg/day in male and female rats, respectively, and 87 and 65 mg/kg/day in male and female mice, respectively (NTP, 2007c). Drinking water concentrations were the same for males and females; the doses vary with difference in drinking water intakes and body weights. At the end of the study, tissues from more than 40 sites were examined from every animal. Survival was similar for animals receiving DBAA and the controls. Male rats

receiving DBAA had significantly increased rates of malignant mesotheliomas. The rates of mononuclear cell leukemia increased in exposed female rats and, to a lesser extent, in exposed male rats. Male and female mice exposed to DBAA had increased rates for a variety of liver tumors; lung tumors were increased in male mice and, to a lesser extent, in female mice. NTP concluded that there was some evidence of carcinogenic activity for mesothelioma in male rats and mononuclear cell leukemia in female rats when administered DBAA in drinking water. NTP concluded that there was clear evidence of carcinogenic activity based on increased incidences of hepatocellular neoplasms in male and female mice and hepatoblastoma in male mice. An increased incidence of lung cancer in male mice was also considered to be exposure related, and a slight increase in lung cancer in female mice may have been related to exposure to DBAA.

Health Canada considers DBAA to be a probable carcinogen to humans based on tumors found in several organs in rats and mice after exposure to DBAA (Health Canada, 2008b).

Mutagenicity/Genotoxicity

Positive results were reported on micronuclei formation in the blood of male mice, but not female mice in a 13-week study on DBAA in drinking water (NTP, 2007c).

Reproductive/Developmental

In a related study, NTP conducted a 13-week study in B6C3F1 mice and F344 rats. In that study, DBAA was administered in drinking water at concentrations of 0, 125, 250, 500, 1,000 and 2,000 mg/L, which resulted in average daily doses of approximately 10, 20, 40, 90 and 166 mg/kg/day in male rats and 16, 30, 56, 155 and 230 mg/kg/day in male mice (NTP, 2007c). Adverse effects in male rats included retained spermatids at 40 and 90 mg/kg/day and decreased testis weights and testicular atrophy at 166 mg/kg/day. The NOEL for testicular effects was 20 mg/kg/day in rats. In mice, the incidence of abnormal testicular morphology was significantly increased at 115 and 230 mg/kg/day, with a NOEL for testicular effects of 56 mg/kg/day.

Relevance for SYR

The 2007 NTP study on DBAA showed clear evidence of carcinogenicity in male and female mice and some evidence of carcinogenicity in male and female rats. These data suggest the need for a new assessment for DBAA (NTP, 2007c).

4.1.1.3 Mode of Action Information Relevant to DBP Carcinogenicity

This section provides a summary of the studies that describe modes of action (MOA) of DBPs that potentially lead to carcinogenicity.

4.1.1.3.1 Overview

The mode of action relates to the genotoxicity (i.e., causing DNA damage or mutation) of the DBPs. DNA damage that is not repaired correctly by the cell can cause loss of cellular viability, or when the cell survives, can result in clonal replication of cells carrying a DNA error, that is, a mutation. Mutations and epigenetic changes (alterations in gene expression) are considered two of the main genetic events that lead to tumor formation when clonal expansion of the altered cell

occurs leading to tumor growth. Thus, structural changes to DNA have the potential to lead to damaged cells which then have the potential to form tumors. When some of the mutated tumor cells migrate to new tissue locations the tumors are said to metastasize.

An understanding of mode of action is important when assessing whether effects observed in *in vitro* assays or in experimental animals could apply to human exposures (Humpage, 2012). Ideally, the first step in determining a MOA is to delineate the pharmacokinetics associated with exposure to a substance, so that the relationship between external dose and the systemic concentrations that produce an effect can be understood. Although this level of quantitative dose-response has not been defined for most DBPs, many studies are available which describe both MOAs (changes that occur at the cellular level) and mechanism of action (changes that occur at the molecular level) associated with exposure to DBPs.

A significant number of DBPs, both regulated and unregulated, including halofuranones, brominated trihalomethanes (BrTHMs), brominated HAAs, haloacetonitriles, haloaldehydes, haloketones and halonitromethanes (HNMs) can induce gene mutations (Richardson et al., 2007; Kundu et al., 2004; Bull, 2011). Some of these DBPs are direct-acting mutagens (e.g., MX) and some require metabolic activation (e.g., BrTHMs). Human polymorphic expression of enzymes that are involved in the mutagenic activation or detoxification of DBPs can apparently affect cancer risks associated with DBP exposure (Cantor et al., 2010; see Appendix A for detailed summary of paper). The role of these enzymes will be discussed further in Section 4.1.1.3.2. The available carcinogenicity data for the unregulated DBPs are in Section 4.4 of this chapter.

Some of the nongenotoxic MOAs that have been associated with DBP exposures include the following:

(1) Reparative hyperplasia occurs in an effort to replace dead cells. As the rate of cell division increases with the number of dead cells that require replacement, the DNA replication errors increase proportionally. One hypothesis is that the tumorigenic effect of some DBPs (e.g., chloroform) is strongly influenced by necrosis and reparative hyperplasia, which generally occur only after exposure to high doses of these DBPs meaning that the mode of action is nonlinear.

(2) DNA methylation is an epigenetic mechanism that down-regulates genes without changing their coding sequence and therefore plays an important role in DNA repair. It modulates gene transcription and is key to histone acetylation and chromosomal stability. DNA hypomethylation may contribute to chromosome instability and aberrant gene expression via a nongenotoxic route (Baylin et al., 1998). The following results suggest that DNA hypomethylation may be involved in the carcinogenic mechanism of DBPs in the kidney, liver and colon of rodents.

    a. DNA hypomethylation was associated with the induction or promotion of mouse liver tumors by DCAA and TCAA (Tao et al., 2004a). Tao et al. (2004b) reported that DBAA caused DNA hypomethylation in mouse liver which corresponds with its carcinogenic and tumor promoting activity (Melnick et al., 2007).

b. Chloroform, BDCM, DCAA and TCAA induced DNA hypomethylation in mouse and/or rat kidney which corresponded to their carcinogenic and/or tumor promoting activity, indicating epigenetic activity (Tao et al., 2005; USEPA, 2005d; USEPA, 2011a).

c. When administered by gavage or in drinking water, BDCM induced DNA hypomethylation in the colon of male F344 rats, but did not decrease DNA methylation in the colon of male B6C3F1 mice (Pereira et al., 2004a). BDCM also induced tumors in the colon of male and female F344 rats but not male or female B6C3F1 mice when administered by gavage in corn oil (NTP, 1987). Administration of BDCM in drinking water did not result in detectable increases in colon tumors in male F344 rats (females not tested) or female B6C3F1 mice (males not tested) when administered in drinking water (NTP, 2006). Neither of the NTP studies evaluated the methylation status of DNA.

d. In a separate study, Pereira et al., (2004b) examined whether supplying methionine, an important source of methyl groups for transmethylation reactions, to DCAA-treated mice in their drinking water would reduce the number of altered pretumor liver foci. At the low methionine dose there was an increase in the number of altered hepatocyte foci compared to controls, while at the higher methionine dose the number of foci was decreased, supporting the hypothesis that the availability of methyl groups from methionine for DNA methylation could be important. After 44 weeks, the livers of the treated animals were removed and examined for adenomas. The number of adenomas was decreased at both methionine doses and there was a methionine dose related increase in DNA methylation. However, some liver adenomas were still present. The results of this study suggested that high dietary methionine slowed the progression of foci to tumors. However, methionine did not totally remove the cancer risk leaving an opportunity for other operative MOAs.

(3) Peroxisome proliferation appears to play a role in the development of liver tumors in animals treated with TCAA by a nongenotoxic mode of action as demonstrated in a number of long-term exposure studies in both rats and mice. Induction of liver tumors by PPARα agonists incorporates the following key events: PPARα ligands activate PPARα and subsequently cause an increase in hepatic peroxisomes, cell cycling/apoptosis and lipid metabolism. These changes lead to perturbations in cell proliferation and apoptosis. Suppression of apoptosis coupled with increased cell proliferation allows DNA-damaged cells to persist and proliferate, resulting in preneoplastic hepatic foci and ultimately in tumors from cells damaged by other MOAs (USEPA, 2011a).

(4) Pals et al. (2011) and Dad et al. (2013) proposed that the monohaloacetic acids, especially monoiodoacetic acid (MIAA), could indirectly induce DNA damage by inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), leading to a severe reduction in cellular ATP levels by repressing the generation of pyruvate and reducing aerobic ATP generation by way of the citric acid cycle. The hypothesis was tested in cultured Chinese hamster ovary (CHO) cells with measurements made for cellular

genomic damage (Comet Assay) and reductions in GAPDH activity. The results indicated that MIAAhad the greater effect on the enzyme activity followed by MBAA and MCAA. The degree of genomic damage was correlated with the inhibition of the enzyme with MIAA displaying the greatest toxicity and GAPDH inhibition. A loss of pyruvate leads to mitochondrial stress, production of reactive oxygen species (ROS) and genomic DNA damage (Pals et al., 2011; Dad et al., 2013. The inhibition of GAPDH was linked to alkylation of a cysteine in the active site of the enzyme causing a resultant downstream reduction in the production of pyruvate from the glycolysis pathway and thereby ATP production via the citric acid cycle leading to cytotoxicity and generation of ROS (Dad et al., 2013). The hypothesis was tested examining the genomic effects with and without the addition of pyruvate to the culture. The presence of pyruvate in the culture reduced the genomic damage as measured by the Comet Assay.

The available animal bioassay data on THMs and HAAs described above have shown some evidence of cancer in several organs including kidney, liver, colon, large intestine, lung, mammary gland, pancreas, mesothelioma and blood, but no evidence of bladder cancer in animal studies. However, due to differences in physiology, metabolism and urinary pH, rodents are generally not considered to be good models for human bladder carcinogenesis (Crallan et al., 2006).

4.1.1.3.2 Role of Human Genetic Polymorphisms in DBP-Metabolizing Enzymes

The genotypes of some enzymes involved in the metabolism of THMs and HAAs have been characterized and are associated with increased risk of bladder cancer in humans consuming chlorinated drinking water (Cantor et al., 2010; see section 4.1.2.1.1 for further elaboration). These enzymes are involved in the metabolism of many compounds, including DBPs other than THMs and HAAs. The genes of the glutathione S-transferase (GST) superfamily of genes encode for multifunctional enzymes that conjugate a compound or its metabolite with glutathione (GSH) and are important in the detoxification of electrophilic molecules, including some carcinogens, mutagens and therapeutic drugs. However, certain GST's can also activate some haloalkanes to DNA-reactive intermediates (Thier et al., 1993, Proc. Natl. Acad. Sci. USA 90: 8576; Pegram et al., 1997). Several genes that code for these enzymes are polymorphic, with specific genotypes that exhibit an association with an increased cancer risk (Curran et al., 2000; Cantor et al., 2010).

Glutathione S-transferase theta-1 (GSTT1) is an enzyme that is encoded by the *GSTT1* gene. GSTT1 catalyzes the conjugation of reduced GSH to a variety of electrophilic and hydrophobic compounds that can result in the production of DNA-reactive metabolites. For example, GSTT1-mediated conjugation of GSH with BDCM produces an unstable $GSCHCl_2$ conjugate that can react with DNA or degrade to at least two additional DNA-reactive metabolites (Ross and Pegram, 2003). GSTT1 is expressed in several tissues of rodents and humans and is polymorphically expressed in human populations, with some individuals having a null genotype (Ross and Pegram, 2004). GSTT1 is expressed in people with GSTT1(+) genotypes, which could increase cancer risk from BrTHMs by increasing formation of mutagenic intermediates. People with the GSTT1 null genotype have no GSTT1 activity, and therefore there is no activation of known chemical substrates (such as BrTHMs) by this enzyme. In the Cantor et al. (2010) study, associations between THM exposure and bladder cancer were stronger among subjects who had the GSTT1(+) genotype. People with the GSTT1 null genotype had no increased bladder cancer

risk. (GSTT1 was considered "null" if a deletion was found in both copies of the gene; it was considered "present" if neither or only one copy of the gene had a deletion.) BrTHMs, which had tested negative for mutagenic activity in previous assays, were found to be mutagenic after activation by GSTT1 in a transgenic strain of *Salmonella* (RSJ100) transfected with the GSTT1 gene (Pegram et al. 1997; DeMarini et al. 1997). In these studies, relative mutagenic potency among BrTHMs was observed as follows: DBCM > bromoform > BDCM. GSTT1 activity is abundant in the human urinary tract; Thier et al. (1998) reported renal activities approximately twice that of the liver. Human hepatic GSTT1 is approximately equal in activity towards electrophilic substrates compared to hepatic GSTT1 in rats, but lower than that of mice (Ross and Pegram, 2003).

Glutathione S-transferase zeta-1 (GSTZ1) is the primary enzyme in the di-HAA metabolism pathway (Anderson et al., 1999) and may also be involved in metabolism of brominated tri-HAAs (Saghir and Schultz, 2005). It is encoded by the *GSTZ1* gene and plays a key role in the metabolism and clearance of HAAs. Single Nucleotide Polymorphisms (SNPs) for GSTZ1 result in modified enzyme activity, including effects on the rate of biotransformation of di-haloacetic acids (Board and Anders, 2011). There are four polymorphic variants of recombinant human GSTZ with differing levels of inhibition by DCAA (Lantum et al. (2002). Cantor et al. (2010) examined the effect of single nucleotide polymorphisms of the GSTZ1 gene on bladder cancer incidence.

The single nucleotide polymorphism (SNP) for GSTZ1 considered by Cantor et al. (2010) had the three genotypes of CC, CT and TT where C and T refer to the DNA bases cytosine and thymine involved in the SNP. For their GSTZ1 analyses, Cantor et al. (2010) combined the populations having either CT or TT genotypes, i.e, GSTZ1 CT/TT. Individuals with with genotypes resulting in lower GSTZ1 activity (i.e., the GSTZ1 CT/TT group) were likely to have higher sustained blood levels of HAAs and an increased bladder cancer risk in the Cantor et al. (2010) study.

Cytochrome P450 2E1 (CYP2E1) is a member of the mixed function oxidase system and is encoded by the CYP2E1 gene. CYP2E1 has a number of functions, including catalyzing the primary oxidation of THMs leading to the formation of dihalocarbonyls (phosgene and its brominated congeners), which rapidly degrade to carbon dioxide (the major oxidation product), CO, and other minor end-products. Hepatic CYP2E1-mediated oxidation is the predominant metabolic pathway for the THMs in rodent liver, especially as it related to chloroform (USEPA, 2001a). Although CYP2E1 is abundant in the rodent kidney (Ross and Pegram, 2004; Krajka-Kuźniak et al., 2005), very little to no CYP2E1 activity has been found in the human kidney (Amet et al., 1997; Baker et al., 2005). Additional pathways of parent THM metabolism, which compete with the oxidative pathway, include reductive dehalogenation (CYP2B-mediated) and GSH conjugation via GSTT1 leading to the formation of mutagenic intermediates. As indicated above, the BrTHMs are much more likely to proceed through the genotoxic GSH conjugation pathway than is chloroform, which proceeds predominately through the CYP2E1 pathway. GSTT1-mediated conjugation of chloroform to GSH occurs only at very high chloroform concentrations (Pegram et al., 1997). Cantor et al. (2010) examined the effect of single nucleotide polymorphisms of the CYP2E1 gene on bladder cancer incidence. The single nucleotide polymorphism (SNP) for CYP2E1 considered by Cantor et al. (2010) also had the three genotypes of CC, CT and TT where C and T refer to the DNA bases cytosine and thymine

involved in the SNP. Similar to their GSTZ1 analyses, Cantor et al. (2010) combined the CYP2E1 populations having either CT or TT genotypes, i.e, GSTZ1 CT/TT. They observed that individuals with the CYP2E1 CC genotype had a higher incidence of bladder cancer.

Genetic polymorphisms in the genes that code for these enzymes have been studied for their potential role in cancer susceptibility and drug response in humans. Notable, in the case-control study by Cantor et al. (2010) mentioned above and discussed further in Section 4.1.2.1.1, a subset of the cohort was used to investigate gene-environment interactions. Polymorphisms in three GST genes (GSTT1, Glutathione S-Transferase Mu 1 (GSTM1) and GSTZ1), as well as in CYP2E1 and N-acetyltransferase 2 (NAT2), were evaluated for possible association with risk of bladder cancer from long-term exposure to DBPs in drinking water. DNA was extracted from leukocytes or buccal cells for the genotype assays.

The association between genotypes and long-term THM exposures in humans was evaluated by Cantor et al. (2010) to determine whether the odds ratios for various genotypes within quartiles of THM exposure correlated with the risk for bladder cancer and whether THM odds ratios within genotype categories differed significantly from each other. As indicated above, Cantor et al. (2010) found that people with the GSTT1(+) genotype were at significantly greater risk for developing bladder cancer than GSTT1-null subjects when exposed to THMs, as were those with the GSTZ1 CT/TT or CYP2E1 CC polymorphisms. A potentially sensitive populations based on individuals having both GSTT1-null and the GSTZ1 CT/TT polymorphism was also identified.

Cantor et al. (2010) acknowledged that while THMs are common components in disinfected water, they may not be the most toxic or carcinogenic. Thus, it is possible that one or more of the polymorphisms of interest could be acting through other substances whose occurrence is correlated with THMs and explain the epidemiological associations between THMs in water and bladder cancer in humans receiving disinfected water.

4.1.1.3.3 Mode of Action for the THMs

The following section describes the cancer MOA for the following THMs: chloroform, BrTHMs and BDCM.

MOA for Chloroform

Chloroform produces cancer in the rodent liver and kidney by killing cells and not by a genotoxic mechanism (Larson et al., 1996). Chloroform is metabolized by CYP2E1 and produces phosgene, a toxic intermediate (Bull et al., 2012). Chloroform-induced tumors in the rodent liver and kidney appear to be produced only at dose levels that result in repeated or sustained cytotoxicity and regenerative cell proliferation from oxidative CYP2E1 metabolism (USEPA, 2001a). As chloroform toxicity in the rodent liver and kidney becomes more severe, the rate of cell division increases and stimulates the outgrowth of abnormal cells. The toxicokinetic modeling to support this hypothesis is not available, therefore EPA's chloroform mode of action assessment is based on chloroform's cytotoxicity leading to cellular necrosis.

Publications that became available after the Stage 2 rule suggest that the MOA for cancer linked to chloroform could be more complex for the kidney. Tao et al. (2005) asserted that chloroform caused synergistic DNA hypomethylation that increased with dose in combination with DCAA,

but not in combination with TCAA. Following sacrifice, the levels of renal DNA methylation of the c-*myc* gene were measured. DNA was isolated from the kidney and methylation of DNA was determined by dot-blot analysis and use of a monoclonal antibody for 5-methylcytosine. In male, but not female, mouse kidneys, DCAA, TCAA and to a lesser extent chloroform decreased DNA methylation. Coadministration of chloroform increased DCAA but not TCAA induced DNA methylation. Tao et al. (2005) concluded that the correlation between the ability to promote kidney tumors and the ability to induce DNA hypomethylation suggests that DNA hypomethylation is involved in the carcinogenic mechanisms in the kidney with these DBPs.

MOA for Brominated THMs

The predominant pathway of BrTHM metabolism, like chloroform, is oxidation by CYP2E1, producing dihalocarbonyl intermediates (X_2CO) that can bind to macromolecules (especially proteins) or be hydrolyzed to CO_2 (the primary clearance mechanism). Reductive metabolism of BrTHMs by CYPs, resulting in dihalomethyl radicals, is more extensive than for chloroform. The oxidative and reductive pathways are generally considered to be responsible for the acute cytotoxic effects of BrTHMs, which occur mainly in the liver and kidneys after high-dose exposures (Pegram, 2001). The types of reactive metabolites generated by the oxidative and reductive pathways could form adducts with the purine and pyrimidine bases in DNA (USEPA, 2005d) but this has not been demonstrated experimentally for any of the THMs.

Unlike chloroform, BrTHMs can also be metabolized by a competing pathway mediated by GSTT1 that results in the production of highly reactive mutagenic metabolites (Pegram et al., 1997; DeMarini et al., 1997; Ross and Pegram 2003, 2004). The metabolites of the GSTT1 pathway covalently bind DNA via formation of deoxyguanosine adducts leading to mutations (GC → AT transitions) (DeMarini et al., 1997; Ross and Pegram 2003, 2004).

Agents or genetic polymorphisms that result in increased or decreased activities of the GSTT1 enzymes responsible for BrTHM metabolism can modify the risk for carcinogenicity. Those with a null phenotype will have a lower risk than those with a homozygous positive phenotype (Cantor et al., 2010).

Increased liver, kidney and large intestinal tumors were observed in rodent studies following oral exposure to BrTHMs; however, scientific opinions vary regarding the causal relationship between exposure to BrTHMs and tumors in animals as well as humans (bladder tumors). Shokeer and Mannevik (2010) demonstrated lower hepatic activity of GSTT1 enzyme in humans than in rodents, but haloalkanes were not tested as substrates in this study. Ross and Pegram (2003) compared hepatic GSTT1-mediated metabolism of BDCM across species and found that rat and human activities were similar and were both lower than in mice. Mouse liver cytosol was 13-fold more efficient in catalyzing GSH conjugation to dichloromethane than to BDCM, while rat and human liver cytosols were three and seven fold more efficient (Reitz et al., 1989 as cited by Ross and Pegram, 2003).

The balance between the competing CYP2E1 and GSTT1 pathways may be an important determinant of tissue susceptibility to BrTHM-induced carcinogenesis (Ross and Pegram, 2004). Target tissues for BrTHM-induced carcinomas in rodents had higher ratios of GSTT1:CYP2E1

activities. Potential differences between rodent and human enzyme activities in the bladder epithelium relative to the liver are as yet not known.

Bull (2012) proposed a pharmacokinetic analysis that suggests that in humans THMs would only be metabolized by CYP2E1. However, the metabolic constants used in that analysis were derived from enzyme activities in rodent livers and *Salmonella*, which should not be assumed to be relevant or comparable to activities in the human urinary and intestinal tracts.

GSTT1 activity is significant in the human urinary tract (Thier et al., 1998). CYP2E1, on the other hand, has been reported to be either not present or present only at very low levels in the human kidney (Amet et al., 1997; Cummings et al., 2000; Baker et al., 2005). This increases the likelihood of significant GSTT1 metabolism in the urinary tract of humans. In contrast to humans, renal CYP2E1 levels are substantial in rodents (Ross and Pegram, 2004; Kuzniak et al., 2005; Tabrez and Ahmad, 2010), suggesting that rodents could be less susceptible than humans to BrTHM-induced genotoxic damage in the urinary tract but more sensitive to the phosgene-like dibromomethaldehyde metabolites.

The chronic bioassays and the majority of animal studies with BrTHMs used oral exposures. Because human exposures occur via multiple routes, an understanding of the volatility and dermal permeability of the THMs is relevant. Based on data compiled from ChemIDPlus (ChemIDPlus, 2015) and HSDB (HSDB, 2015), chloroform has the highest vapor pressure of the chorinated/brominated THMs and is therefore more volatile than the BrTHMs, indicating it is more likely to result in exposure via inhalation than the BrTHMs. Xu et al. (2002) examined the skin permeability of the THMs. They found that the skin permeability coefficients, K_p, (cm/h) were 0.16 for chloroform, 0.18 for BDCM, 0.20 for DBCM and 0.21 for bromoform. This indicates that the BrTHMs would tend to be absorbed dermally more readily than chloroform. However, the K_p differences are not large and the authors of this study noted that the THM K_p values suggest that all THMs may be significantly absorbed through the skin during dermal exposure. BrTHM pharmacokinetics are route-dependent, with dermal and inhalation exposures leading to much higher blood levels and extra-hepatic tissue doses than oral exposure (Backer et al., 2000; Leavens et al., 2007; Kenyon et al., 2015). This could be an important contributing factor in the etiology of DBP-associated human bladder cancer (discussed in greater detail in Section 4.1.2.1.1).

Based on results from a number of studies (Pegram et al., 1997; DeMarini et al., 1997; Ross and Pegram, 2003, 2004; Leavens et al., 2007; Richardson et al., 2007; Cantor et al., 2010; Kogevinas et al., 2010; Kenyon et al., 2015), there is a suggestion of a causal relationship between exposure to BrTHMs (perhaps in combination with other DBPs) and bladder cancer in humans. Additional research would help to address gaps in the current understanding of the causal relationship. The supporting information includes the following:

- BrTHMs, and not chloroform, are mutagenic via activation by GSTT1 (Pegram et al., 1997; DeMarini et al., 1997). The GSTT1-mediated metabolism of BDCM forms reactive intermediates that covalently bind with deoxyguanosine bases in DNA. This evidence is consistent with BrTHMs being mutagenic and carcinogenic (Ross and Pegram, 2003, 2004).

- Cantor et al. (2010) reported that the association between bladder cancer and THM exposure was stronger in GSTT1(+) subjects and that people who were GSTT1(-/-) had no increased risk. People with susceptible genotypes for both GSTT1 and GSTZ1 (HAAs) had up to a 5.9-fold increased risk.
- Kogevinas et al. (2010) studied swimmers exposed to DBPs in pools and showed increases in biomarkers for genotoxicity (micronuclei and DNA damage in peripheral lymphocytes, mutagenicity of urine (Ames assay) and micronuclei in exfoliated urothelial cells). This provides additional evidence in support of the role of BrTHMs in producing genotoxic effects leading to bladder cancer.
- Stayner et al. (2014) showed an increase in micronuclei frequency in maternal blood associated with BrTHM exposure from all sources (including ingestion, dermal and inhalation) especially during the first and second trimesters of pregnancy and notably from exposure due to bathing.

Bull (2012) and Hrudey et al. (2015 a,b) have noted that other DBPs in disinfected water may co-occur with THMs and contribute to the cancer risk in humans, and that existing data are insufficient to determine causality of the BrTHMs. Bull (2012) made the following points to support this view, and for each one, EPA has concerns as indicated:

(1) The same enzymes that are involved in the metabolism of THMs are involved in the metabolism of other DBPs and in the metabolism of lipids. Thus, they could contribute to carcinogenesis. *Concern*: EPA's understanding is that the only DBP listed by Bull (2012) that was actually shown to be a GSTT1 substrate is 1,3-dichloroacetone, which occurs at much lower levels in drinking water than the THMs (Serrano et al., 2014).

(2) At least one transcription factor has been shown to be modified by a GST, which modifies the activity of the transcription factor, often playing a role in carcinogenesis. *Concern*: The transcription factor example given by Bull (2012) is a modification by GSTP1 (not GSTT1) and is therefore not relevant to the findings of Cantor et al. (2010) or to a hypothesis involving GSTT1-mediated metabolism of BrTHMs in bladder carcinogenesis.

(3) The rate of THM metabolism at low blood levels from oral and dermal exposures will be independent of the enzyme isoforms present, and other DBPs may be better substrates than THMs for the genotypes that express the active isoforms of the GSTT1 enzyme. *Concern*: This statement on the rate of THM metabolism is based on liver metabolism in rodents and pharmacokinetic constants derived from *Salmonella* data which, for the reasons stated above, should not be extrapolated to human bladder metabolism. Bull (2012) suggested that at the low blood concentrations of BDCM in humans from exposure through drinking water, the mutagenic metabolite of BDCM produced by GSTT1 metabolism will be essentially zero. However, EPA contends that Bull's analysis is based on inappropriate estimates of K_m (the substrate concentration at ½ the maximum rate of reaction or V_{max}) for these enzymes, with no consideration of $V_{max)}$. In Bull (2012), the "human" CYP2E1 K_m estimate was based on rat *in vivo* data which reflects primarily liver metabolism by CYP2E1 and other CYPs, and the "human" GSTT1 Km estimate is derived from *Salmonella* mutation data rather than a value derived from

studies using relevant human data. EPA further contends that Bull's analysis is not relevant to human bladder metabolism of BrTHMs.

(4) The differences in expression of the GSTT1 enzymes across species (humans, rats, mice) are small and unlikely to account for interspecies differences in sensitivity. *Concern*: This statement does not consider the tissue-specific species difference in the expression of the key enzymes (such as CYP2E1) described above.

(5) Human GSTT1 has low activity on electrophilic substrates compared to GSTT1 activity in rats and mice and could explain the species differences in detoxification of DBPs other than THMs. *Concern*: EPA's understanding is that the statement that GSTT1 has lower activity on electrophilic substrates in humans than in rats is not supported by information available for halomethane substrates (Reitz et al., 1989; Ross and Pegram, 2003).

Despite EPA's articulated concerns, the points made by Bull (2012) and Hrudey et al. (2015a, b) also support a need for additional research that would help to address gaps in the current understanding of the causal relationship (i.e., mechanistic research) between exposure to BrTHMs (in combination with other DBPs) and bladder cancer in humans.

Cantor et al. (2010) acknowledged that although THMs and HAAs are the most common chemical species within the DBP mixture, they may not be the most toxic/carcinogenic. One or more of the GST polymorphisms of interest could be acting in important ways on other DBP compounds whose levels correlate with THM levels. However, at present, dichloroacetone is the only additional DBP that has been identified as a GSTT1 substrate. Both the kidneys and the bladder would receive greater internal exposure to THMs that are absorbed via dermal or inhalation routes of exposure (see Backer et al., 2000; Leavens et al., 2007; Kenyon et al., 2015). Although epidemiological findings suggest an increased bladder cancer risk with greater DBP exposure from showering/bathing (Villanueva et al., 2007), it is not yet confirmed whether BrTHMs are a causal factor in human bladder cancer. Research to support quantitative risk assessment via these routes of exposure could further inform this question.

MOA for Bromodichloromethane (BDCM)

BDCM is generally the most prevalent and most extensively studied BrTHM. BDCM can be metabolized by three potential pathways that give rise to reactive intermediates (Pegram, 2001; NTP, 2006):

(1) oxidative metabolism by cytochrome P450, primarily the CYP2E1 isoform which results in reactive dihalocarbonyls and dihalomethyl radicals,

(2) reductive metabolism mediated by cytochrome P450 (CYP2B isoforms), which generates dihalomethyl radicals, and

(3) GSTT1-catalyzed conjugation with GSH, which results in the formation of DNA reactive species and S-dihalomethyl metabolites.

The activity of these enzymes is species dependent, tissue-specific and genetically determined. Biotransformation during the detoxification of BDCM might explain why the acutely toxic effects are primarily found in the liver and kidney (Health Council of the Netherlands, 2007). BDCM is metabolized by GST-catalyzed conjugation with GSH, via GSTT1, and by the CYP450 oxidative pathway (Pegram et al., 1997; Ross and Pegram, 2003, 2004). It is hypothesized that bioactivation of BrTHMs catalyzed by GSTT1 could result in cell transformations that lead to cancers. When considering the genotoxic effects that could occur at environmental exposure levels, CYP2E1-mediated metabolism could act as a detoxification or clearance pathway, because the ultimate product of this pathway is carbon dioxide. CYP2E1 concentrations are much higher in the liver than the kidney, resulting in detoxification of BDCM by rat hepatic microsomes, but the efficacy of this pathway was found to be reduced in rat kidney and large intestine (Ross and Pegram, 2004), and kidney CYP2E1 levels in humans are much lower than in rodents. The path leading to DNA damage from BDCM could be more pronounced in extra-hepatic tissues (due to a higher GSTT1:CYP2E1 ratio). Moreover, these tissues, including the bladder, would be expected to receive higher doses of THMs via inhalation and dermal routes of exposure than by the oral route where there is initial first pass metabolism in the liver.

Differences in the distribution of BDCM among different organs after administration by gavage versus by drinking water in rodents were addressed by pharmacokinetic modeling of BDCM. Dose-response analyses of the carcinogenic effects using peak and cumulative rates of metabolism via GST and CYP450 oxidative pathways in target organs were used as surrogate dose metrics in the studies by NTP (2006) and Ross and Pegram (2004). Using a physiologically based pharmacokinetic model for oral administration of BDCM in F344/N rats, 90 percent of total metabolism occurs during first-pass clearance by the liver. Allocating this 90 percent of total metabolism that occurs in the liver between the P450-mediated and GSTTT1 metabolic pathways, approximately 99 percent occurs via the CYP450-mediated pathway and approximately 1 percent through the GSTT1 pathway. Considering the kidney and the large intestine, 87–88 percent of BDCM metabolism in these two organs occurs via the CYP450 pathway and 12-13 percent via the GSTT1 pathway. These organ-specific differences in the relative importance of CYP450- and GST-mediated BDCM metabolism indicates greater relative metabolism through the GSTT1 pathway in the kidney and large intestine than in the liver. Due to the species and route differences in BDCM pharamacokinetics described above, humans exposed to BDCM via dermal or inhalation exposures would be expected to experience tissue distributions that are different from oral exposure. Extrahepatic tissues, such as organs in the urinary tract, would receive a higher percentage of the absorbed dose following inhalation and/or dermal exposures where more of the dose would be expected to be metabolized by GSTT1.

The products of GSTT1 metabolism have been shown to be mutagenic, which leaves open the possibility that BrTHMs could be carcinogenic by a genotoxic mechanism in humans when exposures are via inhalation or dermal contact because there is no first-pass metabolism by the liver to reduce the unmetabolized BDCM reaching other tissues. After acute oral, high dose rodent exposures to THMs, metabolites of CYP-mediated pathways can overwhelm detoxification mechanisms, leading to cytotoxicity with a consequent increased risk for tumors.

Given the siginificant tissue-specific and species differences in the activities of key enzymes involved in BDCM metabolism, it is important to realize that hepatic metabolism kinetics in

rodents cannot be assumed to be equivalent to human urothelial metabolism. Ross and Pegram (2004) indicate that in the extrahepatic target tissues, GSTT1 products can be generated at low BrTHM concentrations and account for a higher percentage of total metabolism than suggested by Bull (2012). The case for substantial human GSTT1 metabolism in the urinary tract is even stronger given the lack of significant CYP2E1 activity in the kidney (Amet et al., 1997; Cummings et al., 2000; Baker et al., 2005). Inhalation and dermal exposures increase extra-hepatic tissue concentrations due to the lack of hepatic and intestinal first-pass clearance. The quantitative impacts of this difference on measures of internal dose in humans is discussed in section 4.1.2.1.2.

Consistent with the findings that GSTT1-mediated metabolism of BDCM leads to DNA modification and mutations, the Health Council of the Netherlands (2007) concluded that BDCM could exert its carcinogenic effect by a stochastic genotoxic mechanism. According to the Dutch Guideline to the Classification of Carcinogenic Compounds, stochastic genotoxins include compounds that, as parent or as reactive metabolites, interact directly with DNA causing damage such as adducts or strand breaks, leading to gene mutations or chromosome abnormalities that occur at sites associated with carcinogenesis. As described in section 4.1.1.3.1, there is also some evidence implicating an epigenetic carcinogenic mechanism for BDCM. BDCM has been shown to induce DNA hypomethylation of the *c-myc* tumor promoter gene in B6C3F1 mice and to cause hypomethylation in kidney DNA in male B6C3F1 mice and male F344 rats (Tao et al., 2005), suggesting carcinogenic potential in the kidney. DNA hypomethylation occurs with BDCM exposure in rat but not mouse colon and correlates with its carcinogenic activity in rats and lack of carcinogenic activity in mice (Pereira et al., 2004a; George et al., 2002).

4.1.1.3.4 Mode of Action for the HAAs

The toxic potency of some of the five regulated HAAs is associated with enzyme inhibition (e.g., GAPDH, GSTzeta (Pals et al., 2011; Saghir and Schultz, 2005)). Dad et al. (2013) reported inhibition of GAPDH by mono-HAAs can lead to ROS and subsequent damage to DNA.

Saghir and Schultz (2005) studied the toxicokinetics of HAA mixtures in naïve and GSH transferase zeta 1 (GSTZ1)-depleted male F344 rats administered oral or IV mixtures of HAAs. Rats were pretreated for seven days with drinking water containing DCAA to deplete GSTZ1 activity in the liver. The GSTZ1 pathway is susceptible to inactivation by exposure to DCAA and other chlorobromo- di-HAAs. This reduction in GSTZ1 activity reduces the clearance of chloro- and bromochloro- di-HAAs through inhibition of hepaticGSTzeta and leads to production of alkylating metabolites from the amino acids tyrosine and phenylananine metabolized via the GST zeta pathway. The results of low-dose exposures to HAA mixtures suggest competitive interactions between tri- and di-HAAs. Total dose is important, as clearance is dose dependent due to competition for GSTZ1. Polymorphic expression of GSTZ1 can affect bladder cancer risk associated with DBP exposures, with genotypes resulting in lower GSTZ1 activity (and presumably lower HAA clearance) being associated with greater risk (Cantor et al., 2010).

DCAA has been proposed to produce cancer by a nongenotoxic mechanism (Miller et al., 2000). The mode of action for DCAA consists of selective stimulation of tumor cells, which arise spontaneously, and suppression of normal division in hepatocytes, including suppressed

apoptosis, which causes small eosinophilic foci (Stauber and Bull, 1997; Miller et al., 2000). DCAA was not associated with either liver peroxisome or hepatocyte proliferation in the studies by DeAngelo et al. (1999). Stauber and Bull (1997) reported increased proliferation of selected cell lines (e.g. c-Jun positive cells, following DCAA exposures).

EPA concluded that DCAA may potentially be genotoxic under *in vivo* exposure levels that increase tumor incidence (USEPA, 2003c). It causes point mutations and chromosomal aberrations at relatively high exposure levels, but mutations are viewed as exhibiting linear low-dose response for cancer risk assessment. International Agency for Research on Cancer (IARC) (2014) concluded that weak to moderate evidence is available to suggest that DCAA is a genotoxic agent but that it may also act through multiple non-genotoxic mechanisms in liver carcinogenisis. WHO (2000) concluded that there is some evidence of genotoxicity but only at such high levels as to not be relevant for tumorigenesis. Regenerative hyperplasia is not likely to play a role in DCAA-induced hepatocarcinogenicity (USEPA, 2003c).

DCAA caused DNA hypomethylation in male mouse kidneys, particularly hypomethylation of the *c-myc* growth promoter gene (Tao et al., 2005). While Tao et al. (2005) reported that chloroform in combination with DCAA caused synergistic hypomethylation, the data analysis approach, as pointed out above, does not allow assessment of deviations from additivity. DCAA did not induce renal DNA hypomethylation in female mice and does not induce kidney tumors in female mice.

Repeated exposure to DCAA results in a decreased ability to metabolize it, attributed to DCAA's inhibition of GSTZ which metabolizes the parent compound. DCAA induced inhibition of liver GSTZ activity is greater in rats than in mice or humans, but this potential mode of action for its carcinogenicity is not yet fully characterized (USEPA, 2003c). Humans with low GSTZ activity may be more susceptible to DCAA toxicity. The carcinogenic and genotoxic effects of DCAA are strongly associated with higher doses where DCAA metabolism is inhibited.

Many studies have found TCAA not to be genotoxic. TCAA produces liver tumors in mice, but not in rats, and it is not considered a cancer risk at concentrations in drinking water (Bull, 2000). Tao et al. (2005) noted that TCAA caused hypomethylation of DNA in male mouse kidneys but not in female mice. TCAA does not induce DNA hypomethylation in female mice. While TCAA was noted in Section 4.1.1 as being classified as a suggestive carcinogen, it has an unidentified MOA and data supporting an important role for a nongenotoxic MOA with a strong link to the peroxisome proliferation MOA.

4.1.2 Epidemiology and Weight of Evidence

4.1.2.1 Cancer

4.1.2.1.1 Bladder Cancer

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the development of the benefits analysis for both the Stage 1 and the Stage 2 D/DBPRs, EPA used five bladder cancer case-control epidemiology studies that were conducted in the 1980s and 1990s:

- Cantor et al. (1985, 1987)
- McGeehin et al. (1993)
- King and Marrett (1996)
- Freedman et al. (1997)
- Cantor et al. (1998)

(Note that the Cantor et al. (1985) and Cantor et al. (1987) studies both used the same case-control data.) Details for each of the above studies are summarized in Exhibit 6.3 of the EA for the Stage 2 D/DBR (USEPA, 2005g).

These five case-control studies used similar (though not identical) exposure metrics based on years of exposure to chlorinated drinking water (primarily chlorinated surface water) to estimate odds ratios, although some of the studies used other metrics as well. For example, both the King and Marrett (1996) and the Cantor (1998) studies also provided information on changes in risk related to THM4 concentrations in the drinking water. All five studies showed an increase in the odds ratio for bladder cancer incidence with an increased duration of exposure. Using the published odds ratio results from these five studies, EPA calculated an estimate for the lifetime cancer risk population attributable risk (PAR) range of 2 to 17 percent. Between 2 and 17 percent of bladder cancers occurring in the United States could be attributed to long-term exposure to chlorinated drinking water at the time of the Stage 1 D/DBPR. PAR is the reduction in incidence that would be observed if the population were entirely unexposed from the presumed contributing causative factor of incidence (in this case chlorination DBPs). Detailed explanations of these PAR calculations, as well as for those described using additional studies, can be found in the benefits analysis for the Stage 2 D/DBPR (USEPA, 2005g).

To support the Stage 2 D/DBPR, EPA used two additional published epidemiological studies:

- Villanueva et al. (2003)
- Villanueva et al. (2004)

The Villanueva et al. (2003) study was a meta-analysis that used an exposure metric of "ever exposed to chlorinated drinking water" in the populations from the several studies included in the analysis. Villanueva et al. (2003) calculated odds ratios from the combined results of six case-control studies. Four of the five case-control studies used by EPA for Stage 1 D/DBPR were used by Villanueva et al. 2003 in the meta-analysis and accounted for over 90 percent of the

weighting applied to the six studies to calculate a combined odds ratio of 1.2 (confidence bounds = 1.1 - 1.4). The study by Freedman et al. (1997) was not included in the meta-analysis since the underlying cohort study (Wilkins and Comstock, 1981) of the same population was included in the meta-analysis. This study and one new study (Koivusalo et al., 1998) accounted for the remaining weighting. Summary details of the studies used for the meta-analysis are described in Exhibit 6.4 of the EA for the Stage 2 D/DBPR (USEPA, 2005g). EPA used the meta-analysis by Villanueva et al. (2003) to calculate a pre-Stage 1 PAR estimate of 15.8 percent (95 percent CI (Confidence Interval) = 8.5 – 27.2).

Villanueva et al. (2004) conducted a pooled data analysis using six studies that included both a THM4 concentration metric and duration of exposure to chlorinated water to estimate odds ratios for bladder cancer. Two of the six studies used in the pooled analysis of Villanueva et al. (2004), King and Marrett (1996) and Cantor et al. (1998), were used by EPA to develop the Stage 1 and Stage 2 D/DBPRs, as described above. Data on THMs from three of the six studies used, (Koivusalo et al., 1998; Cordier et al., 1993; Porru unpublished) had not been previously published; and for the sixth study, detailed THM information from part of a large U.S. study (Cantor et al., 1987; Lynch et al., 1989) was used. Summary details of these six studies are described in Exhibit 6.5 of the EA for the Stage 2 D/DBPR (USEPA, 2005g). For Stage 2, EPA used the THM4 average concentrations (with additional data provided by the authors) to develop a THM4 concentration-response relationship to predict the odds ratio as a function of average THM4 exposure. Using a pre-Stage 1 average THM4 concentration in the U.S. of approximately 38 µg/L, EPA derived a PAR value of 17.1 percent (95 percent CI = 2.5 – 33.1).

EPA concluded that the PAR values estimated from the three approaches noted above (i.e., the 2 – 17 percent range from the five case control studies, the 15.8 percent value from the Villanueva et al. (2003) meta-analysis and the 17.1 percent derived from the Villanueva et al. (2004) pooled data study) provided a reasonable estimate of the percentage range of bladder cancer nationally that is associated with chlorination DBPs in drinking water. In the Stage 2 EA (USEPA, 2005g), EPA concluded that more evidence was available to support a potential association (though not an established causality) between bladder cancer and DBP exposure than for other cancers considered. At the same time, EPA acknowledged that there were gaps in the understanding of bladder cancer etiology as it relates to chlorination DBPs that could lead to some uncertainty, including reasons for inconsistent results across the various studies, particularly for populations of males versus females and smokers versus nonsmokers. Males tended to have higher risks of bladder cancer, as did smokers (USEPA, 2005g).

In summary, for the Stage 2 D/DBPR, EPA used the five case-control studies used for Stage 1, the Villanueva et al. (2003) meta-analysis and the Villanueva et al. (2004) pooled data analysis to obtain PAR values for pre-Stage 1 bladder cancer incidence ranging from 2 percent to 17 percent, with an indication from the more recent of the studies that the PAR values tended toward the higher end of that range. Although these studies and the analyses performed using the data from them to obtain the PAR values suggested an association of exposure to chlorinated drinking water and to some extent to THM4 specifically and bladder cancer incidence, the information was insufficient to draw a definitive conclusion regarding causality.

New Information Available Since Development of Stage 2 D/DBPR

As part of the SYR, EPA conducted a literature search to identify new epidemiology studies about bladder cancer that became available subsequent to the promulgation of the Stage 2 D/DBPR. Eight new studies were identified: five case-control studies, two pooled and meta-analysis studies, and one ecological study:

- Case-control studies:
    - Chang et al. (2007)
    - Bove et al. (2007b)
    - Villanueva et al. (2007)
    - Michaud et al. (2007)
    - Cantor et al. (2010)
- Pooled data and meta-analysis studies:
    - Villanueva et al. (2006)
    - Costet et al. (2011)
- Ecological study:
    - Llopis-Gonzalez et al. (2011)

Overviews of these studies are presented below, with additional details provided in the relevant sections of Appendix A. There is some overlap among these eight new studies in terms of the populations analyzed. Specifically, of the five case-control studies, three of them (Michaud et al., 2007; Villanueva et al., 2007; Cantor et al., 2010) are based on the same study population enrolled in Spain between 1998 and 2001. This same Spanish population was also included in Costet et al. (2011), one of the two new pooled and meta-analysis papers.

Costet et al. (2011) also included case-control populations from two earlier studies from Finland (Koivusalo et al., 1998) and France (Cordier et al., 1993) that were included in the Villanueva et al. (2004) pooled analysis study used to develop the Stage 2 D/DBPR. In addition, the new pooled data analysis by Villanueva et al. (2006) used the same six case-control studies used by Villanueva et al. (2004) supporting the Stage 2 D/DBPR.

Therefore, in arriving at conclusions regarding the extent to which these eight new studies support or alter the conclusions reached in developing the Stage 2 D/DBPR, this overlap of study populations within these eight studies and with the studies used for Stage 1 and 2 D/DBPRs should be kept in mind. There are different implications for this overlap depending on the issue being informed and these will be discussed in subsequent discussion of the specific studies.

Also, whereas the primary exposure metric used in the studies supporting the Stage 1 and Stage 2 D/DBPRs was duration of exposure to chlorinated drinking water, the exposure metrics used in these new studies to estimate odds ratios for bladder cancer were THM4 exposures and to some extent fluid consumption and duration of water use activities that lead to dermal and inhalation exposures.

The overall conclusions from the eight new studies are as follows:

(1) The five case control studies all provide continued support suggesting an association between exposure to DBPs, and THM4 specifically, from drinking water sources and bladder cancer.

a. The three studies that used the same Spanish population from 1998 – 2001 (Michaud et al., 2007; Villanueva et al., 2007; Cantor et al., 2010) each looked at different exposure-related characteristics that provided some additional new insights to this association. Many of the individuals examined in these studies were exposed to drinking water with THM4 concentrations having a higher proportion of BrTHMs than in most U.S. drinking water supplies (Hrudey et al. 2015; Regli et al. 2015). Thus, the exposure-response relationship observed between exposure from THM4 concentrations and bladder cancer risk in these may be more pronounced than what might be found for the general U.S. population. The polymorphism distributions for these are not expected to be very different from those in the United States (discussed more specifically following).

i. Michaud et al. (2007) focused on the relationship between water intake, THM4 levels and bladder cancer. They observed that for a given THM4 concentration exposure range the bladder cancer risk decreased with water intake. They detected an increased odds ratio in this population subset with >26.0–49.0 μg/L (OR = 2.34; 95 percent CI = 1.16 – 4.71) and >49.0 μg/L (OR = 2.06; 95 percent CI = 0.83 – 5.08) that were comparable to that reported by Villanueva et al. (2007). However, they saw limited evidence of an interaction and no clear exposure-response relationships when considering both exposure measures. (See Appendix A for more detail.)

ii. Villanueva et al. (2007) provided results showing increased risk of bladder cancer in this population both with increased THM4 levels and increased duration of exposure. Long-term THM4 exposure from all exposure routes was associated with a two-fold increase in odds of bladder cancer incidence (OR = 2.1; 95 percent CI = 1.09 – 4.02) comparing those in the highest quartile of average household THM4 level (>49 μg/L) to those in the lowest THM4 quartile (≤8 μg/L), with a statistically significant positive trend observed in the odds of bladder cancer for increasing quartiles of average residential THM4 level (p value for trend<0.01). They also provided results showing that in addition to increased risk from ingestion with increasing THM4 levels, there was evidence of higher risks from increased time spent showering and/or bathing, and with exposure from swimming pools. (See Appendix A for more details.)

iii. Cantor et al. (2010) provided particularly novel information based on the Spanish 1998 – 2001 population in showing that there was an association between bladder cancer and the presence of polymorphisms in key metabolizing enzymes that, although not showing a clear causal relationship between DBPs and bladder cancer, suggested a possible mechanism of action. Cantor et al. (2010) found that people with the GSTT1(+) genotype were at significantly greater risk (OR = 2.2;

95 percent CI = 1.1 – 4.3) for developing bladder cancer when exposed to the upper THM4 exposure quartile (>49 μg/L) compared to GSTT1-null participants who had no increased risk at the same exposure level. Cantor et al. (2010) noted that > 20 percent of their study population were joint carriers of the high risk genotypes of the three genes evaluated and that for subjects with two of these genotypes (GSTT1(+) and GSTZ1 CT/TT) OR increased monotonically to 5.9 percent (95 percent CI = 1.8 – 19.0) in the highest quartile of THM4 (> 49 μg/l). Note that the two key polymorphisms, GSTT1(+) and GSTZ1 CT/TT, may be present in approximately 80 percent and 30 percent of the U.S. population, respectively, and that 24 percent (estimated from 0.8 x 0.3) may have both of those polymorphisms (Regli et al., 2015). Because GSTT1 metabolizes BrTHMs, and GSTZ1 metabolizes HAAs, these findings implicate these two prevalent DBP classes in the etiology of DBP-associated bladder cancer.

b. The Bove et al. (2007b) case-control study involved a New York State population of white males and showed relatively high ORs for bladder cancer, with increased risk associated with increased concentrations of THM4 and of individual THMs. This study also found substantially higher risks associated with two of the species — bromoform and BDCM — compared with DBCM and chloroform.

c. The case-control study by Chang et al. (2007) considered a Taiwan population from 1996 to 2005 and also found increasing risk with increasing THM4 levels, where the THM concentrations in the three groups considered were relatively low: <13.9 μg/L (median 4.9); 13.9-21.1 μg/L (median 15.5); and ≥21.2 μg/L (median 21.2). It should be noted that this study used an endpoint of bladder cancer deaths, not incident bladder cancer cases and so is not directly comparable to the other studies.

(2) The two pooled data and meta-analysis studies also provided support for the association of bladder cancer incidence and exposure to disinfected water and DBPs.

a. The Villanueva et al. (2006) pooled data study used the same underlying study populations as those used in the third approach for estimation of PAR values under the Stage 2 D/DBPR. The additional insight from this study, similar to the Michaud et al. (2007) case-control study, was consideration of joint effects of THM4 levels and water intake. In the pooled analysis by Villanueva et al. (2006), the authors found both decreased risk for increased tap water consumption for a given THM4 concentration range, as well as increased risk for increased THM4 level given a tap water intake range.

b. The Costet et al. (2011) study was a pooled data and meta-analysis of three European populations that were considered in other case-control studies, including the Spanish 1998–2001 population as noted above and two of the European populations (from Finland and France) that were included in the pooled data analysis of Villanueva et al. (2004) that was used to derive one of the PAR estimates for the Stage 2 D/DBPR. The focus of this study was to compare the combined European results with previous results from combined North American (United States and Canada) populations to see

if there was a geographic difference in results. The authors continued to find increased bladder cancer risk with increased THM4 concentrations and found no difference in those risks between the North American and European populations for comparable ranges of THM4 exposures. While populations in Europe may have higher smoking rates than in the United States (a key causative factor associated with bladder cancer) this confounding factor was controlled for in the respective study populations.

(3) The eighth study was an ecological study by Llopis-Gonzalez et al. (2011) that also used a Spanish population but one different from the previously noted Spanish study. The authors considered various districts in and near Valencia, Spain, all having THM4 concentrations in a range of 40 to 80 μg/L. The authors considered an endpoint of bladder cancer mortality rather than cancer incidence. Somewhat different from most other studies using bladder cancer incidence and even the Chang et al. (2007) case-control study using cancer mortality, the authors found a slight increase in risk for women, but no increased risk for men. However, it is important to note that ecological studies are typically intended to generate hypotheses and by themselves are less informative for drawing causal inference compared to other study designs that examine individual-level data. In ecological studies exposure is often characterized at the aggregate level (e.g., by county) versus the individual level data in other study designs, and therefore there is generally greater likelihood for unaccounted confounding factors.

Route of Exposure Considerations

Studies by Villanueva et al. (2007), Kogevinas et al. (2010) and Stayner et al. (2014) mentioned previously underscore the significance of considering exposure to DBPs from disinfected water by routes in addition to ingestion, notably from dermal and inhalation associated with bathing, showering and swimming. Studies that only consider oral ingestion of drinking water may not reflect potential risks from dermal or inhalation exposures, which are not subject to first-pass liver metabolism and may result in relatively greater extra-hepatic distributions than oral exposures. This has been shown in other studies as well. For example, Backer et al. (2000) evaluated the combined effects of dermal and inhalation exposure. Mean concentrations in the tap water used by the subjects were 20-32 μg/l for chloroform, ~ 6 μg/l for BDCM, ~ 1 μg/l DBCM and below the detection limit for bromoform. Backer et al. (2000) found that blood levels of THMs were 4-5 times higher in people who took a 10-minute shower or bath than in people who drank one liter of the same tap water source in 10 minutes.

In a study with human volunteers, Leavens et al. (2007) examined the relationship between oral exposure (single 0.25 L drink, mean dose 146 ng/kg) and dermal exposure (forearm immersion for one hour, estimated mean dose 155 ng/kg) to BDCM in water and BDCM pharmacokinetics. Peak venous blood concentrations of BDCM ranged from 0.4 to 4.1 ng/L following oral exposure and 39 to 170 ng/L for dermal exposure. This study demonstrates that activities involving dermal exposure result in much higher blood concentrations and hence greater overall distribution of BDCM to the systemic circulation compared to oral exposure.

Given the potential for multi-route exposures for some DBPs (e.g., the volatile THMs), the aforementioned studies highlight the need to consider the impact of exposure by all relevant

routes of exposure (oral, dermal, inhalation) at internal target sites of interest. Most of the studies conducted to date characterized exposure only relative to ingestion metrics, with the exception of Villanuenva et al. (2007), who included information on total exposure from ingestion, bathing and showering as well as exposures from each.

Taken together, new information available since promulgation of the Stage 2 D/DBPR (including information pertaining to mode of action already discussed), suggests that:

- Bladder cancer risk may be significantly associated with non-oral routes of exposure (dermal and inhalation from bathing, showering, swimming) as well as from direct ingestion.
- There may be a higher risk from some of the brominated DBP species.
- There may be a relationship between cancer risk and the presence of certain genetic factors in the population that affect metabolism and which could point to a mechanism of action for bladder cancer.

Regli et al. (2015) elaborated on why the above factors may contribute to increased bladder cancer risk in populations served by systems using chlorination. Given the concern for increased bromide levels in source drinking waters from anthropogenic sources they developed a methodology for estimating potential increased incidence of bladder cancer incidence from hypothetical increased levels of bromide in source waters. By better accounting for the uncertainty of the exposure data from Villanueva et al. (2004), they refined the dose-response function that EPA used in its benefits analysis for the Stage 2 D/DBPR to estimate potential bladder cancer risk as a function of THM4 concentration (USEPA, 2005g). Regli et al. (2015) estimated that for roughly every 1 µg/L increase of THM4 (due to an increase in bromide in the source water), excess lifetime bladder cancer risk could increase by about 1×10^{-4}. Although they qualified their overall risk estimates as uncertain since causality between bladder cancer risk and exposure from chlorinated DBPs has not been established, the authors report that there is currently more evidence than at the time of the Stage 2 D/DBPR to suggest a basis for causality (Regli et al., 2015).

Kenyon et al. (2015) published a refined human multi-route PBPK model for BDCM that included chemical-specific parameters that were experimentally derived using human tissues and data. In addition, human data from diverse sources were used to evaluate and demonstrate the predictive capability of the model. Analyses using this model suggested a large contribution of inhalation and especially dermal exposure (e.g., from showering) to internal dose of BDCM reaching the systemic circulation and thus available for extra-hepatic metabolism. For example, using a liter equivalency approach (L-eq) they estimated the BDCM concentration in a liter of water consumed by the oral route that would be required to produce the same internal dose of BDCM resulting from a 10-minute shower in water containing 10 µg/L BDCM. The oral L-eq concentrations for showering are 282, 312 and 2.1 µg/L BDCM for maximum venous blood concentration, area under the curve and amount metabolized in liver/hr, respectively. Based on the hypothesis that metabolism in target tissues is important for toxicity and the development of cancer, they found that non-oral exposures could contribute significantly to the amount of BDCM available for metabolism in tissue and hence the potential for adverse effects. Overall, the authors concluded that their analyses (1) demonstrated the importance of considering the contribution of multiple routes of exposure to BDCM and similarly metabolized chemicals to

provide a more complete evaluation of potential risk of adverse health outcomes and (2) that this refined human PBPK model could be used to estimate internal doses from real-world exposures.

The new information reviewed here strengthens the weight of evidence for the association between bladder cancer in humans and exposure to chlorinated drinking water, with continued indications of higher risks for both increased duration of exposure and increased concentrations of THM4.

Notwithstanding the above, a causal relationship has not yet been established between bladder cancer and exposure to any individual DBP or combinations of DBPs (oral, dermal, inhalation) as noted by others (Hrudey et al., 2015). As new information continues to become available this issue will be further informed. In this regard, the IARC advisory panel has nominated disinfected water used for showering, bathing, swimming or drinking for evaluation for carcinogenicity, based on ubiquitous exposure and extensive new mechanistic evidence of specific DBP toxicity, including molecular epidemiology studies (IARC, 2014).

4.1.2.1.2 Colon/Rectal Cancer

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

In the analyses supporting the Stage 1 D/DBPR, the data provided by the epidemiological studies available at that time suggested a small increase in rectal and colon cancers from exposure to chlorinated surface waters. The database of studies completed on colon and rectal cancers at the time of the Stage 2 D/DBPR continued to support an association, but evidence remained mixed. For colon cancer, one newer study supported an association (King et al., 2000) while others showed inconsistent findings (Hildesheim et al., 1998; Yang et al., 1998). Rectal cancer study results were mixed. Hildesheim et al. (1998) and Yang et al. (1998) supported an association with rectal cancer whereas King et al. (2000) did not. A review of the colon and rectal cancer epidemiological data by Mills et al. (1998) found that the evidence was inconclusive but that there was a stronger association for rectal cancer and chlorination DBPs than for colon cancer. A World Health Organization review (WHO 2000) reported that studies showed weak to moderate associations with colon and rectal cancers and chlorinated surface water or THMs but that evidence was inadequate to evaluate those associations.

EPA did not quantify the risk or risk reduction from colon or rectal cancer as part of its benefits analysis for the Stage 2 D/DBPR but did include a brief "sensitivity analysis." Using the King et al. (2000) study data for colon cancer in males only (showing ORs of 1.0 to 1.53), and the Hildesheim et al. (1998) study data for rectal cancer in both sexes (showing ORs of 0.88 to 2.13), EPA estimated that exposure to chlorinated drinking water could account for approximately 25 percent of male colon cancer and 12 percent of all rectal cancers. However, while those estimates were provided to give some insight to the potential risk, they were not considered sufficiently reliable to use in the risk or risk reduction analyses supporting the Stage 2 D/DBPR (USEPA, 2005g).

New Information Available Since Development of Stage 2 D/DBPR

Four studies identified since promulgation of the Stage 1 and 2 D/DBPR address colon and/or rectal cancers: two case-control studies, one meta-analysis study and one ecological study.

- Case-control studies:
  - Bove et al. (2007a)
  - Kuo et al. (2009)
- Meta-analysis study
  - Rahman et al. (2010)
- Ecological study
  - Rahman et al. (2014)

Appendix A provides detailed summaries about each of these studies relating to colon and/or rectal cancers.

Bove et al. (2007a) compared the risk of rectal cancer with exposure to THM4 and their individual species. THM levels varied spatially within the study county; although risk for rectal cancer did not increase with total level of THMs, increasing levels of the component bromoform (measured in ug/day) corresponded with an increase in odds ratios (OR = 1.85; 95 percent CI = 1.25 – 2.74) for rectal cancer. The highest quartiles of estimated consumption of bromoform (1.69 – 15.43 ug/day) led to increased risk for rectal cancer (OR = 2.32; 95 percent CI = 1.22 – 4.39). Two other THMs were associated with an increase in risk for rectal cancer – DBCM (OR = 1.78, 95 percent CI = 1.00 – 3.19) and BDCM (OR = 1.15; 95 percent CI = 1.00 – 1.32).

Kuo et al. (2009) evaluated whether exposure to THM4 in drinking water is associated with the risk of death attributed to colon cancer in 65 municipalities in Taiwan. All colon cancer deaths of the 65 municipalities from 1997 through 2006 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. Controls were deaths from other causes and were pair-matched to the cancer cases by gender, year of birth and year of death. Each matched control was selected randomly from the set of possible controls for each cancer case. Data on THM4 levels in drinking water in study municipalities were collected from the Taiwan Environmental Protection Administration. The municipality of residence for cancer cases and controls was assumed to be the source of the subject's THM4 exposure via drinking water. The adjusted ORs for colon cancer death for those with high THM4 levels (greater than 14.8 µg/L) in their drinking water were 1.02 (95 percent CI = 0.87 – 1.2) and 1.04 (95 percent CI = 0.89 – 1.21) compared to the lowest group (less than 6.03 µg/L). The results of the study showed no statistically significant association between THM4 in drinking water at levels in this study and risk of death from colon cancer. However, the relatively low THM4 concentrations in both the high and low exposure groups in this study may have precluded detecting associations that might occur at higher concentrations.

Rahman et al. (2010) identified relevant case–control and cohort studies. Separate risk estimates for colon and rectal cancer were extracted from studies meeting the inclusion criteria. Relative risks (RRs) from the cohort studies or odds ratios (ORs) from the case-control studies comparing the highest exposure category with the lowest were pooled using random effects methods. A total of 13 studies (3 cohort and 10 case–control) were analyzed. For colon cancer, the pooled RR/OR

estimates were 1.11 [95 percent CI = 0.73 – 1.70] for cohort studies, 1.33 (95 percent CI = 1.12 – 1.57) for case–control studies and 1.27 (95 percent CI = 1.08 – 1.50) combining both study types. For rectal cancer, the corresponding RR estimates were 0.88 (95 percent CI = 0.57 – 1.35), 1.40 (95 percent CI = 1.15 – 1.70) and 1.30 (95 percent CI = 1.06 – 1.59). Sensitivity analysis showed these results were not importantly influenced by any single study. Publication bias was not evident for the colon cancer analysis but may have been a minor issue for the rectal cancer analysis. The results for rectal cancer may have been influenced by the quality of the studies.

Rahman et al. (2014) examined colon and rectal cancer incidence and water THM concentrations in New South Wales, Australia. Average yearly concentrations of total and individual species of THMs were obtained for 50 local government areas (LGAs). Indirectly-standardized incidence rates of colon and rectal cancers in LGAs for the period 1995 to 2001 were regressed against mean THM concentrations lagged five years, adjusting for socioeconomic status, high risk drinking, smoking status, usual source of water and year of diagnosis, including local and global random effects within a Bayesian framework. The statistical measure used by these authors was the incidence rate ratios (IRRs) for an interquartile range increase in THMs, which were based on the observed incidence of colon and/or rectal cancers relative to the expected incidence for the 50 LGAs. Using five-year lag of exposure there was a positive association between bromoform concentration and colo-rectal cancer in men (IRR = 1.025; 95 percent CI = 1.010 – 1.040) but not in women (IRR = 1.003; 95 percent CI = 0.987 – 1.018). The association in men was mainly found in colon cancer with bromoform (IRR = 1.035; 95 percent CI = 1.017 – 1.053). There was no appreciable association of colorectal cancer with other species of THMs. Sensitivity analyses did not materially change the associations observed. The authors concluded that a positive association was observed between colon cancer and water bromoform concentrations in men.

Conclusions: Collectively, the post-Stage 2 studies of DBP exposure and colon and rectal cancer risk support a continuing concern that long-term exposure to chlorination DBPs increases the risk of colon and rectal cancers. It should be noted that the meta-analysis presented here by Rahman et al. (2010) included studies that were completed prior to the Stage 2 D/DBPR. More information on these studies can be found in the Stage 2 D/DBPR EA (USEPA, 2005g). Two of these studies that reported associations on populations relying on waters with different levels of bromoform supports the hypothesis that bromoform or other DBPs co-ocurring with bromoform may increase the risk of colon cancer.

4.1.2.1.3 Other Cancers

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

At the time of the Stage 1 D/DBPR, EPA evaluated epidemiology data for bladder, colon and rectal cancers. The Agency did not evaluate data related to other cancers. During the development of the Stage 2 D/DBPR, EPA reviewed studies related to other cancers as part of the overall weight of evidence analysis (USEPA, 2005g). Studies on kidney, brain and lung cancers and DBP exposure support a possible association (Kidney: Yang et al., 1998, Koivusalo et al., 1998; Brain: Cantor et al., 1999; Lung: Yang et al., 1998). Definitive conclusions on other cancers could not be made, because so few studies had examined these other endpoints. Studies on leukemia found little or no association with DBPs (Infante-Rivard et al., 2001, 2002). Another

study did not find an association between pancreatic cancer and DBPs (Do et al., 2005). A study researching multiple cancer endpoints found an association between THM4 exposure and all cancer mortality when grouped together (Vinceti et al., 2004). EPA did not include quantification of the risk or risk reduction from any of these other cancers as part of its risk and benefits analyses for the Stage 2 D/DBPR (USEPA, 2005g).

New Information Available Since Development of Stage 2 D/DBPR

Three studies were identified that evaluated other cancer risks subsequent to promulgation of the Stage 2 D/DBPR:

- Chiu et al. (2010)
- Kasim et al. (2006)
- Karagas et al. (2008)

Appendix A provides detailed summaries about each of these studies relating to other cancers.

For cancer endpoints other than bladder, colon and rectal cancers, the post-Stage 2 epidemiology studies provide only weak evidence of associations between drinking water DBP exposure and pancreatic cancer, leukemia and skin cancer. Based on the available evidence, the observed increases in risk are low and often not statistically significant. Limitations in the study designs further diminish the strength of the evidence for positive associations.

4.1.2.1.4 Genotoxic Biomarkers

Four published studies have looked at the presence of biomarkers of genotoxicity in humans as they relate to exposure from DBPs. One of these was published prior to the Stage 2 D/DBPR and was mentioned briefly in the economic analysis supporting that rule (USEPA, 2005g). The other three were published subsequent to the Stage 2 D/DBPR.

Ranmuthugala et al. (2003) reported that they found no effects on a biomarker of genotoxicity in urinary bladder cells from THM4 exposure based on a cohort study undertaken in three Australian communities in 1997. The three communities had varying levels of DBPs in their water supplies (one had no measurable THM4, one had a median of 64 µg/L and one had a median of 138 µg/L). The authors looked for micronuclei in bladder epithelial cells as the biomarker. The authors considered exposure both in terms of THM4 concentrations in the water supply, and as an intake dose (µg/kg per day) calculated by considering individual differences in ingestion, inhalation and dermal absorption. There were 228 participants in the study, of whom 63 percent were exposed to DBPs (at concentrations ranging from 38–157 µg/L and doses from 3–469 µg/kg per day). The authors reported RRs for DNA damage to bladder cells in relation to DBPs, separately for smokers and nonsmokers as follows:

RR per 10 µg/L:

Smokers 1.01 (95 percent CI = 0.97 – 1.06)

Nonsmokers 0.996 (95 percent CI = 0.961 – 1.032)

RR per 10 µg/kg per day:

Smokers 0.99 (95 percent CI = 0.96 – 1.03)

Nonsmokers 1.003 (95 percent CI = 0.984 – 1.023)

The authors also found that the while the proportion of abnormal cells did not differ among the three communities, the median unadjusted frequency of micronuclei was highest in the unexposed community and lowest in the highest exposed community.

Ranmuthugala et al. (2003) concluded that their study provided no evidence that THM4 concentrations or intake at the levels they investigated are associated with DNA damage to bladder cells. However, in their discussion of the study, Ranmuthugala et al. (2003) also noted that because of the small size of the study population micronuclei might not be a sufficiently sensitive indicator of carcinogenicity, and could also explain the lack of association in this study between smoking and micronuclei frequency. They also noted that the higher prevalence in the unexposed community could have been a result of a higher prevalence of smoking in that community than in the other two.

The Villanueva et al. (2007) study, which focused on bladder cancer related to exposure from ingestion, bathing, showering and swimming (discussed in more detail earlier), provided some limited information on increased micronuclei related to higher THM4 exposures, but the results were generally not statistically significant. However, the authors did note that higher associations with micronuclei were observed for THM4 exposures from showering and bathing than ingestion.

The Kogevinas et al. (2010) study presented results of an experimental study set in Spain that assessed biomarkers of genotoxicity in blood, urine and exhaled air samples from 49 adult nonsmoking volunteers before and after swimming in chlorinated water. The objective of the study was to evaluate the genotoxicity of DBPs in swimming pool water by examining biomarkers of genotoxicity before and after study participants swam for 40 minutes in a chlorinated indoor swimming pool. The authors reported that the mean THM4 concentration in the pool water was 45.4 $\pm$ 7.3 µg/L and that the pool air THM4 mean concentration was 74.1 $\pm$ 23.7 µg/m^3. Biomarkers of genotoxicity included micronuclei and DNA damage (determined by a comet assay) in peripheral blood lymphocytes before and one hour after swimming; urine mutagenicity (determined by Ames assay) before and two hours after swimming; and micronuclei in exfoliated urothelial cells before and two weeks after swimming. The authors compared the biomarkers to concentrations of THM4 in exhaled breath of volunteers. The investigators also evaluated the impact of participants' genotype on biomarker changes relative to THM4 exposure by estimating associations and interactions with polymorphisms in genes related to DBP metabolism and DNA repair.

On average, the concentration of THM4 in participants' exhaled breath was seven times higher after swimming, relative to levels measured before swimming. The average THM4 levels before and after swimming were 1.2 and 7.9 µg/m^3, respectively. The corresponding average levels for the individual THMs were 0.7 and 4.5 µg/m^3 for chloroform, 0.26 and 1.78 µg/m^3 for BDCM, 0.13 and 1.2 µg/m^3 for DBCM, and 0.1 and 0.5 µg/m^3 for bromoform. The average number of

micronuclei-positive cells per 1,000 binucleated lymphocytes increased from 3.4 before swimming to 4.0 after swimming; this increase was not statistically significant. The average frequency of micronuclei in exfoliated urothelial cells and the level of urinary mutagenicity also increased after swimming, but, again, these changes were not statistically significant. Swimming was not associated with DNA damage detectable by the comet assay; the average amount of DNA damage in peripheral blood lymphocytes measured through the comet assay *decreased* significantly after swimming relative to before swimming ($p = 0.008$). An observed increase in the frequency of micronucleated lymphocytes after swimming was positively associated with higher exhaled concentrations of the BrTHMs but not chloroform. The β-coefficients (and 95 percent CIs) representing a change in micronucleated peripheral blood lymphocytes per 1,000 cells for a 1-$\mu g/m^3$ change in the specific BrTHMs in exhaled breath measured after swimming were as follows: 1.92 (95 percent CI = 0.21 – 3.63), $p = 0.03$ for BDCM; 1.71 (95 percent CI = (–0.02) – 3.44), $p = 0.05$ for DBCM; and 5.04 (95 percent CI = 1.23 – 8.84), $p = 0.01$ for bromoform. Urine mutagenicity increased significantly after swimming in association with higher concentrations of exhaled bromoform (representing a change in urine mutagenicity for a 1-$\mu g/m^3$ change in bromoform in exhaled air measured after swimming: β-coefficient = 5.27 (95 percent CI = 1.80 – 8.75), $p = 0.004$. Some effect modification by genetic polymorphisms was observed (see below for further discussion).

This study provides insights into the relationships between swimming in chlorinated water, biomarkers of THM exposure (THM concentrations in exhaled breath) and biomarkers of genotoxicity. The results of Kogevinas et al. (2010) study are consistent with the hypothesis that exposure to BrTHMs by swimming in chlorinated pools induces genotoxicity that may be associated with cancer risk. The authors observed that only BrTHMs were associated with higher genotoxicity; chloroform levels were not.

Kogevinas, et al. (2010) also tested several gene-environment interaction hypotheses in this study, focusing on potential modification of the genotoxic effects of DBPs in chlorinated pool water by variants in genes that code for enzymes thought to be important in DBP metabolism (GSTT1, GSTZ1 and CYP2E1). In this study, subjects with the GSTT1 null genotype had lower frequencies of micronuclei in exfoliated urothelial cells and lower urinary mutagenicity than those with at least one functional allele. Although not statistically significant, these findings are consistent with observations of mutagenesis in bacteria and DNA adducts in rodents. The investigators did not observe modification of effects of THMs on micronuclei in peripheral blood lymphocytes by GSTT1, a finding they argue is consistent with a lack of GSTT1 expression in lymphocytes noted in other research. In contrast, individuals bearing GSTT2B +/+ gene (which encodes the glutathione S-transferase theta 2B enzyme) had higher numbers of micronuclei in peripheral blood lymphocytes than did other subjects. The copy-number variants encompassing GSTT2B, which modifies GSTT2 gene expression, are in linkage disequilibrium with the GSTT1 copy-number variants. All three of these genes are located in the same cluster and combined effects are possible. However, the role of GSTT2 and GSTT2B genes in DBP metabolism is not known. The authors also note that limited experimental data are available in this study for GSTZ1 and CYP2E1 in relation to DBP exposure.

The authors reported that the evaluation of effect modification of the genotoxicity of DBPs present in swimming pool water by genetic polymorphisms in genes active in DBP metabolism and DNA repair was of low statistical power given the relatively small sample size and that their

findings should be interpreted with caution. Although the study had low statistical power to identify the effects of genetic variation on responses to DBP exposures during swimming, such variation is plausible. As such, the authors suggest that their findings of gene-environment interactions be verified in further studies.

Stayner et al. (2014) published a genotoxic biomarker study that focused on micronuclei frequency in maternal and cord blood lymphocytes associated with exposure to BrTHMs during pregnancy. The study population included mothers and newborns from the island of Crete, Greece, who became pregnant during the period of February 2007 to February 2008. There were 1,610 eligible women who agreed to participate and 1,459 were followed through delivery. A subset of 408 donated maternal and/or cord blood for biomarker measurements. There were 214 mothers and 223 newborns (including 162 mother-child pairs) from singleton pregnancies having micronuclei analysis of maternal and cord blood lymphocytes.

The study area, in and around the city of Heraklion, was divided into six zones according to the source of ground water used in each area and corresponding to the six water treatment plants supplying water to the participants. Within these zones, a total of 18 sample points were selected (12 in Heraklion and six in rural areas), where drinking water was sampled for THMs four times between September 2007 and January 2009 (72 samples in all). The authors indicated that they decided to focus on BrTHMs in this study because they constituted >80 percent of the total THMs measured. Detailed results were not presented for individual zones or sample areas. The mean BrTHM concentration in residential water was reported to be 2.1 ± 2.6 µg/L, with a median of 0.8 µg/L, a minimum of 0.06 µg/L and a maximum of 7.1 µg/L. While these relatively low BrTHM concentrations may have precluded detecting associations that might occur at higher concentrations, they may also be markers for other co-occuring DBPs associated with the effects observed.

Exposure routes to BrTHMs from water considered in this study included consumption as drinking water, bathing, showering, swimming pool use and hand dishwashing. Information on maternal water usage habits were combined with BrTHM water concentrations to estimate exposure through all routes (ingestion, dermal absorption and inhalation).

Micronuclei frequency were measured in maternal and cord blood lymphocytes. Maternal blood was collected one day after delivery and cord blood was collected from the placenta immediately after delivery. Micronuclei detections were evaluated for both binucleated (BN) and mononucleated lymphocytes.

The authors concluded that their study suggested that exposure to BrTHMs may increase the frequency of micronuclei in maternal BN lymphocytes. They reported that there was no evidence of BrTHM exposures being associated with micronuclei in maternal MONO lymphocytes nor with micronuclei frequency in either BN or MONO lymphocytes of newborns.

The study reported an increase in the rate ratio[2] of micronuclei in maternal BN lymphocytes per 1 µg/L increase in residential tap water of 1.03 (95 percent CI = 0.99 – 1.07) over the full

[2] The authors use the term "rate ratio (RR)" as an outcome measure. It is the ratio of the frequency of micronuclei in an exposure group to the frequency in a referrant group.

pregnancy, with a slightly higher rate ratio of 1.05 for exposure during the first trimester, the same rate ratio of 1.03 during the second trimester and no change in the rate ratio (i.e., 1.0) for the third trimester.

They also reported an increase in the rate ratio of micronuclei in maternal BN lymphocytes per µg/week intake from all routes of 1.55 (95 percent CI = 0.59 – 4.09) over the full pregnancy, with higher rate ratio increases for the first trimester of 3.14 (95 percent CI = 1.16 – 8.50) and the second trimester of 1.68 (95 percent CI = 0.76 – 3.73); there was a reduction in the rate ratio reported for the third trimester of 0.76 (95 percent CI = 0.40 – 1.45).

In addition, the authors reported that bathing had a particularly marked effect on micronuclei frequency. Mothers who took baths only had an increased rate ratio of micronuclei in maternal BN lymphocytes of 2.08 (95 percent CI = 1.09 – 3.98) compared with those who showered only. Increased micronuclei frequency was also reported with increasing frequency of bathing per week, duration of bathing and the product of frequency and duration.

With respect to the lack of evidence in their study that maternal exposure to BrTHMs had any effect on micronuclei frequency in cord blood, the authors suggested that if the critical window of exposure was during the first trimester (where the highest effects were seen for maternal blood lymphocytes), then the cord blood lymphocytes collected at birth may not have been exposed since the majority of the lymphocytes collected at birth in the cord blood are produced in the third trimester (where no effects were seen for maternal blood lymphocytes). The authors also suggested that another possible explanation was that because BrTHMs are metabolized by GST to reactive mutagens, and that it is likely that *in utero* metabolism of BrTHMs is immature, there might have been a lower exposure of reactive metabolites to the fetus.

4.1.2.2 Reproductive and Developmental Effects

During the development of the Stage 2 D/DBPR, EPA evaluated available epidemiology and toxicology studies that looked at the relationships between exposure to chlorinated drinking water or DBPs and adverse reproductive and developmental effects.

In the Stage 2 D/DBPR Economic Analysis, EPA stated that its evaluation of the best available studies, particularly epidemiology studies, is that they did not at that time support a conclusion as to whether exposure to chlorinated drinking water or DBPs caused adverse reproductive and developmental effects, but that they did provide an indication of a potential health hazard concern that warranted incremental regulatory action beyond the Stage 1 D/DBPR (USEPA, 2005g).

The specific reproductive and developmental endpoints that EPA focused on at that time were:

- Fetal growth (mainly birth weight, small for gestational age (SGA) and pre-term delivery (PTD))
- Fetal viability (spontaneous abortion or still birth)
- Fetal malformations (congenital anomalies)

In addition, EPA noted that there were limited studies addressing both female and male reproductive endpoints. Possible associations between DBPs and reproductive and developmental endpoints were found in a number of animal toxicology studies, and although the majority of them were conducted using high doses, these studies were used to inform biological plausibility for some of the effects observed in epidemiology studies.

The remainder of this section of the document provides a summary of both epidemiology and animal toxicity studies addressing these several reproductive and developmental effects endpoints that were published at the time of the Stage 2 D/DBPR and subsequent to the Stage 2 D/DBPR. In general, approximately 40 post-Stage 2 studies addressing end-points such as fetal growth endpoints and congenital anomalies outcomes continue to support a potential health concern, though the relationship of adverse outcomes to DBP exposure may not be known well enough to quantify risks or benefits from reducing exposures. In addition, recent toxicological studies on mixtures (Narotsky et al., 2011, 2013, 2015) showed diminished concern for many reproductive and developmental endpoints (see Section 4.1.3 and Appendix A to this document for further elaboration on the mixtures studies).

4.1.2.2.1 Epidemiology and Animal Toxicity Studies on Reproductive and Developmental Effects

While most animal toxicity data from DBPs are derived from single-chemical studies, data about potential adverse effects in humans come from human epidemiological studies involving mixtures of DBPs formed during disinfection of drinking water. Both toxicological studies in animals and human epidemiological studies have suggested that adverse reproductive and developmental effects from DBP exposure may be of concern. These studies have not demonstrated a causal relationship between low levels of DBPs in drinking water and reproductive/developmental health risks in humans (Simmons, et al., 2008). EPA undertook a multi-year research initiative involving four Agency laboratories (the "Four Lab Study") to provide experimental data on environmentally-relevant mixtures of DBPs to help estimate the potential health risks in humans exposed to mixtures of DBPs formed during disinfection of drinking water (Simmons, et al., 2002, 2004). This section is intended to summarize key data that are currently available about the adverse reproductive and developmental effects identified in animal toxicology studies and human epidemiological studies following exposure to DBPs in order to inform a "weight-of-evidence" assessment based on the current state of the science.

Exhibit 4.1 provides a summary of the results of the epidemiology and animal toxicity studies published before the Stage 2 D/DBPR promulgation (and evaluated as part of the rule development process) and subsequently to that time, addressing each of the seven primary reproductive and developmental effects identified by EPA to be of potential concern with respect to chlorination DBPs: birth weight; SGA; PTD; congenital anomalies; fetal loss; male reproductive effects; and female reproductive effects.

Appendix A provides detailed summaries of the Pre- and Post-Stage 2 epidemiology reproductive and developmental studies. It also provides brief summaries on the Pre-Stage 2 animal studies relating to reproductive and developmental effects; the Post-Stage 2 animal studies are presented in Section 4.1.

Exhibit 4.1: Summary of Results from Pre-Stage 2 and Post-Stage 2 Epidemiology and Animal Toxicity Reproductive/Developmental Studies

Reproductive/ Developmental Endpoint	*Epidemiology Studies*	*Animal Toxicity Studies*
Birth Weight		
Pre-Stage 2	Based on 13 primary studies (Savitz et al. (2005); Toledano et al.(2005); Wright et al. (2004); Wright et al. (2003); Yang (2004); Jaakkola et al.(2001); Källén and Robert (2000); Dodds et al. (1999); Gallagher et al. (1998); Kanitz et al. (1996); Bove et al. (1995); Savitz et al.(1995); Kramer et al.(1992)) and 8 reviews (Bove et al. (2002); Graves et al.(2001); Villanueva et al. (2001); Nieuwenhuijsen et al. (2000); Reif et al. (2000); WHO (2000); Craun, ed. (1998); Reif et al. (1996)), there was some evidence, although inconsistent, for an association between birth weight outcomes and maternal DBP exposure.	An effect on pup weight was observed with DBCM, BDCM and chlorite (Borzelleca and Carchman, 1982; Christian et al., 2001a; CMA, 1996).
Post-Stage 2	Based on 11 primary studies (Hoffman et al. (2008a); Patelarou et al. (2011); Grazuleviciene et al. (2011); Villanueva et al. (2011); Hinckley et al. (2005); Lewis et al. (2006); Yang et al. (2007); Rivera-Núñez and Wright (2013); Kumar et al. (2013); Danileviciute et al. (2012); Zhou et al. (2012)) and 1 meta-analysis (Grellier et al. (2010), there is suggestive) (but not conclusive) evidence of a small association between increased THM or HAA in drinking water and low birth weight outcomes.	Pup weights were unaffected in rats given water containing mixtures of DBPs (Narotsky et al., 2008, 2013, 2015).
Small for Gestational Age		
Pre-Stage 2	Based on 10 primary studies (Porter et al.(2005); Savitz et al. (2005); Infante-Rivard (2004); Wright et al. (2004); Wright et al. (2003); Jaakkola et al. (2001); Källén and Robert (2000); Dodds et al. (1999); Bove et al. (1995); Kramer et al.(1992)) and 6 reviews (Bove et al. (2002); Graves et al. (2001); Villanueva et al. (2001); Reif et al. (2000); Craun, ed. (1998); Reif et al. (1996)), there was some evidence, although inconsistent, for an association between SGA outcomes and maternal DBP exposure.	Reduced fetal weight was observed at high doses of chloroform, DCAA and TCAA (Epstein et al. (1992); Fisher et al., (2001); Ruddick et al., (1983); Smith et al., (1989b), (1992); Thompson et al., (1974)).
Post-Stage 2	Based on 13 primary studies (Hoffman et al. (2008a); Patelarou et al. (2011); Grazuleviciene et al. (2011); Costet et al. (2012); Hinckley et al. (2005); Yang et al. (2007); Horton et al.(2011); Summerhayes et al. (2012); Rivera-Núñez and Wright (2013); Kumar et al. (2013); Aggazzotti et al. (2004); Danileviciute et al. (2012); Levallois et al. (2012)) and 1 meta-analysis (Grellier et al. (2010)), there is suggestive and consistent evidence of a small positive association between SGA and some DBP exposure metrics.	Warren et al. (2006) showed significantly reduced mean fetal weight with TCAA.

Reproductive/ Developmental Endpoint	*Epidemiology Studies*	*Animal Toxicity Studies*
Pre-Term Delivery		
Pre-Stage 2	Based on 10 primary studies (Savitz et al. (2005); Wright et al. (2004); Wright et al. (2003); Yang (2004); Jaakkola et al. (2001); Jaakkola et al. (2001); Gallagher et al. (1998); Kanitz et al. (1996); Savitz et al.(1995); Kramer et al. (1992)) and 6 reviews (Bove et al. (2002); Graves et al.(2001); Villanueva et al. (2001); Reif et al. (2000); Craun, ed. (1998); Reif et al. (1996)), there was no evidence of PTD outcomes and maternal DBP exposure (and some evidence of an inverse relationship).	No animal studies.
Post-Stage 2	Based on 10 primary studies (Hoffman et al. (2008b); Patelarou et al. (2011); Costet et al. (2012); Hinckley et al. (2005); Yang et al. (2007); Horton et al. (2011); Kumar et al. (2013); Rivera-Núñez and Wright (2013); Aggazzotti et al. (2004); Lewis et al. (2007)) and 1 meta-analysis (Grellier et al. (2010)), there is only weak evidence of PTD outcomes and maternal DBP exposure (a few positive findings, but more null results).	No new animal studies.
Congenital Anomalies		
Pre-Stage 2	Based on 11 primary studies (Shaw et al. (2003); Cedergren et al. (2002); Hwang et al. (2002); Dodds and King (2001); Källén and Robert (2000); Dodds et al. (1999); Klotz and Pyrch (1999); Magnus et al. (1999); Bove et al. (1995); Aschengrau et al.(1993); Shaw et al. (1991); 1 meta-analysis (Hwang and Jakkola (2003)) and 9 reviews (Bove et al. (2002); Graves et al. (2001); Villanueva et al. (2001); Nieuwenhuijsen et al. (2000); Reif et al. (2000); WHO (2000); Craun, ed. (1998); Reif et al. (1996)), there was no strong or consistent evidence of congenital anomalies and maternal DBP exposure (although inconsistent, the strongest association with a specific end-point was for neural tube defects and urinary tract malformations; there were inconsistent results related to cardiac anomalies).	Congenital anomalies were observed in most but not all studies with chloroform, bromoform, BDCM, DCAA, TCAA, MCAA, chlorite, chlorine and trichloroacetonitrile (TCAN), and several of these studies involved cardiac malformations (Abdel-Rahman et al., (1982); Christ et al. (1996); Christian et al., (2001a); Couri et al., (1982); Epstein et al., (1992); Harrington et al., (1995a); Johnson et al., (1998); Meier et al., (1985); Ruddick et al., (1983; Smith et al., (1989b), (1990), (1992); Thompson et al., (1974)).
Post-Stage 2	Based on seven primary studies (Grazuleviciene et al. (2013); Righi et al. (2012); Iszatt et al. (2011); Luben et al. (2008); Hwang et al. (2008); Chisholm et al. (2008); Nieuwenhuijsen et al. (2008)) and 2 meta-analysis studies (Nieuwenhuijsen et al. (2009); Hwang et al. (2008)), there is consistent evidence for an association between THM exposures and cardiac anomalies (observed in 4 of 5 studies addressing this end-point).	No new animal studies.

Reproductive/ Developmental Endpoint	*Epidemiology Studies*	*Animal Toxicity Studies*
Fetal Loss		
Pre-Stage 2	Based on 10 primary studies (Savitz et al. (2005); Toledano et al. (2005); Dodds et al. (2004); Dodds et al. (1999); Swan et al. (1998); Waller et al. (1998); Bove et al. (1995); Savitz et al. (1995); Aschengrau et al. (1993); Aschengrau et al. (1989)) and 9 review papers (Bove et al. (2002); Graves et al.(2001); Villanueva et al. (2001); Nieuwenhuijsen et al. (2000); Reif et al. (2000); WHO (2000); Craun, ed. (1998); Mills et al. (1998); Reif et al. (1996)), there was inconsistent, but suggestive, evidence of an association between maternal DBP exposure and pregnancy loss.	Based on studies with BDCM, TCAA, BCAA, sodium chlorite and chlorine dioxide there was evidence of litter resorption, decreased number of implantation sites, resorbed and dead fetuses and decreased number of live fetuses per litter (Bielmeier et al., (2001), (2004); Couri et al., (1982); Johnson et al., (1998); Narotsky et al., (1997); NTP, (1999); Suh et al., (1983)).
Post-Stage 2	Based on 1 new primary study (Hwang and Jaakkola (2012), which also included a meta-analysis with 5 other studies), some evidence is provided of increased risk of fetal loss and exposure to THMs.	Some evidence of post-implantation loss was observed for TCAA (Singh et al., 2005a,b, 2006). Reviews of the potential mode of action of BDCM induced pregnancy loss suggest it may be due to reduced LH secretion and exposure method (gavage vs. ad libitum drinking water) (NTP, 2006; USEPA, 2006a; Bielmeier et al., 2007). Pre-natal loss was not observed in Sprague-Dawley rats given water containing mixtures of DBPs (Narotsky et al., 2008, 2013, 2015) but was noted on F344 rats (Narotsky, 2011).
Male Reproductive Effects		
Pre-Stage 2	Based on only 1 study (Fenster et al. (2003)), no effects were observed on sperm motility or sperm morphology associated with THMs in drinking water.	Male reproductive effects were observed for BDCM, DCAA, DBAA, BCAA, chlorite and bromate (Bhat et al., (1991); Carlton and Smith, (1985); Christian et al., (2002a), (2002b); Cicmanec et al., (1991); Katz et al., (1981), Klinefelter et al., (1995); Linder et al., (1994a, 1994b, 1995, 1997); Toth et al., (1992); Tully et al., (2005); Wolf and Kaiser, (1996). NTP (1998a) found no effects on male reproductive parameters in rats treated with with BDCM.
Post-Stage 2	Based on 5 new primary studies (Luben et al. (2007); Iszatt et al.(2013); Zeng et al. (2013); Nickmilder and Bernard (2011); Xie et al. (2011)), there were no associations found with sperm quality, although moderate decreases in sperm levels were noted with increases in BDCM and DBCM.	Male reproductive effects, including effects on the testes and on sperm, were observed with TCAA and DBAA (NTP, 2007c; Singh et al., 2005ab, 2006). Effects on sperm counts and motility were observed in Sprague-Dawley rats given water containing mixtures of DBPs (Narotsky et al., 2013, 2015)
Female Reproductive Effects		
Pre-Stage 2	Based on 1 study (Windham et al. (2003)), it was observed that THM exposure may affect ovarian function; also, BrTHMs especially DBCM were associated with shorter menstrual cycles.	There was some evidence, though inconsistent, of female reproductive effects. (Balchak et al., (2000); Christian et al., (2002a); Murr and Goodman, (2005). NTP (1998a) found no effects on female reproductive parameters in rats treated with with BDCM.
Post-Stage 2	Based on 1 new study (MacLehose et al. (2008)), there was no evidence of increased time to pregnancy among women with exposure to increasing levels of THMs.	TCAA via gavage resulted in reduced ovary weights (Singh et al., 2005a,b, 2006). No effects on fertility or pregnancy maintenance were observed in mixtures of regulated DBPs (Narotsky et al., 2015).

4.1.2.2.2 Summary of Epidemiology and Animal Toxicity Studies on Reproductive and Developmental Effects

Birth Weight: DBP-associated birth weight reductions, consistent in magnitude (from 26 to 62 grams), were reported in four epidemiology studies (Hoffman et al., 2008a; Zhou et al., 2012; Grazuleviciene et al., 2013; Rivera-Núñez and Wright, 2013) out of five (not including Villanueva et al., 2011) examined here among post-Stage 2 D/DBPR studies. Zhou et al. (2012) also reported (larger) associations (-160 grams; 95 percent CI = -315 – -4) for maternal urinary TCAA measures among a population subset with more complete questionnaire data.

Collectively, six out of eight studies to date reported statistically significant birth weight reductions for different DBP exposures including five (Bove et al., 1995; Wright et al., 2003, 2004; Rivera-Núñez and Wright, 2013; Grazuleviciene et al., 2013) out of seven (not including Hoffman et al., 2008a; Villanueva et al., 2011) studies that examined THM4. Notably, the associations between specific THMs (chloroform and BDCM) and mean birth weight observed by Rivera-Núñez and Wright (2013) largely did not persist in multi-pollutant models adjusted for HAA5. In its earlier review of 15 articles covering fetal growth endpoints, including birth weight outcomes, in support of the Stage 2 D/DBPR, EPA concluded that the evidence for effects on fetal growth, including birth weight, was "inconsistent" overall, but noted that a few of the more recent, higher quality studies provided some evidence of higher risk of low birth weight associated with maternal DBP exposure during pregnancy (however, such evidence was limited largely to studies of average differences in a continuous measures of birth weight, rather than low birth weight outcomes).

The 12 studies (11 original investigations and 1 meta-analysis) published post-Stage 2 are suggestive of small positive associations between increasing levels of THMs and HAAs in tap water and increased risk of the adverse birth weight outcomes reviewed in this section. The suggestive evidence provided by the studies, however, is not conclusive regarding the existence of an increased risk of adverse low birth weight outcomes due to specific DBP exposures as indicated by any of the following, especially at concentrations below current regulatory standards: THM4, BrTHM, specific THMs, HAA5 and HAA9, specific HAAs and maternal urinary TCAA as biomarkers of DBP exposure. Features of these studies limiting the weight of evidence include the small magnitude of observed effects, errors in classification or estimation of DBP exposures, imprecision of observed associations and inconsistent evidence of exposure-response relationships between increasing categories of DBPs and risk of the adverse low birth weight outcomes.

Animal toxicity studies that addressed low post-natal birth weight (pup weight) are included in this section. Sprague-Dawley pup weights were unaffected in studies using chlorinated drinking water, with or without ozonation; concentrated and chlorinated surface water; or water with concentrated levels of THM4 and HAA5 (Narotsky et al., 2008, 2013, 2015). No other animal toxicity studies published subsequent to the Stage 2 D/DBPR were identified which identified low birth weight as an end-point. Three earlier studies were identified which reported a marginal postnatial body weight in the F2B generation of ICR Swiss mice administered DBCM in drinking water in a two-generation study (Borzelleca and Carchman, 1982), decreased F1 and F2 pup body weight in Sprague-Dawley rats administered chlorite in drinking water (CMA, 1996) and decreased pup weight following parental administration of BDCM in drinking water to

Sprague-Dawley rats (Christian et al., 2001a). No NOAEL or LOAEL values were identified in the latter study due to reduced feed and water consumption of the parental females.

The weight of evidence from epidemiology studies continues to support a potential health concern for an increased risk of the adverse birth weight outcomes; this effect was not observed in recent animal studies using chlorinated water. Based on the limited available animal data, the weight of evidence does not support an effect on birth weight.

Small for Gestational Age: The weight of evidence provided by the fourteen post-Stage 2 epidemiologic articles (13 primary studies and 1 meta-analysis) suggest that there is a small positive association between exposure to DBP during pregnancy and risk of an SGA infant. Although often failing to achieve statistical significance, there was consistency reported in RR estimates for SGA and different exposure metrics including THM4 and DCA.

In its earlier review of 16 articles covering fetal growth endpoints in support of the Stage 2 D/DBPR, EPA concluded that the evidence for effects on fetal growth, including SGA, was "inconsistent" overall, but noted that a few of the more recent, higher quality studies provided some evidence of higher risk of SGA associated with maternal DBP exposure during pregnancy. This suggestion that there are associations with SGA appears to be strengthened in that there is more consistency across the Post-Stage 2 studies and collectively across all studies for some of the DBP metrics. Collectively, most studies (pre- and post-Stage 2 D/DBPR) show consistently elevated effect estimates that are small in magnitude based on high third trimester THM4 exposures.

The DCAA exposures findings measured by using water concentration data are remarkably similar (RR range = 1.05 to 1.28) in four out of five pre- and post-Stage 2 studies examining individual HAAs (Wright et al., 2004; Porter et al., 2005; Hinckley et al., 2005; Levallois et al., 2012; Rivera-Núñez and Wright, 2013). One study reported identical ORs and CIs (OR = 1.4; 95 percent CI = 1.1 – 1.9) for the highest ingestion quartiles for DCAA and HAA9 (Levallois et al., 2012), whereas another study reported higher DCAA ORs than those for HAA5 (Hinckley et al., 2005). An additional study that examined biomonitoring data found a higher OR for SGA (1.8; 95 percent CI = 0.9 – 3.7) for detectable urinary TCAA concentrations (Costet et al., 2012). Consistent results were not noted for other individual DBPs. However, some DBPs (including the brominated HAAs) and other DBP mixture surrogates (e.g., total organic halides (TOX)) have not been sufficiently examined.

Animal studies generally do not use the term Small for Gestational Age (SGA) as an end-point. Studies that used "low fetal weight" as an end-point are discussed here. Warren et al. (2006) administered TCAA via gavage to pregnant Sprague-Dawley rats on GD 6-15. Mean fetal body weights were significantly reduced at this dose. Earlier studies were identified which reported low fetal weight following administration of chloroform, DCAA and TCAA. A decrease in fetal weight was reported in pups of Sprague-Dawley rats administered chloroform by gavage during GD 6-15 (Thompson et al., 1974; Ruddick et al., 1983). Reduced fetal body weight was observed in two studies in which Long-Evans rats were administered DCAA by gavage on GD 6-15 (Epstein et al., 1992; Smith et al., 1992). Fetal weight was decreased in Long-Evans rats administered TCAA by gavage on GD 6-15 (Smith et al., 1989b) and in Sprague-Dawley rats administered TCAA by gavage on GD 6-15 (Fisher et al., 2001).

The weight of evidence from epidemiology studies continues to support a potential health concern for an increased risk of an SGA infant born to women exposed to DBPs during pregnancy; decreased fetal weights were observed in several animal studies following administration of chloroform, DCAA, or TCAA to rat dams during pregnancy. Based on the data from these animal studies, the weight of evidence supports an effect on reduced fetal weights in rats.

Pre-Term Delivery: The 11 post-Stage 2 studies (10 primary studies and 1 meta-analysis) provide weak evidence in support of the hypothesis that exposure to DBP during pregnancy increases the risk of PTD. There are but a few positive findings and a larger set of null findings. There was no consistency in the magnitude of measures of association across studies, statistically significant associations between DBP exposure and PTD were only rarely and inconsistently observed, and exposure-response trends were observed in only two of the studies, namely in one assessment of PTD risk and THM4 (Yang et al., 2007) and one assessment of increasing levels of total organic halides (Horton et al., 2011). In its earlier review of 16 articles covering fetal growth endpoints in support of the Stage 2 D/DBPR, EPA concluded that the evidence for effects on fetal growth, including PTD was "inconsistent" overall.

No animal toxicity studies reporting PTD as an endpoint were identified either prior to and since the Stage 2 D/DBPR.

The weight of evidence from epidemiology studies continues to support a potential health concern for an increased risk of PTD in women exposed to DBPs during pregnancy. The evidence related to DBP exposures remains weak with some inconsistencies; namely, some of the more recent studies have detected associations with different DBP metrics for both PTD (<37 weeks) and very early PTD (<32 weeks).

Congenital Anomalies: There is consistent evidence for an association between THMs and cardiac anomalies in the post-Stage 2 epidemiology studies. Although often failing to achieve statistical significance, there was consistent evidence of an elevated risk, with exposure-response trends observed between THM4 and risk of cardiac defects, as well as observed elevated risks associated with BrTHMs and chloroform. Associations between THM exposures and cardiovascular anomalies were noted in one of three pre-Stage 2 studies that focused on this end-point and in four of five post-Stage 2 studies that included assessment of this endpoint. THM levels were markedly low in the one study (Righi et al., 2012) that reported an odds ratio for major cardiac defects of 1.25 for THM exposures > 2.5 μg/L compared with a referant of ≤ 1 μg/L, but did not observe associations between THMs and major cardiac defects for THM levels > 5 μg/L compared to a referant of ≤ 5 μg/L. Associations with ventricular septal defects, in particular, were noted in three of these studies.

For associations between DBP and other (non-cardiac) anomalies, the seven post-Stage 2 epidemiologic studies (Grazuleviciene et al. (2013); Righi et al. (2012); Iszatt et al. (2011); Luben et al. (2008); Hwang et al. (2008); Chisholm et al. (2008); Nieuwenhuijsen et al. (2008)) provide no evidence or, at most, weak and inconsistent evidence. The two studies evaluating an "any defect" endpoint did not observe exposure-response trends. The three assessments of DBP and risk of hypospadias found no elevations in risk. Associations between DBPs (THM4, BrTHMs, chlorite and chlorate) and urogenital, musculoskeletal, cleft palate and several other

specific anomalies were inconsistently noted in these studies, providing at most limited evidence for an association with these defects.

In its earlier review of 12 articles covering congenital anomaly endpoints in support of the Stage 2 D/DBPR, EPA found seven studies, including a meta-analysis, supporting the hypothesis that DBP exposure is associated with congenital anomalies; one study that showed inconsistent results; and four studies that reported little evidence of an association between DBP and risk of congenital anomalies. Birth defects most consistently identified as being associated with DBPs included neural tube defects and urinary tract malformations. The post-Stage 2 studies also reported evidence for associations between DBP and these endpoints. Hwang et al. (2008) reported a statistically significant association of THM4 exposure (ORs between 1.2 and 1.7) with obstructive urinary tract increases and Chisholm et al. (2008) reported an association of THM4 exposure (ORs between 1.1 and 1.4) with urogenital defects that was not statistically significant. Nieuwenhuijsen et al. (2008) reported no increase in urinary tract defects. Although they had very low THM4 levels in general, Righi et al. (2012) reported a small but not statistically significant association of low level THM4 exposure (ORs between 1.2 and 1.3) and urinary tract defects, but not at slightly higher THM4 levels. Grazuleviciene et al. (2013) reported statistically significant association with BDCM exposure (ORs between 1.7 and 2.9) and urogenital anomalies, as well as associations for THM4 and chloroform (ORs between 2.2 and 2.5) that were not statistically significant. In a meta-analysis, Neiuwenhuijsen et al. (2009) reported an increased risk for urinary tract defects (OR 1.33) comparing high to low chlorination byproduct exposures, although the increased risk was not statistically significant.

None of the three post-Stage 2 studies (Chisholm et al., 2008; Nieuwenhuijsen et al. 2008; Righi et al., 2012) that included neural tube defects observed associations with THM4 exposure.

No animal toxicity studies published subsequent to the Stage 2 D/DBPR were identified which identified congenital anomalies as an end-point. Twelve animal studies were published prior to Stage 2 D/DBPR in which congenital anomalies were observed, including increased frequency of bilateral extra lumbar ribs, increased sternebral anomalies, increased cardiac malformations, decreased fetal crown-rump length, increased soft tissue anomalies, increased number of ossification sites and delayed skeletal ossification. One or more of these effects were observed with chloroform (Thompson et al., 1974), bromoform (Ruddick et al., 1983), BDCM (Christian et al., 2001a), DCAA (Epstein et al., 1992; Smith et al., 1992), TCAA (Smith et al., 1989b; Johnson et al., 1998), MCAA (Smith et al., 1990), chlorite (Harrington et al., 1995a; Couri et al., 1982), chlorine (Abdel-Rahman et al., 1982) and/or TCAN (Meier et al., 1985; Christ et al., 1996) in Sprague-Dawley or Long-Evans rats. Delayed skeletal ossification was observed with chlorite in New Zealand rabbits. No teratogenic effects were observed in Sprague-Dawley rats administered chloroform by gavage in corn oil (Ruddick et al., 1983). Reproductive effects reported for haloacetonitriles which used tricaprylin as a vehicle for gavage are not included here because tricaprylin has been shown to be a developmental toxicant and may potentiate the effects observed in those studies. Based on the data from these animal studies, the weight of evidence supported an effect on the frequency of congenital anomalies.

The weight of evidence from epidemiology studies continues to support a potential health concern for an increased risk of congenital anomalies in humans, including evidence of increased

risk of cardiac defects, neural tube defects and urinary tract malformations from exposure to THM4; animal studies also support the risk of an increased frequency of congenital anomalies.

Fetal Loss Conclusions: The 11 epidemiology studies provide some evidence in support of the hypothesis that exposure to DBP during pregnancy increases the risk of fetal loss/stillbirth. In its review of the 10 studies available at the time of the Stage 2 D/DBPR, EPA concluded that although the evidence was inconsistent overall, there was suggestive evidence of an association between fetal loss and chlorinated water or DBP exposure. Hwang and Jaakkola (2012), the only new publication on this endpoint since the Stage 2 D/DBPR, observed an overall small association with fetal loss (stillbirth) in their own case-control study (OR = 1.10, 95 percent CI = 1.00 – 1.21 for medium exposure and OR = 1.06, 95 percent CI = 0.96 – 1.17 for high exposure) and in their meta-analytic summary of the evidence contributed by five studies (Aschengrau et al. 1993; Bove et al. 1995; Dodds et al. 1999; Toledano et al. 2005; Dodds et al. 2004) plus their own case-control study (OR = 1.11, 95 percent CI = 1.03 – 1.19), albeit with marked heterogeneity across studies.

In addition to the epidemiology evidence noted above on fetal loss/stillbirth, the collective available animal toxicity data at the time of the Stage 2 D/DBPR provided evidence of fetal loss in terms of litter resorption, post-implantation loss and decreased litter size. A study in inbred Charles Foster rats administered TCAA via gavage on GD 6-15 at doses up to 1800 mg/kg/day reported post implantation loss (Singh et al., 2005a,b; 2006). Prenatal survival in Sprague-Dawley rats was unaffected in studies using chlorinated drinking water, with or without ozonation; concentrated and chlorinated surface water; or water with concentrated levels of THM4 and HAA5 (Narotsky et al., 2008, 2013, 2015). However, mixtures of THM4 and HAA5 contributed to pregnancy loss from a mixture of nine DBPs in F344 rats (Narotsky et al., 2013).

Studies published prior to Stage 2 D/DBPR also described full litter resorptions induced by BDCM administered in corn oil or in an aqueous vehicle in F334 rats (Narotsky et al., 1997). Full litter resorptions were observed following aqueous gavage to F344 rats but not to Sprague-Dawley rats (Bielmeier et al., 2001, 2004). In a study conducted in male and female Sprague-Dawley rats administered BCAA in drinking water, the number of live fetuses per litter and the total number of implants per litter were significantly decreased (NTP, 2009). A study in which TCAA was administered in drinking water to pregnant Sprague-Dawley rats resulted in significant increases in the number of resorptions and number of implantation sites (Johnson et al., 1998). In two studies in Sprague-Dawley rats, resorbed and dead fetuses were observed following administration of sodium chlorite in drinking water (Couri et al., 1982) and decreases in number of implants per litter and number of live fetuses per dam were observed following administration of chlorine dioxide in drinking water (Suh et al., 1983).

Reviews of pregnancy loss following BDCM exposure and a discussion of the potential mode of action were published by NTP (2006) and USEPA (2005d). Reduced LH secretion (Bielmeier et al., 2002) and reduced luteal responsiveness to LH (Bielmeier et al., 2003) may both contribute to BDCM-induced full litter resorption in F344 rats (US EPA, 2006a; Bielmeier et al., 2007). However, several investigators have failed to observe full litter resorption in Sprague-Dawley rats exposed to BDCM, suggesting that these effects may be strain-specific (Bielmeier et al., 2001; Christian et al., 2001a; Ruddick et al., 1983). A BDCM expert panel (Health Canada, 2008a) concluded that adverse reproductive and developmental effects of BDCM were observed

only at very high, maternally toxic doses; were not consistent between animal models; and varied with method of administration. Data for mode of action are limited.

The weight of evidence from epidemiology studies continues to support a potential health concern for an increased risk of fetal loss/stillbirth; animal studies provide evidence of fetal loss in terms of litter resorption, post-implantation loss and decreased litter size.

Male Reproductive Effects: Although based on a small number of studies, the weight of evidence provided by the five post-Stage 2 epidemiologic studies suggests that there is either no association, or, at most, a small association, between exposure to DBP and male reproductive outcomes. The four studies of sperm quality and DBP exposure were largely negative, although decreasing sperm concentration with increasing BrTHM exposure was observed in three studies (Zeng et al., 2014; Iszatt et al., 2013; Luben et al., 2007). In its earlier review of one article addressing male reproductive effects endpoints in support of the Stage 2 D/DBPR, EPA concluded that no association was found between THM4 exposure and semen quality.

Adverse male reproductive effects were observed in animal toxicity studies conducted since Stage 2 D/DBPR. TCAA, when administered via gavage on GD 6-15 to inbred Charles Foster rats, resulted in a reduction in mean testes weight and length of the seminiferous tubules (Singh et al., 2005a, b, 2006). In a 13-week study in B6C3F1 mice and F344 rats, DBAA was administered in drinking water and resulted in testicular atrophy, reduced testicular weight, sperm motility and sperm concentration in rats and delayed spermiation in mice and rats (NTP, 2007c). Reduced sperm counts and reduced sperm motility were reported in Sprague-Dawley rats given concentrated and chlorinated surface water, or water with concentrated levels of THM4 and HAA5 (Narotsky et al., 2013, 2015).

In studies conducted prior to Stage 2 D/DBPR, the following effects were observed following BDCM administration in drinking water: sperm velocities were significantly decreased in F344 rats (Klinefelter et al., 1995); delayed sexual maturation in F1 males with reduced body weight in Sprague-Dawley rats (Christian et al., 2002a). No effects on sperm characteristics were noted in studies by NTP (1998a) or Christian et al., (2002a) in Sprague-Dawley rats administered BDCM in drinking water. NTP (1998a) conducted a short-term reproductive and developmental screening test with BDCM administered in drinking water to Sprague-Dawley rats and concluded that BDCM was not a reproductive or developmental toxicant.

Studies were also conducted with DCAA and resulted in adverse effects on the testes, including testicular germinal epithelial degeneration and aspermatogenesis, in Sprague-Dawley rats and beagle dogs (Katz et al., 1981); decreased testis weight, tissue atrophy and few spermatocytes and no mature spermatozoa in the seminiferous tubules in Sprague-Dawley rats (Bhat et al., 1991); testicular changes, including syncytial giant cell formation and degeneration of testicular germinal epithelium, in beagle dogs (Cicmanec et al., 1991); significant reductions in the absolute weight of the preputial gland and epididymis and effects on sperm morphology and decreased sperm counts in Long-Evans rats (Toth et al., 1992); and a decrease in epididymal weight and epididymal sperm count in Sprague-Dawley rats (Linder et al., 1997).

Linder et al. (1994a, b, 1995) conducted gavage studies with DBAA in Sprague-Dawley rats which resulted in reduced testis and epididymis weights, decreased sperm counts and

histopathological evidence of altered spermiation and reduced sperm motility. In another study, DBAA was administered in water to Sprague-Dawley rats and resulted in altered sperm production and some epididymal tubule changes and small or absent epididymis and small testes (Christian et al., 2002b).

Decreased male fertility due to disruption of spermatid differentiation was observed in C57BL/6 mice following BCAA administration (Tully et al., 2005); a decrease in epididymal sperm density was observed in rats following bromate administration in drinking water (Wolf and Kaiser, 1996) and abnormal sperm were observed following administration of chlorite in drinking water to Long-Evans rats (Carlton and Smith, 1985).

The weight of evidence from epidemiology studies appears not to support a potential health concern for an increased risk of male reproductive effects; animal studies provide evidence of a number of adverse effects, including testicular effects and decreased sperm counts.

Female Reproductive Effects: There was only one study available at the time of the Stage 2 D/DBPR on female reproductive effects. Windham et al. (2003) found that exposure to THMs may affect ovarian function. The BrTHMs, notably DBCM, were associated with significantly shorter menstrual cycles. There was also only one new study, MacLehose et al. (2008), since the Stage 2 D/DBPR addressing female reproductive effects, specifically time-to-pregnancy. The authors found no evidence of an increase in time to pregnancy with increased exposure to DBPs.

Reduced ovary weights were observed in an animal toxicity study conducted since Stage 2 D/DBPR in inbred Charles Foster rats administered TCAA via gavage on GD 6-15 (Singh et al., 2005a, b, 2006).

Prior to Stage 2 D/DBPR, NTP (1998a) conducted a short-term reproductive and developmental screening test with BDCM administered in drinking water to Sprague-Dawley rats and concluded that BDCM had no effects on female reproductive parameters in rats treated with with BDCM. Other studies observed effects on female reproductive outcomes. A study in Sprague-Dawley rats administered BDCM in drinking water resulted in a marginal effect on estrous cyclicity in F1 females and a small but significant delay in F1 generation sexual maturity (Christian et al., 2002a); studies with DBAA in Sprageu-Dawley rats resulted in alterations of the estrous cycle (Balchak et al., 2000) and in increased circulating serum estradiol levels with no observed change in the estraou cycle (Murr and Goodman, 2005).

Insufficient epidemiology information is available to inform an updated understanding of adverse female reproductive effects; animal studies provide marginal evidence with respect to effects on the female reproductive system.

4.1.3 Mixtures of Chlorination Organic DBPs

Multiple studies have been conducted researching developmental and reproductive effects from mixtures of DBPs. Narotsky et al. have conducted five studies, including two multi-generational studies, since 2008, researching the reproductive and development effects from regulated DBPs and from environmentally-realistic complex mixtures of DBPs formed during disinfection with chlorine or ozone/chlorine. The most recent Narotsky et al. (2015) evaluated a drinking water mixture of the four regulated THMs and five regulated HAAs in a multi-generational

reproductive toxicity bioassay. Some additional studies addressing DBP mixtures for other end-points are presented in Appendix A.

Simmons et al. (2002, 2004) describes the origins of the "Four-Lab Study", so called because it draws upon the expertise and skills from four EPA Office of Research and Development laboratories/centers. Simmons et al. (2008) presented results from the first series of studies proposed in an EPA peer-reviewed research plan called "Integrated Disinfection Byproducts Mixtures Research: Toxicological and Chemical Evaluation of Alternative Disinfection Treatment Scenarios". The research of this multidisciplinary team focused on integration of toxicological and chemical evaluation of complex mixtures of DBPs and their reproductive/developmental effects. These effects were identified as endpoints of concern in epidemiologic studies and EPA determined it was feasible to conduct *in vivo* animal studies investigating these endpoints. The first series of experiments studied the stability of the DBPs and methods for concentrating them. Sprague-Dawley rats were then exposed to these concentrates in treated water as their sole source of drinking water. These experiments determined that using reverse osmosis membranes to concentrate water samples, with a 100-fold concentration factor as the target reverse osmosis concentration, is the optimal approach for treating water samples to be used in toxicological studies.

The following Narotsky et al. papers present results from the Four-Lab Study of DBP mixtures.

Narotsky et al. (2008) used an *in vivo* toxicity screen to evaluate the developmental effects of a mixture of DBPs, using finished drinking water from a city in Ohio. The water was treated by one of two methods, either conventional treatment with disinfection by chlorination or conventional treatment with disinfection by ozonation followed by chlorination. The water was concentrated approximately 100-fold and administered to Sprague-Dawley rats on GD 6–16. The rat litters were examined on postnatal days (PND) 1 and 6, with no effects observed on prenatal survival, postnatal survival, or pup weights from either the water treated by conventional treatment/chlorination or the water treated by ozonation/chlorination.

Narotsky et al. (2011) assessed the combined toxicity of DBPs. Pregnant F344 rats were administered mixtures of THM4, HAA5, or the full mixture of all the chemicals (nine DBPs) by gavage on GD 6–20. All three mixtures caused pregnancy loss at ≥ 613 µmol/kg-day. Resorption rates were increased in the group administered HAA5 at 613 µmol/kg-day and the group administered the nine DBPs at 307 µmol/kg-day. Eye malformations were increased in the HAA5 group at ≥ 308 µmol/kg-day. The authors concluded that both HAA5 and THM4 contributed to the pregnancy loss from the full mixture of nine DBPs and that the presence of THM4 in the full mixture appeared to reduce the incidence of HAA-induced eye defects.

Narotsky et al. (2013) used a multi-generational bioassay with Sprague-Dawley rats to evaluate an "environmentally relevant whole mixture of DBPs representative of chlorinated drinking water." Surface water used as a source for a utility was treated, filtered and concentrated based on TOC to 136-fold greater than the unconcentrated filtered water. The concentrated water was chlorinated and was provided as drinking water to pregnant female rats (P0 generation) during gestation and lactation. Weanlings (F1 generation) were also exposed to the treated drinking water and were bred to produce an F2 generation. One set of controls received deionized water and another set of controls received the unchlorinated concentrate. However, this latter set of

controls was discontinued on GD19 because of repeated clogging of the water delivery system. The study was conducted with 2 sets of replicates each consisting of 100 animals (60 study, 40 controls), although the second replicate set was conducted for the initial part of the study only and halted on PND 6 of the F1 generation. No evidence of toxicity was observed for the P0 dams. No adverse effects were observed for pup weight, prenatal loss, pregnancy rate, gestation length, puberty onset in males, growth, estrous cycles, hormone levels and most neurobehavioral endpoints. Slight, though statistically significant (at 0.05 level), effects observed included delayed puberty for F1 females, reduced caput epidydimal sperm counts in F1 adult males and increased incidence of thyroid follicular cell hypertrophy in P0 and adult F1 females. The authors concluded that their multigenerational reproductive and developmental study with an environmentally relevant mixture of DBPs yielded predominately negative results, although the slight but significant effects noted warranted further study.

Narotsky et al. (2015) conducted a multi-generational bioassay with Sprague-Dawley rats similar to the Narotsky et al. (2013) study above but with specific concentrations of THM4 and HAA5 rather than the "whole mixture" of DBPs. The THM4 and HAA5 levels studied reflected concentrations that were 0x, 500x, 1000x and 2000x the MCLs of 0.08 mg/L and 0.06 mg/l, respectively. In this study the authors found that the mixtures up to 2000x the MCLs had no adverse effects on fertility, pregnancy maintenance, prenatal survival, postnatal survival or birth weights. F1 pup weights though unaffected at birth were reduced on PND 6 at the 2000x dose and PND 21 at the 1000x dose. Body weights were also reduced for the post-weaning F1 generation at the 2000x dose and water consumption was reduced for the post-weaning F1 generation at 500x dose. Onset of puberty was delayed for both males and females at the 1000x and 200x doses. Males at the 2000x dose had a small but significant increased incidence of retained nipples and compromised sperm motility. The authors concluded that the mixture of THM4 and HAA5 at concentrations 500x greater than the MCLs had no adverse effects and that even at 2000x the MCLs did not affect the animal's ability to reproduce. The authors also noted the lack of effect on prenatal survival and birth weight in this animal study contrasted with associations reported for those end-points in some epidemiological studies. While reproduction was unaffected, delay in the onset of puberty in both sexes and retained nipples and reduced sperm motility in males was observed indicating some effect on endocrine physiology. The authors commented that these latter effects may have been due to reduced water consumption and reduced postnatal body weights.

4.2 Regulated Inorganic DBPs

This section addresses the health effects that are associated with the regulated inorganic DBPs, specifically bromate and chlorite.

An overview of studies is provided below. Additional information for the pre-Stage 2 studies are provided in Appendix A.

4.2.1 Bromate

Basis for the MCLG

In the Stage 1 D/DBPR, EPA established an MCLG of zero for bromate based on a weight of evidence evaluation of both the cancer and noncancer effects indicating that bromate is a "probable or likely human carcinogen" (USEPA, 1994a, 1998b). The MCLG was based on an increase in kidney and thyroid tumors in several rat studies (Kurokawa et al., 1986a, 1986b; DeAngelo et al., 1998). Insufficient evidence exists regarding the mode of carcinogenic action of bromate; thus, the low-dose extrapolation approach was used because it is more protective of public health (USEPA, 1998b). An EPA IRIS assessment established an RfD of 0.004 mg/kg/day for bromate in 2001 (USEPA, 2001b) based on a NOAEL of 1.5 mg/kg/day for potassium bromate (equivalent to 1.1 mg/kg/day bromate) for renal effects (DeAngelo et al., 1998) and the application of an uncertainty factor of 300. The RfD value did not change in the Stage 2 D/DBPR due to the lack of significant new health effects data for systemic effects and EPA did not revise the MCLG at that time (USEPA 2003c, 2006a).

New Information Available Since Development of Stage 2 D/DBPR

Cancer

NTP conducted non-standard, shorter-term bioassays with two different transgenic mouse strains, in which sodium bromate was administered in drinking water for 27 and 43 weeks (NTP, 2007b). These mouse strains, Tg.AC hemizygous (gain of oncogene function (*Ha ras*)) and p53 haploinsufficient (loss of heterogeneity in a critical cancer gene (TrP53)) have been reported to detect both nongenotoxic and genotoxic carcinogens and are susceptible to the rapid development of cancer. Sodium bromate did not cause cancer in Tg.AC hemizygous or p53 haploinsufficient mice exposed to 80, 400 and 800 mg/L. NTP concluded that since sodium bromate did cause cancer in other studies with different rodents, these transgenic mouse models are not a sensitive means of evaluating the carcinogenicity of sodium bromate. Nonneoplastic changes were observed in the thyroid and kidney for the Tg.AC mice.

Other

California Environmental Protection Agency (Cal EPA) (2009) set a Public Health Goal (PHG) of 0.1 ppb for bromate based on the *de minimus* cancer risk level calculated from the DeAngelo et al. (1998) study. A NOAEL of 1.1 mg/kg/day and a LOAEL of 6.1 mg/kg/day based on renal urothelial hyperplasia were identified. The NOAEL was used as the point-of-departure for Cal EPA's PHG. For noncancer effects, Cal EPA calculated an RfD of 0.004 mg/kg/day (identical to EPA's RfD), based on kidney effects from the DeAngelo et al. (1998) study. WHO (2005a) accepted the finding of carcinogenicity for bromate and established a Practical Quantification Level of 10 μg/L based on analytical and technical feasibility limitations.

Mode of Action

Although bromate has been shown to be carcinogenic in animals with species differences in sensitivity (rat>mouse>hamster), bromate has not been found to cause cancer in humans. Possible modes of action for bromate-induced cancer, include thiol-associated (e.g., GSH-

related) oxidative damage to guanine in DNA plus the potential for accumulation of $\alpha_{2\mu}$-globulin in male rat kidneys. These topics and others were addressed during a MOA workshop funded by the American Water Works Association (AWWA) Research Foundation (Bull and Cotruvo, 2006). The workshop participants concluded that there was a "clear path for conducting studies relevant to human health risks and laid out a potential research plan for filling data gaps." The research plan included examination of the presystemic toxicokinetics of bromate at doses representative of exposures through drinking water and studies to identify key events supportive of a nonlinear MOA. Two possible genotoxic effects that might result from carcinogenic doses of bromate in male rats were identified as formation of 8-hydroxyguanine DNA adducts (oxidative damage) and production of micronuclei. Both of these effects can be non-linear with respect to dose. Between 2006 and the present, a number of studies based on elements identified in the workshop research plan have been conducted with results published in the peer reviewed literature as described below.

Dodd et al. (2013) conducted study of male F344 rats exposed to potassium bromate in drinking water at concentrations of 5 to 400 mg/L with observation periods of 2 and 13 weeks. After sacrifice the kidneys, liver, lung, thyroid and tunis vaginalis were examined histologically; liver kidney and thyroids weights were determined. Blood samples were analyzed for aspartate transaminase, alanine transaminase (ALT), blood udea nitrogen, lactic dehydrogenase and creatinine. The NOAEL was 6.2 mg/kg/day with a LOAEL of 12.6 mg/kg/day for bromate ion. At the LOAEL there was a slight increase in kidney weight and hyaline droplets in the kidney tubules. No effects were seen in the other organs. The hyaline droplets were present at 2 and 13 weeks.

The presence of hyaline droplets in the Dodd et al. (2013) study suggests the accumulation of $\alpha_{2\mu}$-globulin in kidneys. Renal accumulation of $\alpha_{2\mu}$-globulin in kidneys is unique to male rats and contributes to their carcinogenic response (Umemura and Kurokawa, 2006). This response is not observed in humans or in female rats. However, bromate is associated with kidney tumors in female rats, thus other MOAs are likely to be involved in the tumor response. It is possible that the cell proliferation observed in female rats could result from oxidative stress and/or cytotoxicity. The correlation between formation of 8-oxodG and tumor response in female rats suggests that dose-response information from the female rat is more relevant to human risk assessment and that oxidative stress is the likely mechanism for cancer risk in humans.

The contribution of oxidative stress to bromate-induced cancer in male F344 rats was evaluated in a drinking water study for exposure ranging from 2 to 100 weeks (Delker et al., 2006). Gene expression analyses were performed on kidney, thyroid and mesothelial cell RNA since chronic exposures to bromate have been shown to cause renal cell tumors in rats, hamsters and mice and testicular mesothelial tumors in rats. The Delker et al. (2006) results suggest that the dose of bromate must reach a threshold before tissue oxidation occurs and that gene expression profiles may be predictive of these changes in the kidney.

Yamaguchi et al. (2008) conducted a 16-week study of potassium bromate in drinking water in cancer prone Big Blue male rats using drinking water with concentrations of 0.02 to 500 ppb (doses of 0.001 to 0.044 mg/kg/day). The NOAEL for the formation of 8-oxodG was 0.007 mg/kg/day and the LOAEL was 0.044 mg/kg/day. The LOAEL dose was accompanied by a significant ($p<0.05$) increase in the GC:TA transversions associated with 8-oxodG nucleotides,

inflammatory cell infiltration, tubular regeneration and histological hyaline degeneration ($p<0.01$). The LOAEL for hyaline degeneration was lower than that for 8-oxodG (0.002 mg/kg/day ($p<0.05$). The authors concluded that there could be a no effect level for bromate mutagenicity to support a nonlinear approach for the cancer assessment, at least as it applied to the kidney tumors. Group sizes in the Yamaguchi et al. (2008) study were five males/dose and histological examinations were only conducted on the kidney. Thus, this study by itself is not sufficient to demonstrate nonlinearity for the bromate-induced tumors that occur in both males and females

Although bromate has been shown to induce genetic damage *in vitro* and to induce mutations in the kidney of exposed rats, it is not clear whether bromate is a mutagenic carcinogen. The evidence suggests that bromate's mutagenic activity is mediated by the formation of oxidative damage to the DNA, resulting in chromosomal damage (Moore and Chen, 2006). Zhang et al. (2011) conducted an *in vitro* study of cytotoxicity and cellular damage using cultures of human and rat kidney cells in combination with assays for cell proliferation, cell morphology, cytotoxicity and generation of ROS using a variety of techniques. The results indicated that bromate can induce DNA damage, cell necrosis and cell cycle arrest. The ROS damage appeared to be independent of or downstream of the DNA damage. DNA adduct formation was accompanied by GSH depletion with the later a possible stimulus for the formation of ROS.

Bromate at concentrations in water of up to 308 mg/L was found to cause bromination of protein tyrosines in the proteins that accumulate in the male kidney and may contribute to kidney tumors in male rats (Koilsetty et al., 2013). The presence of $\alpha 2_{\mu}$ globulin in urine is a characteristic of male rats but not female rats. Other tissue changes including apoptosis, levels of protein expression and production of 8-oxodG were identified in the kidneys of both sexes. Based on their data the authors proposed that a failure to suppress cellular apoptosis could contribute to the mechanism for bromate-induced kidney cancer in males and females.

Relevance for SYR

The EPA IRIS assessment established the RfD of 0.004 mg/kg/day for bromate in 2001 (USEPA, 2001b), which did not change in the Stage 2 D/DBPR due to the lack of significant new health effects data for systemic effects. There has been considerable published research on bromate subsequent to the EPA IRIS assessment. New data on the toxicokinetics of bromate (Bull et al., 2012) demonstrating extensive *in vivo* reduction to bromide and possible mechanisms associated with injury to the kidneys, thyroid and testes (Bull and Cotruvo, 2013; Koilsetty et al., 2013) provide important data to supplement the EPA IRIS MOA assessment (USEPA, 2001b). However, the new data, at present, are not robust enough to alter the finding that bromate is a likely carcinogen with a mode of action that cannot be fully determined. EPA concludes at this time that since data are not available to conclusively demonstrate nonlinearity for the MOA for all three observed tumors sites observed in the animal studies, there is insufficient basis for supporting a change in the MCLG of zero.

4.2.2 Chlorite

Basis for the MCLG

In the Stage 1 D/DBPR, EPA (USEPA, 1994a) proposed an MCLG for chlorite of 0.08 mg/L based on neurodevelopmental effects in a rat study (Mobley et al., 1990; USEPA, 1994a). Subsequent to the proposal, EPA (USEPA, 1997b) reviewed and completed a peer review of a two-generation reproductive study of chlorite in Sprague-Dawley rats (CMA, 1996). In this study, male and female rats were administered sodium chlorite in drinking water at doses ranging up to 300mg/L. Reproduction, fertility, clinical signs and histopathology were evaluated in two-generations of offspring. In the Stage 1 D/DBPR, EPA finalized an MCLG of 0.8 mg/L for chlorite based on the RfD (0.03 mg/kg/day, an adult tap water consumption of 2 liters/day for a 70 kg adult and an assumed drinking water contribution of 80 percent of total exposure (USEPA, 1998b). The RfD of 0.03 mg/kg/day was derived based on a NOAEL of 35 ppm (3 mg/kg/day for the chlorite ion) for decreases in absolute brain and liver weight and lowered auditory startle amplitude at 70 and 300 ppm and the application of an uncertainty factor of 100. Although the RfD differed from that derived from Mobley et al. (1990) of 0.003 mg/kg/day the use of a lower uncertainty factor in the assessment based on the CMA study yielded the same MCLG (USEPA, 1994a, 2000b). EPA did not revise the MCLG for chlorite in the Stage 2 D/DBPR (USEPA, 2003c, 2006a).

New Information Available Since Development of Stage 2 D/DBPR

Righi et al. (2012) conducted a case-control study in Northern Italy to investigate the relationship between drinking water exposure to chlorite, chlorate and THMs and congenital anomalies. A total of 1,917 cases of congenital anomalies (neural tube, cardiac, diaphragm and abdominal wall, esophagus (food pipe or gullet), cleft lip and palate, respiratory, urinary tract and chromosomal anomalies) observed in the period of 2002 to 2005 were studied. The THM exposure levels were reported to be very low (mean 3.8 $\pm$ 3.6 µg/L), and no excess risk of anomalies were associated with THM exposures. The levels of chlorite (mean 427 $\pm$ 184 µg/L) and chlorate (mean 283 $\pm$ 79 µg/L), however, were relatively high. The authors reported that women exposed to chlorite at levels > 700 µg/L were at higher risk of having newborns with renal defects (OR: 3.30; 95 percent CI = 1.35 – 8.09), abdominal wall defects (OR: 6.88; 95 percent CI = 1.67 – 28.33) and cleft palate (OR: 4.1; 95 percent CI = 0.98 – 16.8); women exposed to chlorate at levels >200 µg/l were at higher risk of newborns with obstructive urinary defects (OR: 2.88; 95 percent CI = 1.09 – 7.63), cleft palate (OR: 9.60; 95 percent CI = 1.04 – 88.9) and spina bifida (OR: 4.94; 95 percent CI = 1.10 – 22). The authors noted that this was the first study showing an excess risk of different congenital anomalies associated with chlorite and/or chlorate exposure from drinking water, and that further research using larger datasets was needed to confirm the observed results.

In an earlier population-based, case-control study from the same area, Aggazzotti et al. (2004) examined the association between chlorination byproducts and adverse pregnancy outcomes. The chlorination byproducts investigated in this study were chlorate and chlorite and total and individual THMs: chloroform, dichlorobromomethane, dibromochloromethane and bromoform. A total of 1,194 subjects were evaluated in the study, consisting of 343 pre-term (<37 weeks) births, 239 full-term SGA births (< 10^{th} percentile of birth weight according to standard values

from the Italian Society of Pediatrics) and 612 controls (born ≥37 weeks and > 10th percentile of birth weight). Exposure was assessed both by a questionnaire completed by the mothers on their personal habits during pregnancy and by water samples collected at the homes of the participants. The median concentrations of chlorate for pre-term births, full-term SGA births and controls were: 177.00, 250.00 and 216.50 µg/L, respectively. No association was found between pre-term births and exposure to chlorite or to any of the other chlorination byproducts studied. The authors found, however, that chlorite did show an association with term-SGA births suggesting a dose-response relationship. When chlorite levels were ≥ 200 µg/L and the frequency of bathing/showering was at least daily, they observed an OR of 1.70 (95 percent CI: 0.97 – 3.00) compared to a referent group with chlorite levels < 200 µg/L and a frequency of bathing/showering less than daily. The authors noted that in their study few women consumed tap water and they considered that the increased risk was from exposure via inhalation, noting that while chlorite is not considered volatile, there could be chlorite present in aerosols in shower vapors. They also noted that an alternative explanation could be that chlorite served as a proxy for other chlorination byproducts or as a proxy for residual chlorine dioxide used as the disinfectant (74% of the study population lived in areas where drinking water was treated with chlorine dioxide or a combination of chlorine and chlorine dioxide).

No other new information has been identified about cancer or noncancer effects. However, new information is available that may inform a different relative source contribution for chlorite than was used when EPA developed the MCLG for chlorite under the Stage 1 D/DBPR. If data show the contribution of chlorite from food or other sources than drinking water to be greater than previously thought, then the relative source contribution (RSC) from the drinking water component would decrease.

Data that support lowering the 80 percent RSC contribution from water would support lowering the MCLG of chlorite. Data show that there is more dietary exposure than previously assumed due to the increased use of chlorine dioxide and acidified sodium chlorite as disinfectants in the processing of foods (USEPA, 2006b; WHO, 2008.) Data to support the quantification of exposures as a result of antimicrobial uses are available in the Office of Prevention, Pesticides and Toxic Substances Reregistration Eligibility Decision (USEPA, 2006b) for chlorine dioxide and sodium chlorite and the WHO (2008) assessment of acidified sodium chlorite as a food additive. Additional data on chlorine dioxide sanitizer uses in the United States are included in submissions to the Food and Drug Administration (FDA) (1994). Chapter 6 provides information about co-occurrence of chlorine dioxide, chlorite and chlorate.

Data are also available which support possible common health endpoints from exposures to chlorate, chlorite and chlorine dioxide. Animal studies indicate that these compounds all result in hematological and thyroid effects (Orme et al., 1985; Abdel-Rahman et al., 1984; Couri et al., 1982; Moore and Calabrese, 1982; Bercz et al., 1982; Abdel-Rahman, 1980). Although there are different etiologies for some of the hematological effects, the outcomes of reduced hemoglobin, hematocrit and low red blood cell counts are the same. Less is known about the modes of action for the thyroid effects but there is likely to be synergy when two or more of the members of the group are present in the same matrix (e.g., food or drinking water). Limited findings in humans support concern for exposure to mixtures for the hematological effects and impact on the kidney during development (Lubbers et al., 1981, 1982, 1984). The high probability for co-exposures is an important factor in considering these chemicals as a group.

Relevance for SYR

New information on the relative source contribution of exposure from chorite in drinking water and on the co-occurrence of chlorite and chlorate, along with common health endpoints of concern, indicate a meaningful opportunity for potential risk reduction for chlorite.

4.3 Regulated Disinfectants

This section addresses the health effects that are associated with the regulated disinfectants for which Maximum Residual Disinfectant Levels (MRDLs) and Maximum Residual Disinfectant Level Goals (MRDLGs) have been established under the Stage 1 and Stage 2 D/DBPRs, specifically chlorine, chloramines and chlorine dioxide.

4.3.1 Chlorine

Basis for the MRDLG

In the Stage 1 D/DBPR, EPA finalized an MRDLG of 4 mg/L for chlorine based on a weight of evidence evaluation of both the cancer and noncancer effects and classified chlorine as "not classifiable as to human carcinogenicity" (USEPA, 1994a, 1998b; NTP 1992a). The MRDLG was based on the RfD of 0.1 mg/kg/day, an adult tap water consumption of 2 liters/day for a 70 kg adult and an assumed drinking water contribution of 80 percent of total exposure (USEPA, 1994a). The RfD was based on a NOAEL of 14 mg/kg/day for no treatment-related effects from NTP (1992a), a two-year drinking water study in rats and mice, with the application of an uncertainty factor of 100. Due to a lack of significant new health effects data available for the Stage 2 D/DBPR, the RfD value did not change, and EPA did not revise the MRDLG for chlorine at that time (USEPA, 2003c, 2006a).

New Information Since Stage 1 and Stage 2 D/DBPRs

No new, relevant information about cancer or noncancer effects has been identified for chlorine.

Relevance for SYR

Insufficient evidence is available to support a change in the MRDLG for chlorine.

4.3.2 Chloramines

Basis for the MRDLG

In the Stage 1 D/DBPR, EPA established a MRDLG of 4 mg/L for chloramine (USEPA, 1994a, 1998b, NTP 1992a) based on a weight of evidence evaluation of both the cancer and noncancer effects and classified chloramines as "not classifiable as to human carcinogenicity." EPA has not set an RfD for chloramines. The MRDLG was based on a NOAEL of 9.5 mg/kg/day for no treatment-related effects for monochloramine from a two-year drinking water study in rats and mice (NTP, 1990), an uncertainty factor of 100, adult tap water consumption of 2 liters/day for a 70 kg adult and an assumed drinking water contribution of 80 percent of total exposure (USEPA,

1994a). Due to the lack of significant new health effects data available for the Stage 2 D/DBPR, EPA did not revise the MRDLG for chloramines at that time (USEPA, 2003c, 2006a).

New Information Since Stage 1 and Stage 2 D/DBPRs

No new information about cancer or noncancer effects has been identified that would change the basis for the existing MRDLG. Since promulgation of the Stage 1 D/DBPR, EPA has developed an EPA website (http://www.epa.gov/dwreginfo/basic-information-about-chloramines-and-drinking-water-disinfection) that provides basic information about chloramines and chloramine-related research and answers questions which address issues raised by the public related to exposure to chloramines.

Relevance for SYR

Insufficient evidence is available to support a change in the MRDLG for chloramines. New information is available about various DBPs of potential health concern, such as nitrosamines, that may be formed in systems that use chloramination. Additional information about the formation of nitrosamines in systems that use chloramines is provided in the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d).

4.3.3 Chlorine Dioxide

Basis for the MRDLG

In the Stage 1 D/DBPR, USEPA (1994a) proposed a MRDLG of 0.3 mg/L for chlorine dioxide based on an RfD of 0.01 mg/kg/day from a developmental rat study (Orme et al., 1985). EPA (1997a) reviewed and completed a peer review of a two-generation reproductive study of chlorite in Sprague-Dawley rats (CMA, 1996). In this study, male and female rats were administered sodium chlorite in drinking water at doses ranging up to 300 ppm. Reproduction, fertility, clinical signs and histopathology were evaluated in 2-generations of offspring. These data are relevant to chlorine dioxide because chlorine dioxide is rapidly reduced to chlorite and chlorite is oxidized to chlorate. In the Stage 1 D/DBPR, EPA finalized an MRDLG of 0.8 mg/L for chlorine dioxide based on the same data used to derive the MCLG for chlorite (USEPA, 1998b); the RfD of 0.03 mg/kg/day, an adult tap water consumption of 2 liters/day for a 70 kg adult and an assumed drinking water contribution of 80 percent of total exposure. The RfD was derived based on a NOAEL of 35 ppm (3 mg/kg/day for the chlorite ion) for decreases in absolute brain and liver weight and lowered auditory startle amplitude at 70 and 300 ppm and the application of an uncertainty factor of 100. In the Stage 1 D/DBPR, the final MRDLG was not changed from the proposed value because a lower uncertainty factor (100 vs. 300) was applied with the use of the multigeneration CMA (1996) study. EPA did not revise the MRDLG for chlorine dioxide in the Stage 2 D/DBPR (USEPA, 2003c, 2006a).

New Information Since Stage 1 and Stage D/DBPRs

No new information has been identified about cancer or noncancer effects for chlorine dioxide.

Please refer to section 4.2.2 on chlorite for a discussion about possible common health endpoints from exposures to chlorate, chlorite and chlorine dioxide. The short half-life for chlorine dioxide mitigates the concern from its increased use by the food industry and for other applications.

Relevance for SYR

Information about possible common health endpoints from exposures to chlorate, chlorite and chlorine dioxide indicate meaningful opportunity for potential risk reduction for chlorine dioxide.

4.4 Unregulated DBPs

This section provides health effects information on several organic and inorganic DBPs that are not currently regulated in the Stage 1 or Stage 2 D/DBPRs. There are many DBPs (e.g., brominated HAAs, haloacetonitriles, nitrosamines, MX and chlorate) that are unregulated. The unregulated term can be misleading in that exposures may be reduced through treatment because of actions taken to comply with the MCL and TT requirements of the D/DBPRs.

Health effects information in this section is based on data in assessments conducted by EPA and other agencies (e.g., ATSDR, Cal EPA, NTP and WHO) plus published articles that were not considered under the evaluations conducted for the Stage 2 D/DBPR. Chemicals are grouped by chemical families in the sections that follow.

4.4.1 Chlorate

Information on the health effects of chlorate is presented in Chapter 3 of *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e).

4.4.2 Nitrosamines

Information on the health effects of nitrosamines is presented in Chapter 3 of *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d).

4.4.3 Haloacetic Acids

Unregulated HAAs include bromochloracetic acid (BCAA), bromodichloroacetic acid (BDCAA), dibromoacetic acid (DBAA), dibromochloroacetic acid (DBCAA), tribromoacetic acid (TBAA) and iodinated acetic acid compounds. The USEPA (2005e) Criteria Document for Brominated Acetic Acids includes monitoring data for monobromoacetic acid (MBAA) and DBAA collected during the ICR monitoring for the Stage 2 rule demonstrating occurrence in public drinking water supplies. The Criteria Document did not develop RfDs for any of the brominated HAAs. The data for the cancer endpoint justified a classification of "*inadequate information to assess carcinogenic potential*" at that time. Subsequent to the publication of the criteria document the NTP published the findings from bioassays of BCAA, BDCAA and DBAA. DBAA is currently regulated as part of HAA5 but lacks an MCLG.

Plewa et al. (2002) developed an *in vitro* model using Chinese hamster ovary (CHO) cells for determining a relative ranking of cytotoxic potency for a direct comparison to DBP-induced

cytotoxicity in *S. typhimurium*, analyzing DBPs for their ability to induce genomic DNA damage in mammalian cells, and determining a relative rank order of their genotoxic potency and comparing these results with data derived from *Salmonella* mutagenesis studies.

Using the Plewa et al. (2002) model, Plewa et al. (2010) provided a comparative systematic analysis of chronic cytotoxicity and acute genomic DNA damaging capacity of 12 individual HAAs in mammalian cells. In addition to the HAA5, they analyzed MIAA, diiodoacetic acid (DIAA), bromoiodoacetic acid (BIAA), TBAA, DBCAA, BDCAA and BCAA. They identified a rank order of chronic cytotoxicity was MIAA > MBAA > TBAA > DBCAA > DIAA > DBAA > BDCAA > BCAA > MCAA > BIAA > TCAA > DCAA. The rank order for genotoxicity was MIAA > MBAA > MCAA > DBAA > DIAA > TBAA > BCAA > BIAA > DBCAA. They found that DCAA, TCAA and BDCAA were not genotoxic. The trend for both cytotoxicity and genotoxicity is iodinated HAAs > brominated HAAs > chlorinated HAAs (Plewa et al., 2010).

The cytotoxicity for haloacids was low compared to other classes of DBPs based on results using the CHO cell model. Using this model, the rank order from most cytotoxic to least cytotoxic for the DBP classes was haloacetaldehydes (HALs) > haloacetamides > HNMs > haloacetonitriles > 2C-haloacids > HAAs > halomethanes. Similarly, when looking at induced genomic DNA damage in CHO cells, the relative genotoxicity of haloacids was low compared to other classes of DBPs. Again, using this model, the rank order from the most genotoxic to the least genotoxic of the DBP classes showed that haloacetonitriles > haloacetamides > HNMs > HALs > HAAs > >2C-haloacids > halomethanes (Plewa and Wagner, 2009).

Additional information about specific compounds are described below.

4.4.3.1 Bromochloroacetic acid

Cancer

The NTP (2009) completed a toxicological and carcinogenic assessment for BCAA subsequent to the Stage 2 Rule as part of their research agenda on water disinfectants and disinfection byproducts. BCAA was administered to F344/N rats and B6C3F1 mice in drinking water at daily doses up to 40 and 50 mg/kg/day in male and female rats, respectively, and 90 and 60 mg/kg/day in male and female mice, respectively in a two-year study (NTP, 2009). NTP concluded that there is clear evidence of carcinogenic activity in rats based on an increased incidence of malignant mesotheliomas in males, multiple fibroadenomas of the mammary gland in females and adenomas of the large intestine in males and females. There was also clear evidence of carcinogenic activity in mice based on increased incidences of hepatocellular neoplasms in male and female mice and hepatoblastoma in male mice. The lowest dose in rats that demonstrated an increased incidence of malignant mesotheliomas and pancreatic islet adenoma compared to controls was 20 mg/kg/day. The lowest dose in the mouse study with an increase in tumors compared to controls was 15 mg/kg/day for hepatoblastomas.

Reproductive and Developmental

NTP (2009) conducted a study in male and female Sprague-Dawley rats administered BCAA in drinking water for various times during a 35-day period. The number of live fetuses per litter and the total number of implants per litter were significantly decreased at the highest dose of 50

mg/kg/day. The NOAEL was 50 mg/kg/day based on decreased implants and number of live fetuses per litter.

Tully at al. (2005) evaluated reproductive performance in juvenile and adult C57BL/6 male mice administered BCAA for 14 days in a continuous breeding assay. Juvenile mice were exposed from PND 8 to 21, allowed to mature and then mated. Effects on fertility were observed in mice exposed as adults and included decreases in mean number of litters per male, percentage of litters per female bred and total number of fetuses per male. The decreased male fertility was attributed to disruption of spermatid differentiation.

Systemic toxicity

The NTP (2009) reported the results from a subchronic study in both male and female rats and male and female mice. In male and female rats there were effects on liver weight and kidney weight. The NOAEL for the effects on liver weight was 20 mg/kg/day with a LOAEL of 40 mg/kg/day in both males and females. Kidney weights were increased at a higher dose. In male mice there was a LOAEL of 8 mg/kg/day for cell proliferation in the spleen and no NOAEL for this effect. In females the 8 mg/kg/day was a NOAEL with a LOAEL of 17 mg/kg/day for this effect. At higher doses effects on liver weight and body weight, plus liver periportal hepatic cellular vacuolization, were noted.

Genotoxicity

Richardson et al. (2007) reported that BCAA had little or no toxicology data and lacked genotoxicity data. The NTP (2009) reported that BCAA was positive for mutagenicity in *S. typhimuriam* strain 100 with and without activation but not in strain 98. No micronuclei were found in the erythrocytes from male and female mice exposed to bromochloroactic acid for 3 months (NTP, 2009).

4.4.3.2 Bromodichloroacetic acid

Cancer

NTP (2015) conducted a 2-year bioassay of BDCAA in treated F344/NTac rats and B6C3F1 mice. BDCAA administration in drinking water to rats resulted in increased incidences of malignant mesothelioma and combined incidences of epithelial tumors of the skin in males, increased incidences of fibroadenoma and carcinoma of the mammary gland in females, along with adenoma or carcinoma of the Harderian gland in males and hepatocellular adenoma in females.

In mice there was an increased incidence of hepatocellular carcinoma and hepatoblastoma in males and females (NTP, 2015). The lowest dose to induce tumors at levels above controls in female rats was 13 mg/kg/day for mammary gland fibroadenoma. In male rats, the lowest dose to observe increased incidence of keratoaceanthoma, basal cell ademona or carcinoma, squamous cell carcinoma (SCC) and other carcinogenic endpoints was 43 mg/kg/day. The lowest dose with evidence of carcinogenicity in male and female mice was 23 mg/kg/day based on an increased incidence of hepatocellular adenoma. The NTP (2015) concluded that there was clear evidence of carcinogenicity in male and female rats and mice.

Systemic toxicity

In the subchronic component of the NTP (2015) studies of bromodichloracetic acid, the high dose of 72 mg/kg/day was a LOAEL for decreased testes weights and sperm motility in male rats while in females a dose of 69 mg/kg/day (also the high dose) was a LOAEL for increased kidney weight. The NOAELs for male and female rats were 37 and 43 mg/kg/day respectively. In male mice the NOAEL was 30 mg/kg/day with a LOAEL of 59 mg/kg/day for increased liver weight. In female mice there was a marginal LOAEL of 129 mg/kg/day for hepatic glycogen depletion with a NOAEL of 70 mg/kg/day in the NTP subchronic study.

Genotoxicity

Studies of genotoxicity showed that the responses were positive for *S. typhimurium* strains TA97, TA98 and TA100 in the absence of S9 and equivocal in the presence of rat S9. For *E. coli* strain WP2 *uvrA*/pkM101 the results were positive in the presence and absence of S9. No significant increases in the frequencies of micronucleated normochromatic erythrocytes or the percent of polychromatic erythrocytes (reticulocytes) were seen in blood samples from treated mice (NTP, 2015).

4.4.3.3 Dibromochloroacetic acid

NTP (2000) performed a short-term reproductive and developmental toxicity study with dibromochloroacetic acid administered in drinking water to rats. For the first part of the study, no significant test-article related effects were observed at doses ranging from 30-500 ppm. There was no estimated conversion to mg/kg/day so no NOAEL was set.

4.4.3.4 Tribromoacetic acid

Reproductive and Developmental

NTP conducted a short-term study on the reproductive and developmental effects of TBAA (NTP, 1998b). Doses up to 400 ppm were administered in drinking water to male and female rats (peri-conception and gestational exposure) for two weeks. No reproductive effects were observed in males or females and evaluation of the newborn heart and brain did not reveal any treatment-related effects. However, not data from a study that used a standard one or two generation protocal. Thus, additional research is needed.

The International Programme on Chemical Safety (IPCS) reviewed studies on TBAA toxicity in the Environmental Health Criteria 216 (WHO 2000). The only information provided was from a mutagenicity study showing positive results for Ames and SOS chromotest assays.

4.4.3.5 Iodinated acids

Iodinated acids identified in drinking water in the United States include MIAAand BIAA. Several longer-chain iodinated acids were also identified as present in treated drinking water: (*Z*)- and (*E*)-3-bromo-3-iodopropenoic acid and (*E*)-2-iodo-3-methylbutenedioic acid (Plewa et al., 2004a; Richardson et al., 2008).

Cytotoxicity and Genotoxicity

MIAA is the most cytotoxic and genotoxic HAA in mammalian cell assays that has been reported in the literature. Similar results are seen when comparing MIAA mutagenicity in *S. typhimurium* and genotoxicity in CHO cells compared to MBAA and MCAA (Plewa et al., 2004a; Richardson et al., 2008; Plewa et al., 2010).

Wei et al. (2013) examined cytotoxicity, genotoxicity and ability to transform NIH3T3 cells to tumorigenic lines and found that prolonged exposure of NIH3T3 cells to MIAA increased the frequencies of transformed cells with anchorage-independent growth and agglutination with concanavalin A. They found that neither MIAA (nor iodoform) increased micronucleus frequency, but that MIAA-transformed cells formed aggressive fibrosarcomas after inoculation into Balb/c nude mice. They concluded that MIAA has a biological activity that is consistent with a carcinogen and that human exposure should be of concern.

Reproductive and Development

MIAA has been shown to induce neural tube closure defects and other developmental abnormalities in mouse embryos (Hunter and Tugman, 1995; Hunter et al., 1996). According to Plewa and Wagner (2009), the ability to induce neural tube defects in an *ex vivo* mouse embryo assay is strongly correlated with CHO cell chronic cytotoxicity and has good correlation with CHO genotoxicity. No genotoxicity data were identified for the iodinated propenoic and butenedioic acids.

4.4.4 Iodinated THMs

Iodinated THMs identified in drinking water in the United States include iodoform, bromodiiodomethane, dichloroiodomethane, bromochloroiodomethane, dibromoiodomethane and chlorodiiodomethane (Plewa et al., 2004a; Richardson et al., 2008).

Cytotoxicity and Genotoxicity

Richardson et al. (2008) found the iodinated THMs to be much less cytotoxic than the iodinated acids, with the exception of iodoform. Iodoform was found to be mutagenic in bacteria but did not induce chromosome aberrations in Syrian hamster embryo cells *in vitro* (Richardson et al., 2007).

Of the iodinated THMs studied by Richardson et al. (2008), only chlorodiiodomethane was found to be genotoxic. Richardson et al. (2008) noted that BrTHMs require glutathione-S-transferase-theta1 (GSTT1) mediated metabolism to form mutagenic intermediates, and it is not known whether this is expressed in the CHO cells used in the Richardson et al. (2008) experiment with the iodinated acetic acids.

4.4.5 Haloketones

As described by Krasner et al. (2006), EPA selected the following haloketones as priority DBPs for a nationwide occurrence study: chloropropanone, 1,3-dichloropropanone, 1,1-dibromopropanone, 1,1,3-trichloropropanone, 1-bromo-1,1-dichloropropanone, 1,1,3,3-

tetrachloropropanone, 1,1,1,3-tetrachloropropanone, 1,1,1,3,3-pentachloropropanone and hexachloropropanone. In this study, 1,1,3,3-pentachloropropanone and hexachloropropanone were not analyzed because they are not stable in water. While 1,1,3,3-tetrabromopropanone was not initially prioritized, it was identified in drinking water after the initial prioritization and was included in the monitoring study report due to its similarity to the other priority compounds. Several haloketone species were identified in drinking water, with the priority haloketone 1-bromo-1,1-dichloropropanone reaching a maximum concentration of 3 μg/L in a distribution sample from a plant using ozone-chlorine disinfection (Krasner et al., 2006).

Systemic effects

WHO (2003a) investigated the data for chlorinated acetones (propanones) and determined that the data on dose-response were limited. Single doses of 1,1-dichloroacetone revealed effects on the liver at 325 mg/kg and no toxicity was observed below 130 mg/kg (Laurie et al. 1986). No liver toxicity was observed for 1,3-dichloracetone at doses up to 20 mg/kg, but it was shown to potentially act as a tumor initiator in mouse skin. No guideline or regulatory value was derived by WHO (2003a).

4.4.6 Haloacetaldehydes

Chloroacetaldehyde (CAL), dichloroacetaldehyde (DCAL), bromochloroacetaldehyde (BCAL), trichloroacetaldehyde monohydrate (chloral hydrate) and tribromoacetaldehydes (TBAL) have been identified in disinfected drinking water (Richardson et al., 2007). HALs are the third largest group by weight of identified DBPs in drinking water. Jeong et al. (2015) provided a quantitative comparison of HAL toxicity in Chinese hamster ovary cells. The rank order of HAL cytotoxicity was found to be TBAL ≈ CAL > dibromoacetaldehyde (DBAL) ≈ BCAL ≈ dibromochloroacetaldehyde (DBCAL) > iodoacetaldehyde (IAL) > bromoacetaldehyde (BAL) ≈ bromodichloroacetaldehyde (BDCAL) > DCAL > trichloroacetaldehyde (TCAL). The HALs were found to be highly cytotoxic compared to other DBP chemical classes. Jeong et al. found that the rank order of HAL genotoxicity is DBAL > CAL ≈ DBCAL > TBAL ≈ BAL > BDCAL > BCAL ≈ DCAL > IAL. TCAL was not genotoxic (Jeong et al., 2015).

4.4.6.1 2-Chloroacetaldehyde

Cancer

2-Chloroacetaldehyde (2-CAA) was examined for carcinogenicity in rats by Daniel et al. (1992). B6C3F1 mice were exposed to 0.1 g/L of 2-CAA (17 mg/kg/day) in a cancer bioassay. There were significant increases for hepatic necrosis and hepatic tumors but not liver weights in the treated rats. Only one dose was evaluated for comparison with the controls.

Genotoxicity

CAL was mutagenic in bacteria and in mammalian cells *in vitro* but not in mice (Richardson et al., 2007).

4.4.6.2 Chloral hydrate (trichloroacetaldehyde monohydrate)

Cancer

USEPA (2000c) examined the toxicological effects of chloral hydrate and developed a reference dose of 0.1 mg/kg/day based protection for central nervous system depression and gastrointestinal irritation in humans. Chloral hydrate is used pharmacologically for sedation. The LOAEL used in the derivation of the RfD (10.7 mg/kg/day) is based on the clinical dose used in the sedation of adults. USEPA (2000c) considered chloral hydrate to be a weak mutagen and clastogen based on a NTP oral gavage study. The finding for cancer under the 1996/1999 proposed cancer guidelines was that the evidence for carcinogenicity is suggestive. No quantification for dose response was presented.

WHO (2005c) evaluated the carcinogenicity of trichloroacetaldehyde monohydrate (chloral hydrate) and concluded that it was not classifiable for cancer based on inadequate evidence in humans and limited evidence in animals. They derived a TDI of 0.0045/kg for systemic liver effects based on increased proliferative lesions in the liver of mice (Geroge et al., 2000) using a 1000-fold uncertainty factor with extra uncertainty factor of 3 for the limited evidence of carcinogenicity.

Genotoxicity

Chloral hydrate is a direct acting mutagen *in vitro* and it induced base-substitution mutations in bacteria, as well as aneuploidy and micronuclei in mammals in vivo and in mammalian cells *in vitro*. Chloral hydrate also induced chromosomal aberrations, gene mutations and cell transformations in mammalian cells *in vitro* (Richardson et al., 2007).

4.4.7 Halonitromethanes

As described by Plewa et al. (2004b), the following HNMs were identified by EPA as target analytes for occurrence and toxicology studies: bromonitromethane, dibromonitromethane, tribromonitromethane, bromochloronitromethane, dibromochloronitromethane, bromodichloronitromethane, chloronitromethane, dichloronitromethane and trichloronitromethane (chloropicrin).). In Section 4.4.3, EPA described the relative cytotoxicity and genotoxicity among classes of DBPs including HNMs.

Cancer

WHO (2003b) evaluated the carcinogenic studies of chloropicrin and determined that the high mortality in the National Cancer Instititue (NCI) (1978) bioassays and the limited endpoints examined did not support development of a guideline value for chloropicrin.

The California Department of Pesticide Regulation (Cal EPA, 2010) released a summary of toxicological studies with chloropicrin. Chloropicrin is used as a soil fumigant and most of the studies involve inhalation exposures. There are few studies of oral administration. The effects seen in a 10-day and a 90-day study in rats (Condie et al., 1994) included reduced body weights, changes in thymus, liver and spleen weights, changes in hematological and clinical chemistry values and histopathological lesions in the forestomach (nonglandular stomach). The NOEL in

the 90-day oral gavage study appeared to be 8 mg/kg/day based on body weight reduction, hematological changes and histological changes in the forestomach. There is a NCI cancer study from 1978 in rats that used the oral exposure route (gavage). There was high mortality early in the study that caused several adjustments to dosing. Mammary gland fibroadenomas as seen in surviving females demonstrated a dose-response trend but is confounded by the high mortality and dosing alterations during the study. In another study (gavage in corn oil) (Lauter at al., 1995) there was an increased incident of stomach papilloma in males and mammary fibroadenomas in females at doses above 10 mg/kg/day (Cal EPA, 2010). No tumors were observed at 1.0 mg/kg/day.

Cytotoxicity and Genotoxicity

The HNMs are weak mutagens in *S. typhimurium* TA100, were potent genotoxicants in mammalian cells and induced DNA damage in CHO cells. Dibromonitromethane is the most cytotoxic and mutagenic HNM tested in both S. typhimurium and CHO cells (Richardson et al., 2007). The HNMs are more cytotoxic than the corresponding HAAs. The brominated nitromethanes and the mixed bromo- and chloro- nitromethanes were more genotoxic than the chlorinated nitromethanes (Richardson et al., 2007).

Developmental and Reproductive

There are no oral exposure data on the developmental and reproductive effects of chlorpicrin according to the Cal EPA (2010) assessment.

4.4.8 Haloacetonitriles

Acetonitriles, including chloro-, bromochloro-, dibromo- and trichloro- acetonitrile, are the most commonly measured haloacetonitriles in drinking water in the United States (Richardson et al., 2007). Several other haloacetonitriles were also measured in a recent study, including bromo-, dibromo-, bromodichloro - and tribromoacetonitriles.). In Section 4.4.3, EPA described the relative cytotoxicity and genotoxicity among classes of DBPs including HANs.

WHO (2004c) developed TDIs for dichloroacetonitrile and dibromoacetonitrile (DBAN) using studies of systemic toxicity that did not use tricaprylin for the control. A Total Daily intake (TDI) of 2.7 µg/kg/day for dichloroacetonitrile was set based on a LOAEL of 8 mg/kg/day for increased relative liver weight in male and female rats in a 90-day study (Hayes et al. 1986). A TDI of 11 µg/kg/day for DBAN was set based on the NOAEL of 11.3 mg/kg/day for decreased body weight in male F344 rats in a 90-day drinking water study by NTP (2001a,b; 2002a,b).

Reproductive and Developmental

In studies summarized by WHO (2004c), dichloroacetonitrile, DBAN, bromochloroacetonitrile and trichloroacetonitrile were linked to reproductive and developmental effects in rats. However, many of these reproductive and developmental studies were conducted with tricaprylin as a vehicle for gavage, and tricaprylin has subsequently been demonstrated to be a developmental toxicant that potentiates the effects of trichloroacetonitrile (Christ et al., 1995) and, presumably, of other HANs. Therefore, WHO (2004c) concluded that the studies using tricaprylin likely overestimate the developmental toxicity of these HANs.

Cytotoxicity and Genotoxicity

The Ames assay for DBAN was positive in TA97 and TA1535 in the presence of S9. There were no increases in the frequencies of micronucleated erythrocytes in peripheral blood of male or female mice from the subchronic study. DBAN also did not induce sex-linked recessive lethal mutations in germ cells of male *D. melanogaster* exposed by feeding or by injection (NTP, 2010).

The brominated acetonitriles are generally not mutagenic in *Salmonella*, while the chlorinated acetonitriles are mutagenic, both with and without metabolic activation (Richardson et al., 2007). All of the haloacetonitriles tested induced DNA damage in mammalian cells. Plewa and Wagner (2009) provided a slightly different ranking for direct acting genotoxic activity for these chemicals, identifying chloroacetonitrile as the least genotoxic. As a class, the haloacetonitriles are highly reactive, causing DNA damage in mammalian cells *in vitro*, but not inducing mutations in bacteria (Richardson et al., 2007).

4.4.8.1 Dibromoacetonitrile

Cancer

The NTP (2010) conducted a two-year bioassay for DBAN dissolved in drinking water in male and female F344 rats plus male and female B6C3F1 mice. As a result of this study, the NTP concluded that there was clear evidence of carcinogenicity in male rats, male mice and female mice. Some evidence for carcinogencity was the finding for female rats. In the male rats at the high dose of 7 mg/kg/day there were two rare glandular stomach adenomas. The incidence of squamous epithelial hyperplasia of the tongue was significantly increased at a dose of 7 mg/kg/day in males while both males and females exhibited hyperkeratosis of the tongue at a dose of 4 mg/kg/day. Precancerous papilloma and keratoacanthoma of the skin displayed a positive trend across the 2, 4 and 8 mg/kg/day doses in females. Due to a low response, this finding was classified as equivocal for DBAN.

Tumors were also evident in the forestomach of male and female mice (squamous cell papilloma or carcinoma, combined). They were significantly increased as compared to controls at the high dose of 13 mg/kg/day in males and 11 mg/kg/day in females. In males, hyperplasia of the stomach tissues was present even at the low dose of 4 mg/kg/day. Male mice of the 4 and 7 mg/kg/day dose groups had hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined), theses finding were high in all dose groups and were classified as equivocal.

Water intake was less than that of the control for both the rats and mice suggesting possible taste aversion for the treated drinking water

Systemic

Given the carcinogenic responses in the rats and mice in the two year chronic study it is surprising that evidence for epithelial irritation and inflammation of the oral cavity, esophagus and forestomach was lacking in the subchronic study in both the rats and mice. The high doses of 13 and 11 mg/kg/day were NOAELs for the male and female mice, respectively. In the mice the subchronic NOAEL was 18 mg/kg/day for males and females (NTP, 2010).

Reproductive and Developmental

Meier et al. (1985) conducted a reproductive and developmental screening assay in young, male Sprague-Dawley rats administered DBAN in drinking water on study days 6–34. No reproductive effects or altered sperm morphology was observed. One group of female Sprague-Dawley rats was administered the same doses of dichloroacetonitrile (DCAN) in drinking water on study days 1–34, which included a 5-day cohabitation with the treated males (study days 13–17) and gestation. No effects on mating, fertility, pregnancy or development were observed. A second group of females was cohabitated with treated males and then exposed on GD 6 through PND 1 to the same doses of DCAN. The NOAEL for female reproductive effects and for developmental effects was the highest dose tested, 10.8 mg/kg/day. No treatment related effects were observed for maternal body weights, or for gross necropsy or number of resorptions or implantation sites.

4.4.8.2 Dichloroacetonitrile

Reproductive and Developmental

Meier et al. (1985) observed no effect on sperm head morphology in a study conducted in male B6C3F1 mice treated with DCAN by gavage.

Smith et al. (1986) conducted a developmental toxicity screening study with DCAN administered in a tricaprylin vehicle to pregnant Long-Evans rats on GDs 7–21. The percentage of females delivering litters was significantly reduced and fetal resorptions were increased. Fetal birth weights and postnatal pup survival were decreased. The LOAEL for developmental toxicity was 55 mg/kg/day, which was the only dose tested.

Smith et al. (1989a) administered DCAN to pregnant Long-Evans rats by gavage in a tricaprylin vehicle at GDs 6 through 18. Effects were noted at 25 mg/kg/day and greater, including increased post-implantation loss and fetal resorptions; an increase in the incidence of soft tissue malformations of the cardiovascular, digestive and urogenital systems; a decreased number of viable litters; and decreased fetal weight and length. The NOAEL for both maternal and developmental toxicity was 15 mg/kg/day based on increased liver weight in the dams and decreased fetal weight and length and an increase in soft tissue malformations, respectively.

4.4.8.3 Bromochloroacetonitrile

Reproductive and Developmental

Meier et al. (1985) observed no effect on sperm head morphology in a study conducted in male B6C3F1 mice treated with Bromochloroacetonitrile (BCAN) by gavage.

Smith et al. (1986) evaluated pups of Long-Evans rats administered BCAN on GD 7–21 in a tricaprylin vehicle and observed significantly reduced mean birth weights and reduced body weight gain.

Christ et al. (1995) administered BCAN to pregnant Long-Evans rats by gavage in a tricaprylin vehicle on GD 6–18. A decrease in fetal crown-rump length and an increase in fetal

cardiovascular malformations were observed in all dose groups; an increase in total soft tissue malformations was observed at 25 mg/kg/day and greater; an increase in full-litter resorptions, resorbed fetuses per litter and skeletal malformations and a decrease in the number of viable litters were observed at 45 mg/kg/day and greater. The maternal NOAEL and LOAEL were 45 and 65 mg/kg/day, respectively, based on decreased maternal weight and increased dam mortality. The LOAEL for developmental and teratogenic effects was 5 mg/kg/day, the lowest dose tested. It should be noted that the tricaprylin vehicle alone had significant embryotoxicity and teratogenicity effects when compared with the water vehicle.

4.4.8.4 Trichloroacetonitrile

Reproductive and Developmental

Meier et al. (1985) observed no effect on sperm head morphology in studies conducted in male B6C3F1 mice treated with TCAN by gavage.

Meier et al. (1985) administered TCAN by gavage in corn oil to pregnant Long-Evans rats on GDs 6–18. An additional group of rats was given TCAN in a tricaprylin vehicle. Effects noted in rats administered TCAN in corn oil included full-litter resorptions, decreased pregnancy rate, maternal weight gain and liver, spleen and kidney weights; increased post-implantation loss; decreases in live fetuses per litter, fetal body weight and fetal crown-rump length; and increases in fetuses per litter with skeletal and soft tissue malformations. The maternal and fetal NOAELs were 15 and 35 mg/kg/day, respectively. Fetal malformations were primarily external craniofacial malformations and positional cardiovascular malformations when corn oil was used as the vehicle and structural cardiovascular defects and urogenital effects when tricaprylin was used as the vehicle.

Smith et al. (1986) conducted a developmental screening study in pregnant Long-Evans rats administered TCAN in a tricaprylin vehicle on GDs 7–21. Effects noted included increased maternal deaths and full-litter resorptions, fewer females becoming pregnant or delivering viable litters and decreased pup survival and decreased weight gain in surviving pups. The only dose tested, 55 mg/kg/day, was a LOAEL for maternal and developmental toxicity.

Smith et al. (1988) administered TCAN to pregnant Long-Evans rats by gavage in a tricaprylin vehicle on GDs 6–18. The high dose of 55 mg/kg/day was lethal to 4 of 19 dams and caused 100 percent fetal resorption in 67 percent of surviving, pregnant dams. Increases in full-litter resorptions and cardiovascular malformations in litters were observed in a dose-related manner at doses of 7.5 mg/kg/day and greater. At 15 mg/kg/day and greater, post-implantation loss and urogenital malformations increased; and at 35 mg/kg/day and greater, fetal weight decreased. The NOAEL for teratogenic effects was the lowest dose tested, 1 mg/kg/day.

Christ (1996) administered TCAN to pregnant Long-Evans rats by gavage in corn oil on GDs 6–18 at doses up to 75 mg/kg/day. An additional group of rats was administered 15 mg/kg/day TCAN in tricaprylin on GDs 6–18. The following effects were noted from exposure to TCAN in corn oil: mortality; full litter resorptions; decreased pregnancy rate; depressed maternal weight gain; increased maternal liver, spleen and kidney weights; increased post-implantation loss; decreased number of live fetuses per litter; and increased number of fetuses with external,

skeletal and soft tissue malformations. Decreased fetal weights and increased soft tissue and cardiovascular malformations were observed in the rats exposed to TCAN in tricaprylin. The NOAEL for developmental toxicity and teratogenicity was 35 mg/kg/day and the LOAEL was 55 mg/kg/day when TCAN was administered in corn oil. The LOAEL was 15 mg/kg/day, the only dose tested, when tricaprylin was used as the vehicle.

4.4.9 Haloacetamides

Chloro-, bromo-, dichloro- trichloro-, bromo- and dibromoacetamide were identified as contaminants in drinking water in the United States (Richardson et al., 2007). The monitoring also detected bromochloro-, bromodichloro- and dibromochloroacetamide. A new iodinated DBP, bromoiodoacetamide, that was not detected at the time of the Richardson et al. (2007) publication was identified as present in disinfected water by Plewa and Wagner (2009). In Section 4.4.3, EPA described the relative cytotoxicity and genotoxicity among classes of DBPs including haloacetamides.

Plewa et al. (2008) provided a rank order of cytotoxicity for 13 haloacetamides (DIAcAm > IAcAm > BAcAm > TBAcAm > BIAcAm > DBCAcAm > CIAcAm > BDCAcAm > DBAcAm > BCAcAm > CAcAm > DCAcAm > TCAcAm). They also provided a rank order of their genotoxicity (TBAcAm > DIAcAm approximately equal to IAcAm > BAcAm > DBCAcAm > BIAcAm > BDCAcAm > CIAcAm > BCAcAm > DBAcAm > CAcAm > TCAcAm). DCAcAm was shown to be not genotoxic. Plewa et al. reported that cytotoxicity and genotoxicity followed the class order I > Br > > Cl, and that, with the exception of brominated trihaloacetamides, most of the toxicity rank order was consistent with structure-activity relationship expectations. (Plewa et al., 2008).

Reproductive and Developmental Toxicity

The European Commission's Scientific Committee on Consumer Safety (SCCS) reviewed the toxicity of chloroacetamide (SCCS, 2011). Though there were no guideline-compliant developmental or reproductive studies available, the review derived a LOAEL of 24 mg/kg/day based on maternal body weight reduction and skeletal findings in offspring when chloroacetamide was administered from GD 14 to PND 2. The NOAEL for this effect was 3 mg/kg/day. Christian (1991) examined a variety of developmental, reproductive and systemic toxicological endpoints of chloroacetamide. In a 13-week oral study in rats, chloroacetamide produced testicular atrophy at doses of 12.5 mg/kg/day and above. In a 90-day developmental toxicity study in rats, chloroacetamide did not induce any teratogenicity in doses up to 50 mg/kg/day.

Systemic toxicity

The SCCS (2011) review of chloroacetamide concluded that the human data demonstrated allergic reactions can be elicited at concentrations lower than 0.3 percent allowable amount in cosmetic products. The review also saw studies demonstrating that chloroacetamide causes GSH depletion and lipid peroxidation, resulting in cell damage and morphological changes in the liver.

Cytotoxicity and Genotoxicity

A study on the cytotoxicity and genotoxicity of haloacetamides in CHO cells ranked diiodoacetamide as the most cytotoxic and trichloroacetamide as the least cytotoxic (Plewa and Wagner, 2009). Tribromoacetamide was ranked as the most genotoxic and trichloroacetamide as the least. Dichloroacetamide was not found to be genotoxic.

4.4.10 Cyanogen halides

4.4.10.1 Cyanogen Bromide

USEPA (1988a) established a low confidence RfD of 0.09 mg/kg/day for cyanogen bromide based on a NOAEL for weight loss, thyroid effects and myelin loss in rats with than uncertainty factor of 100 and a modifying factor of 5 to account for the use a study of cyanide for the assessment. CNBr dissociates into cyanide in water. USEPA (2012a) examined cyanogen bromide (CNBr) under the program for peer reviewed provisional threshold values and chose not to establish an p-RfD for settings relevant to the Superfund Program due to the lack of pharmacokinetic, dissociation rates, issues linking CNBr to simple cyanides and lack of toxicological data specific to CNBr. The EPA (USEPA, 2012a) assessment calls attention to the current IRIS RfD for cyanide of 0.00063 mg/kg/day for decreased cauda epididymis weight in male #344/N rats (USEPA, 2010b) as a value that could be applicable in scenarios where dissociation of cyanogen bromide dissociation is expected.

4.4.10.2 Cyanogen Chloride

Cyanogen chloride toxicity was evaluated by WHO (2009). They determined that since it is unlikely to find cyanogen chloride in the water, due to rapid transformation to cyanide in water, it was unnecessary to develop a formal guideline. In place of a TDI for cyanogen chloride, they develop a TDI using cyanide toxicity data since it is shown that cyanogen chloride is not only transformed in water, but also rapidly metabolized to cyanide in the body. The TDI developed was 0.11 mg/kg/day based on cyanide toxicity information. The WHO health-based value for long-term exposure is 0.3 mg/l as cyanide or 0.6 mg/l as cyanogen chloride (rounded values).

The Office of Water (USEPA, 2005i) derived a 10-day health advisory value for cyanogen chloride of 0.1 mg/L base on a LOAEL of 14 mg/kg/day in a study of cyanide by Palmer and Olsen (1979), with the application of a 1000-fold uncertainty factor. As mentioned above, cyanogen chloride is transformed to cyanide in water with any residuals metabolized to cyanide when consumed. Free cyanide in water is currently regulated with a MCL/MCLG of 0.2 mg/L based on protection against nerve damage and thyroid problems (USEPA, 1992b). The recent IRIS assessment (USEPA, 2010b) updated the hydrogen cyanide and cyanide salts RfD to a value of 0.0006 mg/kg/day based on testicular effect in male rats (NTP, 1993). The new RfD supports a lowering of the cyanide MCLG to 0.004 mg/L assuming the application of the same water intake, body weight and RSC variables as those used when deriving the current MCLG/MCL.

4.4.11 Halogenated furanones

3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) has been identified in drinking water in the United States (Richardson et al., 2007). Other halogenated furanones that have been studied include bromine-, chlorine- and mixed halogen-substituted 4-methyl-2(5H)-furanones, including 3-chloro-4-(dibromomethyl)-5-hydroxy-2(5H)-furanone (BMX-2) and (Z)-2,3-dichloro-4-oxo-butenoic acid (mucochloric acid).

4.4.11.1 Mutagen X

Cancer

Mutagen X (MX) is a halogenated hydroxyfuranone that has been identified in chlorinated drinking water. A carcinogenicity study was conducted in Wistar rats administered MX in drinking water (Komulainen et al., 1997). Increased incidences of cholangioma (cancer of bile ducts cells) in the liver, follicular adenoma and carcinoma in the thyroid and cortical adenomas of the adrenal gland were observed in both sexes. The Office of Water (USEPA, 2000d) completed a quantitative assessment of the carcinogenicity of MX classifying it as acting through a mutagenic mode of action (USEPA, 2000d). The two-year oral exposure study by Komulainen et al. (1997) was selected for quantitative evaluation. Data for occurrence of thyroid (follicular adenoma and adenocarcinoma) and liver (adenoma, carcinoma, cholangioma and cholangiocarcinoma) tumors were evaluated resulting in an oral slope factor of 3.7 $(mg/kg/day)^{-1}$. Confidence in this quantification was rated as medium. Based on the slope factor the concentration associated with a 1 in 1,000,000 increased risk for cancer was 9.5 ng/L.

McDonald and Komulainen (2005) derived a combined cancer potency of MX for each gender based on the incidence of all tumors. The drinking water concentration associated with a 1 in 1,000,000 increased cancer risk was calculated to be 7.8 ng/L. IARC (2004) has classified MX as Group 2B, "*possibly carcinogenic to humans*."

Genotoxicity

MX is one of the most potent agents tested for mutagenicity in *S. typhimurium*, and the concentration of MX in drinking water accounts for as much as 50 percent of the total mutagenicity of these samples (Richardson et al., 2007). The addition of rat liver extract (S9 fraction) reduces its potency. It induced DNA damage, mutations and prophage induction in *E. coli*. MX is also a potent genotoxicant in mammalian cells. It induced unscheduled DNA synthesis, sister chromatid exchanges, micronuclei, chromosome aberrations, mutations and DNA strand breaks; however, it has been found to be negative for micronucleus induction in vivo in rodents.

Reproductive and Developmental

Huuskonen et al. (1997) administered MX to pregnant Han: Wistar rats by gavage on GDs 6–19. There were no increases in gross, visceral, or skeletal malformations or in mortality in the fetuses.

Teramoto et al. (1998) conducted an *in vitro* assay using 12-day-old rat embryo midbrain and limb bud cells to evaluate the teratogenic properties of MX. There was no or minimal effect in the presence of S9 fraction; a significant decrease in the number of differentiated foci in the Central Nervous System and limb bud cells was observed in the absence of S9 fraction. The *in vivo* significance is not known.

4.4.11.2 Other halogenated furanones

The Office of Water (USEPA, 2000d) completed a health assessment of chlorohydroxyfuranones (CHFs) in 2000 that summarized the available data at that time. Many of the CHF compounds have data that identify these compounds as genotoxins with differing relative potencies, however studies of their carcinogenic potency were lacking at that time.

Mucochloric acid toxicity was evaluated by OECD SIDS (2003) and a NOAEL for developmental toxicity of 60 mg/kg/day was observed with no LOAEL. Systemic toxicity was found at 30 mg/kg/day shown as reduced food consumption and bodyweight gain. Mucochloric acid is mutagenic in *S. typhimurium* and CHO cells and has induced DNA damage in *E. coli* cells injected into mice.

The brominated halofuranones are generally less mutagenic than MX except for BMX-2, which caused a 140 percent increase in mutagenicity in *S. typhimurium* compared to MX (Richardson et al., 2007).

4.4.12 Halogenated benzoquinones (HBQs) and haloquinones (HQ)

Cancer

The halogenated benzoquinones (HBQs), may be important bladder carcinogens in chlorinated drinking water. They have been confirmed as DBPs in drinking water and may have toxicological significance according to Bull et al. (2006).

IARC (1999a) evaluated haloquinones (HQ) as Group 3: not classifiable as to its carcinogenicity to humans, based on inadequate evidence in humans and limited evidence in animals. HQ produced benign tumors in the kidneys of male F344 rats dosed by gavage or in the diet. In the gavage study, the tumors appeared to be the end-stage of chronic progressive nephropathy. A nongenotoxic mode of action has been proposed based on exacerbation of spontaneously occurring renal disease in male rats, for which there is no known relevance in humans.

4.4.13 Halogenated pyrroles

2,3,5-Tribromopyrrole was identified in drinking water in the United States (Richardson et al., 2007). No toxicological information was identified for 2,3,5-Tribromopyrrole, bromopyrrole, dibromopyrrole, chloropyrrole, dichloropyrrole or tricholorpyrrole.

Cytotoxicity and Genotoxicity

2,3,5-Tribromopyrrole is both highly genotoxic and highly cytotoxic in CHO cells (Richardson et al., 2007).

4.4.14 Aldehydes

Aldehydes identified in drinking water include formaldehyde, acetaldehyde (Richardson et al., 2007), glyoxal and methylglyoxal (USEPA, 2004). Both formaldehyde and acetaldehyde are on the EPA fourth contaminant Candidate List (CCL4).

4.4.14.1 Formaldehyde

Cancer

USEPA (1990a) evaluated the carcinogenic potential of formaldehyde and categorized it as "*probable human carcinogen"* based inhalation exposures in animals. WHO (2005b) also classified formaldehyde in group 2A, "*probably carcinogenic to humans"* following inhalation exposures. Several other agencies have examined the toxicity of formaldehyde. The California Department of Pesticide Regulation (Cal DPR; 1997) compiled a summary of studies deemed acceptable or unacceptable for formaldehyde toxicity and established a 2 ppm concentration from Kerns et al. (1983) as the lowest value with an effect for nasal epithelial toxicity. USEPA (1990) used this same inhalation study to quantify the slope factor for nasal SCC for carcinogenicity (USEPA, 1988b).

Genotoxicity

The genotoxicity of formaldehyde has been reported in numerous studies (Richardson et al., 2007). It induced gene mutation in bacteria, mammalian cells and rat nasal epithelium *in vivo*. It was mutagenic *in vitro* in the presence of S9. It induced SCEs in mammalian cells and micronuclei and chromosomal aberrations in mammalian cells and in rodents. It induced DNA damage in bacteria and mammalian cells and DNA-protein cross-links *in vitro* and in rodents and humans. It has also induced gene mutations in mouse lymphoma cells which contained large deletions and recombinant events.

Systemic Toxicity

USEPA (1990a) generated an RfD for formaldehyde of 0.2 mg/kg/day based on reduced weight gain a gastrointestinal histopathology in rats. The animals were exposed to concentrations of 2 to 82 mg/l in drinking water for two years. Only the high dose had an effect. Many other agencies have reported the various toxicological endpoints of formaldehyde (ATSDR, 1999; Health Canada, 1997; WHO, 2002; WHO, 2005b). WHO and Health Canada used the same data as EPA to derive their respective TDIs (0.35 mg/L Health Canada; 2.6 mg/L WHO).

4.4.14.2 Acetaldehyde

Although there is considerable toxicological information for acetaldehyde, the only risk values determined are from inhalation exposures (USEPA, 1988b; Health Canada, 1997). The USEPA (2004a) Office of Water Criteria Document did not establish RfDs for methylglyoxal and glyoxal because of dose response limitations the studies that provided dose-response information.

Cancer

Inhaled acetaldehyde causes tumors in the nose and trachea of hamsters and nasal cancers in rats (USEPA, 1988b). In human it is considered a cocarcinogen with ethanol in the development of upper digestive track cancers in alcoholics (Seitz and Stickel, 2007) especially for individuals with certain acetaldehyde dehydogenase genotypes.

IARC (1999b) determined that acetaldehyde is "*possibly carcinogenic to humans"* (Group 2B) because there is *inadequate evidence* in humans for the carcinogenicity of acetaldehyde and *sufficient evidence* in experimental animals. The strongest evidence for its's carcinogenicity in humans comes from high alcohol consumers. A lifetime study of female and male rats given drinking water containing acetaldehyde at concentrations of 0, 50, 250, 500, 1500 or 2500 mg/L demonstrates an increase in total malignant tumors in various organs and tissues (Soffritti et al., 2002).

Genotoxicity

The genotoxicity has been reported in numerous studies (Richardson et al., 2007). It was not mutagenic in bacteria. It caused gene mutations, SCEs, micronuclei and chromosomal aberrations in mammalian cells and SCEs and protein-DNA binding cross-links in rodents.

Systemic toxicity

The studies of oral exposure to acetaldehyde and few. A two-year study by Til et al. (1988) identified irritation and changes in the GI tract after doses of ≥82 mg/kg/day in rats.

4.4.14.3 Glyoxal and Methylglyoxal

Cancer

USEPA (2004a) categorized the carcinogenic potential of both chemicals as cannot be determined due to lack of human epidemiological studies and acceptable long-term animal studies.

Genotoxicity

Glyoxal is mutagenic in the Ames assay with many strains of *Salmonella typhimurium* and has been shown to cause base-pair substitutions and some frameshift mutations at G:C base pairs. Methylglyoxal is mutagenic in bacterial systems and weakly clastogenic in rats, causing increased micronuclei in liver and bone marrow (USEPA, 2004a).

Systemic toxicity

Both glyoxal and methyl glyoxal are associated with the formation of advanced glycosylation end products in humans and animals as a result of crosslinking their potential to act as cross-linking agents consequence of reacting with proteins or lipids (USEPA, 2004a). Normally this occurs when these compounds are generated endogenously in individuals with diabetes, atherscloersis, Alzheimer's disease and kidney failure.

4.5 Unregulated DBPs Data Availability Summary

Exhibit 4.2 shows the unregulated DBPs identified in drinking water systems that have quantitative toxicity assessments which can be used in the assessment of risk in cases where concentration information is available from public water systems (PWSs). The chemicals with assessments that include RfDs or equivalents (e.g., TDI values), estimates of cancer risk concentrations or drinking water guidelines include the following: chloral hydrate, cyanogen chloride (based on cyanide), DBAN, dichloroacetonitrile, nitrosamines, formaldehyde and chlorate.

Exhibit 4.2: Available Quantitative Assessments for Unregulated DBPs Discussed in this Document

DBPs	Chemical	Reference value	Type	Biological Effect	Citation
Aldehydes	Formaldehyde	0.2 mg/kg/day	RfD	GI tract histopath.	USEPA, 1990a
		0.35 mg/L	TDI		Health Canada, 1997
		2.6 mg/L	TDI		WHO, 2005b
Chlorate	Chlorate	0.03 mg/kg/day	RfD	Increased thyroid gland follicular cell hypertrophy	USEPA, 2006b
Cyanogen halides	Cyanogen chloride	0.11 mg/kg/day	TDI	Value developed based on cyanide toxicity	WHO, 2009
		0.0006 mg/kg/day	RfD (CN^{1-})	decreased cauda epididymis weight	USEPA, 2010b
Haloacetoaldehydes	Trichloroacetaldehyde monohydrate (chloral hydrate)	0.1 mg/kg/day	RfD	Liver toxicity	USEPA, 2000c
		16 µg/kg/day	TDI	Liver toxicity	WHO, 2005c Health Canada, 2008c
Haloacetonitriles	Dichloroacetonitrile	0.002.7 mg/kg/day	TDI	Increased relative liver weight in male and female rats	WHO 2004
	Dibromoacetonitrile	0.011 mg/kg/day	TDI	Decreased body weight in male rats	WHO, 2004
Nitrosamines	NDBA	0.03 µg/L	E-6 conc.	Cancer	USEPA, 2016d
	NDEA	0.0004 µg/L	E-6 conc.		
	NDMA	0.0006 µg/L	E-6 conc.		
	NDPA	0.007 µg/L	E-6 conc.		
	NMEA	0.003 µg/L	E-6 conc.		
	NPYR	0.002 µg/L	E-6 conc.		

In addition to the quantitative toxicity assessment information provided in Exhibit 4.2, EPA notes the following information that has become available since the time of the Stage 2 D/DBPR and discussed previously in this chapter. Toxicology data (subchronic, chronic) on some of the brominated HAAs and DBAN have become available as a result of research conducted by the NTP. These data may be used to support a quantitative evaluation of their carcinogenic effects and possible identification of an RfD. The NTP bioassays for BCAA, BDCAA, DBAA and DBAN are peer reviewed and published. The draft risk assessment for the halogenated furanones (MX) requires completion and peer review.

Many of the other unregulated DBPs lack studies with dose-response to support an evaluation of their potential to cause adverse health effects in humans. In many cases, the available data only provide information on cytotoxicity and genotoxicity. These include the iodinated acetic acids, iodinated trihalomethanes, HNMs, haloacetamides, halogenated benzoquinnones and halogenated pyrazoles. Additional information is needed to more fully evaluate the health effects of these chemicals.

5 Analytical Methods

This chapter summarizes information relevant to analytical methods for regulated and unregulated DBPs. It provides a brief synopsis of the analytical methods developed by EPA and others, covering methods for treatment technique (TT) requirements for removal of DBP precursors, methods for DBPs and methods for disinfectant residuals.

For the Disinfectants and Disinfection Byproducts Rules (D/DBPR), there are no contaminants for which the MCL/MRDL is limited by analytical feasibility. This chapter presents the analytical methods that are currently available for D/DBPs and summarizes their performance in cases where performance data are readily available.

Exhibit 5.1 summarizes the analytical methods developed by EPA and other method developers (e.g., Standard Methods (SM), American Society of Testing and Materials (ASTM) International, U.S. Geological Survey (USGS)) approved as part of the Stage 1 D/DBPR (USEPA, 1998b) and Stage 2 D/DBPR (USEPA, 2006a), as well as those methods (referred to as alternate testing methods) that have been approved via EPA's Expedited Method Approval process[3] since Stage 2 D/DBPR promulgation. The alternate testing methods are listed in the Code of Federal Regulations (CFR), in Appendix A to Subpart C of 40 CFR § 141.[4]

Exhibit 5.1: Analytical Methods Approved in the Stage 1 and Stage 2 D/DBPRs and via the Expedited Method Approval Process[1]

Analyte	Approved in Stage 1 or Stage 2 D/DBPR[2]	EPA-Developed Methods	Other Methods	Additional Methods Approved via Expedited Approval Since Stage 2 D/DBPR
Water Quality Parameters				
Alkalinity	Stage 1	None	SM 2320 B (18^{th}-19^{th} ed.); SM online 2320 B-97 ASTM D1067-92 B USGS I-1030-85	ASTM D1067-06 B ASTM D1067-11 B SM 2320 B (21^{st}-22^{nd} ed.)
	Stage 2	None	SM 2320 B (20^{th} ed.) ASTM D1067-02 B	
Bromide	Stage 1	300.0, Rev. 2.1; 300.1	None	None
	Stage 2	317.0, Rev. 2.0; 326.0	ASTM D 6581-00	

[3] The Safe Drinking Water Act provides for the approval of "equally effective alternate test methods. The drinking water Alternate Test Procedure program evaluates alternate test methods to verify that they are equally effective in terms of method performance to approved methods in the regulations. The Expedited Method Approval process formalizes method approvals through publication of a Federal Register notice. This process allows EPA to announce the approval of alternate methods to laboratories and Public Water Systems in a more timely manner than traditional rulemaking: http://water.epa.gov/scitech/drinkingwater/labcert/analyticalmethods_expedited.cfm

[4] http://www.ecfr.gov/cgi-bin/text-idx?SID=1ab89b8c14cb76ecd23585c6c2130ea2&node=pt40.23.141&rgn=div5#_top

Analyte	Approved in Stage 1 or Stage 2 D/DBPR[2]	EPA-Developed Methods	Other Methods	Additional Methods Approved via Expedited Approval Since Stage 2 D/DBPR
Total Organic Carbon (TOC)	Stage 1	None	SM 5310 B (19th ed.) SM 5310 C (19th ed.) SM 5310 D (19th ed.)	EPA 415.3, Rev. 1.2; SM 5310 B (21st-22nd ed.); SM 5310 C (21st-22nd ed.); SM 5310 D (21st-22nd ed.)
	Stage 2	415.3, Rev. 1.1	SM 5310 B (20th ed.); SM 5310 C (20th ed.); SM 5310 D (20th ed.); SM online 5310 B-00; SM online 5310 C-00; SM online 5310 D-00	
Dissolved Organic Carbon (DOC)	Stage 1	None	SM 5310 B (19th ed.); SM 5310 C (19thed.); SM 5310 D (19thed.)	EPA 415.3, Rev. 1.2; SM 5310 B (21st-22nd ed.); SM 5310 C (21st-22nd ed.); SM 5310 D (21st-22nd ed.)
	Stage 2	415.3, Rev. 1.1	SM 5310 B (20th ed.); SM 5310 C (20th ed.); SM 5310 D (20th ed.); SM online 5310 B-00; SM online 5310 C-00; SM online 5310 D-00	
UV_{254} and Specific Ultraviolet Light Absorbance (SUVA)[3]	Stage 1	None	SM 5910 B (19th ed.) (UV_{254})	EPA 415.3, Rev. 1.2; SM online 5910 B-11 (UV_{254}); SM 5910 B (21st-22nd ed.) (UV_{254})
	Stage 2	415.3, Rev. 1.1	SM 5910 B (20th ed.); SM online 5910 B-00 (UV_{254})	
Regulated DBPs				
Trihalomethanes (THM)	Stage 1	502.2, Rev. 2.1; 524.2, Rev. 4.1; 551.1	None	EPA 524.3; EPA 524.4
Haloacetic Acids (HAA5 – MCAA, DCAA, TCAA, MBAA, DBAA[4])	Stage 1	552.1; 552.2	SM 6251 B (formerly SM 6233 B) (19thed.)	EPA 557; SM 6251 B (21st-22nd ed.); SM online 6251 B-07
	Stage 2	552.3	SM 6251 B (20th ed.); SM online 6251 B-94	
Chlorite	Stage 1	300.0, Rev. 2.1 (monthly or daily); 300.1 (monthly or daily)	SM 4500-ClO_2 E (19thed.; daily only)	SM 4500-ClO_2 E (21st-22nd ed., daily only); ASTM D 6581-08 A; ASTM D 6581-08 B; ChlordioX Plus (daily only)
	Stage 2	317.0, Rev. 2.0 (monthly or daily); 326.0 (monthly or daily); 327.0, Rev. 1.1 (daily only)	SM 4500-ClO_2 E (20th ed., daily only); SM online 4500-ClO_2 E-00 (daily only); ASTM D 6581-00	

Analyte	Approved in Stage 1 or Stage 2 D/DBPR[2]	EPA-Developed Methods	Other Methods	Additional Methods Approved via Expedited Approval Since Stage 2 D/DBPR
Bromate	Stage 1	300.1	None	EPA 302.0; EPA 557 ASTM D 6581-08 A; ASTM D 6581-08 B
	Stage 2	321.8; 317.0, Rev. 2.0; 326.0	ASTM D 6581-00	
Disinfectant Residuals				
Chloramines	N/A	N/A	N/A	N/A
Chlorine (free, combined, total)	Stage 1	None	SM 4500-Cl D (19th ed.); SM 4500-Cl F (19th ed.); SM 4500-Cl G (19th ed.); ASTM D1253-86	ASTM D1253-08; SM 4500-Cl D (21st-22nd ed.); SM 4500-Cl F (21st – 22nd ed.); SM 4500-Cl G (21st-22nd ed.); Hach Method 10260
	Stage 2	None	SM 4500-Cl D (20th ed.); SM 4500-Cl F (20th ed.); SM 4500-Cl G (20th ed.); SM online 4500-Cl D-00; SM online 4500-Cl F-00; SM online 4500-Cl G-00; ASTM D1253-86(96); ASTM D1253-03	
Chlorine (total) in addition to those listed above for free, combined, total	Stage 1	None	SM 4500-Cl E (19th ed.); SM 4500-Cl I (19th ed.)	EPA 334.0; ChloroSense; SM 4500-Cl E (21st-22nd ed.); SM 4500-Cl I (21st-22nd ed.)
	Stage 2	None	SM 4500-Cl E (20th ed.); SM 4500-Cl I (20th ed.); SM online 4500-Cl E-00; SM online 4500-Cl I-00	
Chlorine (free) in addition to those listed above for free, combined, total	Stage 1	None	SM 4500-Cl H (19th ed.)	EPA 334.0; ChloroSense; SM 4500-Cl H (21st-22nd ed.); Method D99-003 (if approved by state)
	Stage 2	None	SM 4500-Cl H (20th ed.); SM online 4500-Cl H-00	
Chlorine Dioxide	Stage 1	None	SM 4500-ClO_2 D (19th ed.); SM 4500-ClO_2 E (19th ed.)	4500-ClO_2 E (21st-22nd ed.) ChlordioX Plus
	Stage 2	327.0, Rev. 1.1	SM 4500-ClO_2 D (20th ed.); SM 4500-ClO_2 E (20th ed.); SM online 4500-ClO_2 E-00	

EPA Methods Cited:
EPA Method 300.0, Rev. 2.1 (USEPA, 1993b)
EPA Method 300.1 (USEPA, 1997c)
EPA Method 302.0 (USEPA, 2009a)
EPA Method 317.0, Rev. 2.0 (USEPA, 2001c)
EPA Method 321.8 (USEPA, 1997d)
EPA Method 326.0 (USEPA, 2002)
EPA Method 327.0, Rev. 1.1 (USEPA, 2005j)
EPA Method 334.0 (USEPA, 2009b)
EPA Method 415.3, Rev. 1.1 (USEPA, 2005k)
EPA Method 415.3, Rev. 1.2 (USEPA, 2009c)
EPA Method 502.2, Rev. 2.1 (USEPA, 1995a)
EPA Method 524.2, Rev. 4.1 (USEPA, 1995b)
EPA Method 524.3 (USEPA, 2009d)
EPA Method 524.4 (USEPA, 2013)
EPA Method 551.1 (USEPA, 1995c)
EPA Method 552.1 (USEPA, 1992c)
EPA Method 552.2 (USEPA, 1995d)
EPA Method 552.3 (USEPA, 2003e)
EPA Method 557 (USEPA, 2009e)

[1] EPA's Expedited Method Approval Process was implemented in 2007, subsequent to the publication of the Final Stage 2 D/DBPR in 2006, and includes those analytical methods that may provide opportunities for improved performance and/or increased method sensitivity relative to the analytical methods approved in Stage 1 or Stage 2: http://water.epa.gov/scitech/drinkingwater/labcert/analyticalmethods_expedited.cfm
[2] Any analytical method approved under the Stage 1 D/DBPR was also approved for use under Stage 2. Specifically, 40 CFR §141.131(a)(1) of the Stage 2 D/DBPR states that the analytical methods specified for compliance monitoring are effective February 16, 1999, which is the effective date of the Stage 1 D/DBPR. The Stage 2 D/DBPR also includes additional methods that are specified for compliance monitoring.
[3] SUVA = UV_{254} / DOC
[4] MCAA = monochloroacetic acid; DCAA = dichloroacetic acid; TCAA = trichloroacetic acid; MBAA = monobromoacetic acid; DBAA = dibromoacetic acid

Exhibit 5.2 summarizes the analytical methods developed by EPA and approved via expedited approval or other EPA rulemaking for the unregulated DBPs.

Exhibit 5.2: Analytical Methods for Unregulated DBPs Approved via the Expedited Method Approval Process or Other EPA Rulemaking

Analyte	EPA-Developed Methods	Other Methods	Additional Methods Approved via Expedited Approval or Other EPA Rulemaking[1]
HAAs (BCAA, BDCAA, DBCAA, TBAA[2])	EPA 552.2	N/A	EPA 552.3; EPA 557
Nitrosamines	N/A	N/A	EPA 521
Chlorate	N/A	N/A	EPA 300.0, Rev. 2.1; EPA 300.1; EPA 317.0, Rev. 2.0; EPA 326.0; SM 4110 D (21st ed.); ASTM D 6581-00; ASTM D 6581-08

EPA Methods Cited:
EPA Method 300.0, Rev. 2.1 (USEPA, 1993b)
EPA Method 300.1 (USEPA, 1997c)
EPA Method 317.0, Rev. 2.0 (USEPA, 2001c)
EPA Method 326.0 (USEPA, 2002)
EPA Method 521 (USEPA, 2004b)
EPA Method 557 (USEPA, 2009e)
EPA Method 552.2 (USEPA, 1995d)
EPA Method 552.3 (USEPA, 2003e)

[1] For the unregulated DBPs, methods that are approved for compliance monitoring of related regulated analytes, or methods that have been specified for analytes listed in EPA's Unregulated Contaminant Monitoring Rule (UCMR), or other recently-developed methods are listed.
[2] BCAA = bromochloroacetic acid; BDCAA = bromodichloroacetic acid; DBCAA = dibromochloroacetic acid; TBAA = tribromoacetic acid. The regulated HAA5 plus these four unregulated HAAs = HAA9.

The following discussion defines method performance metrics for the DBPs and disinfectant residuals listed in Exhibit 5.1 and Exhibit 5.2. These metrics are presented in subsequent sections of Chapter 5 for new methods approved since the Stage 2 D/DBPR was published in January 2006. This allows a comparison of method performance for those methods approved under the Stage 1 or Stage 2 D/DBPRs and those methods approved via the Expedited Method Approval process since the final Stage 2 D/DBPR was published. These metrics include the following:

Method detection limit (MDL) and detection limit (DL) –The MDL is defined as "the minimum concentration of a substance that can be reported with 99 percent confidence that the analyte concentration is greater than zero."[5] The steps for determining the MDL are outlined in 40 CFR § 136, Appendix B. Over time, drinking water compliance methods have migrated away from requiring MDL determinations in favor of confirming minimum reporting levels (see discussion

[5] 40 CFR § 136 Appendix B: http://www.gpo.gov/fdsys/granule/CFR-2011-title40-vol23/CFR-2011-title40-vol23-part136-appB/content-detail.html

below). Various regulatory bodies, however, still require determination of detection limits. As a result, most of the newer drinking water analytical methods incorporate a detection limit (DL) determination that is defined and conducted exactly like the MDL (e.g., EPA Method 524.3). The MDLs and DLs are shown in Exhibit 5.3 through Exhibit 5.9.

The lowest concentration minimum reporting level (LCMRL) – the LCMRL is defined as the lowest spiking concentration such that the probability of spike recovery in the 50 to 150 percent range is at least 99 percent (USEPA, 2010c). The LCMRL appears in recently developed analytical methods from EPA and serves as a laboratory- and analyte-specific reporting level. Different analysts using different equipment in different laboratories will not necessarily be able to achieve LCMRLs that are published in EPA analytical methods; however, EPA's published LCMRLs are an indication that low analyte concentrations can be reliably reported. The LCMRL has been used in EPA's second and third Unregulated Contaminant Monitoring Rules (UCMR 2 and UCMR 3). With the exception of the LCMRL for chlorate, the LCMRLs summarized in Section 5.2 are listed in the analytical methods represented in Exhibit 5.3 through Exhibit 5.9. The LCMRLs for chlorate were developed internally by EPA during UCMR 3.

The minimum reporting level (MRL) – the MRL has evolved over time in EPA programs. In the preamble to the proposed Stage 2 D/DBPR,[6] MRLs were initially established for DBPs as part of the 1996 Information Collection Rule. These MRLs were also proposed in the proposed Stage 2 D/DBPR and were established in the final Stage 2 D/DBPR.[7] The MRLs were not determined through a formal, statistical procedure; rather, they were based on recommendations from experts with experience in the analysis of DBPs. The MRLs were established at concentrations at which most laboratories could meet the precision and accuracy criteria of the analytical methods designated for the analysis of DBPs in drinking water. These "consensus" MRLs were developed for the trihalomethanes (THMs), the five regulated haloacetic acids (HAA5), chlorite and bromate.

At about the same time the Stage 2 D/DBPR proposal was moving forward, EPA began exploring development of a statistical procedure for determining laboratory- and analyte-specific LCMRLs. In conjunction with the LCMRL, a statistically derived MRL procedure was also developed. This MRL is determined using raw LCMRL study data and represents an estimate of the lowest concentration of a contaminant that can be reliably measured by members of a group of experienced drinking water laboratories (USEPA, 2007a). For six nitrosamines (*N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodi-n-propylamine (NDPA), *N*-nitrosodi-n-butylamine (NDBA), *N*-nitrosomethylethylamine (NMEA) and *N*-nitrosopyrrolidine (NPYR)), the MRL served as a national reporting level for laboratories that participated in the analysis of drinking water samples under UCMR 2 using EPA Method 521. For chlorate, the MRL served as a national reporting level for laboratories that participated in the

[6] 68 FR 49548, National Primary Drinking Water Regulations: Stage 2 Disinfectants and Disinfection Byproducts Rule; National Primary and Secondary Drinking Water Regulations: Approval of Analytical Methods for Chemical Contaminants, Proposed Rule, August 2003. Available on the Internet at: http://www.gpo.gov/fdsys/pkg/FR-2003-08-18/pdf/03-18149.pdf

[7] 71 FR 388, National Primary Drinking Water Regulations: Stage 2 Disinfectants and Disinfection Byproducts Rule; Final Rule, January 2006. Available in the Internet at: http://www.gpo.gov/fdsys/pkg/FR-2006-01-04/pdf/06-3.pdf

analysis of drinking water samples under UCMR 3 using EPA Method 300.1, ASTM D6581-08, or SM 4110D (21st ed.). For DBPs, MRLs that are statistically derived from LCMRL study data are currently only available for the six nitrosamines and chlorate.

Percent recovery range and percent relative standard deviation (RSD) – the percent recovery range demonstrates the overall accuracy of the methods for each analyte, and the percent RSDs demonstrate the overall precision of the methods for each analyte. The data are summarized for precision and accuracy studies documented in each analytical method, but the data do not include holding time study nor MDL study recovery percentages or percent RSDs, since holding time studies are less about method performance than about analyte stability and since MDL studies are typically conducted at concentrations well below those used in precision and accuracy studies. The precision and accuracy studies are typically performed in reagent water and/or finished drinking water from either ground water or surface water sources. In some cases, challenging environmental matrices are simulated by fortifying reagent water with additives such as humic acids, or other organic or inorganic additives.

The following sections illustrate the complexity and variety in the sources of analytical methods that were approved as part of the Stage 1 and/or Stage 2 D/DBPRs and those methods that have subsequently been approved via EPA's Expedited Method Approval process.

EPA also used the National Environmental Methods Index (NEMI) to search for performance metrics for methods not developed by EPA to provide some context for the data that might be available for these other methods (see Section 5.1.1 for examples). NEMI is a database of analytical methods and summary data for analytical methods and is run by the National Water Quality Monitoring Council in conjunction with EPA and USGS. NEMI can be searched by analytical method number.[8] The following sections compare analytical method performance for methods approved for the analysis of DBPs and disinfection residuals for EPA-developed analytical methods and SMs (APHA, AWWA and WEF, 2012) that contain performance data. Method performance data are shown in exhibits, where data for multiple EPA-developed analytical methods are available. Issues associated with analytical methods developed by organizations other than EPA are also discussed. The purpose of the comparison is to provide information on the performance of analytical methods that have been approved by EPA since the Stage 2 D/DBPR relative to those analytical methods that were approved in the Stage 1 or Stage 2 D/DBPR.

5.1 Methods for Treatment Technique Requirement for Removal of DBP Precursors

5.1.1 Alkalinity

For alkalinity, only non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs, and only non-EPA-developed analytical methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published.

[8] https://www.nemi.gov/home/

For the Stage 1 D/DBPR, SM 2320 B (18^{th}-19^{th} ed.), ASTM D1067-92 B and USGS I-1030-85 were approved for compliance monitoring. These same methods remained approved under the Stage 2 D/DBPR including the updated version of SM 2320 B in the 20^{th} edition of *Standard Methods for the Examination of Water and Wastewater* (APHA, AWWA and WEF, 1995) and ASTM D1067-02 B. Since publication of the Stage 2 D/DBPR in January 2006, alternate testing methods that have been approved for alkalinity via EPA's Expedited Method Approval process include ASTM D1067-06 B, ASTM D1067-11 B and SM 2320 B in the 21^{st} and 22^{nd} editions.

Although a record for ASTM D1067 is available in NEMI, there are no details regarding method performance, and the method is not available for downloading. USGS 1-1030-85 is included in NEMI. The only metrics available in NEMI for method performance are mean recovery, standard deviation and percent RSD for the analysis of a single sample by 21 different laboratories. A mean result of 26.0 mg/L as H^+ was reported, with a standard deviation of 0.9 mg/L as H^+ and a percent RSD of 3.5 percent.

A review of SM 2320 B indicates that the lowest concentration that can be determined is 20 mg $CaCO_3$/L. Lower concentrations must be determined using Part 4d of SM 2320 B. SM 2320 B is reported to be of low bias (APHA, AWWA and WEF, 2012);[9] however, percent recovery and percent RSD are not included in the method.

5.1.2 Bromide

For bromide both EPA-developed and non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs; however, no analytical methods have been approved via EPA's Expedited Method Approval process.

For the Stage 1 D/DBPR, EPA Methods 300.0 (Rev. 2.1) and 300.1 were approved for compliance monitoring. These same methods remained approved under the Stage 2 D/DBPR, and EPA Methods 317.0 (Rev. 2.0) and 326.0, as well as ASTM D 6581-00, were also approved for compliance monitoring under Stage 2. Since publication of the Stage 2 D/DBPR, no alternate testing methods have been approved for bromide via EPA's Expedited Method Approval process. Since no analytical methods have been approved for the monitoring of bromide since publication of the Stage 2 D/DBPR, no performance data for the bromide methods are presented.

5.1.3 Total Organic Carbon (TOC) and Dissolved Organic Carbon (DOC)

For TOC and DOC, both EPA-developed and non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs, and one EPA-developed method and updated non-EPA methods have been approved via EPA's Expedited Method Approval process.

[9] APHA, AWWA and WEF, 2012 refers to the 22nd edition of SM. In a discussion with Dr. Glynda Smith of EPA's Technical Support Center on March 19, 2015, she indicated that performance data do not change for SM methods from edition to edition. If the method changes to the extent that performance changes, this is considered a major modification and a new method number is assigned by SM. Thus, performance data from the 22nd edition are applicable to the 18th – 21st editions also.

Methods that have been approved for the monitoring of TOC are also approved for DOC; hence, they are combined into a single section here. For the Stage 1 D/DBPR, SM 5310 B (19th ed.), 5310 C (19th ed.) and 5310 D (19th ed.) were approved for compliance monitoring. These same methods remained approved in the Stage 2 D/DBPR, including the updated versions in the 20th edition of *Standard Methods for the Examination of Water and Wastewater*. EPA Method 415.3 (Rev. 1.1) and SM online 5310 B-00, 5310 C-00 and 5310 D-00 were also approved for compliance monitoring. Since publication of the Stage 2 D/DBPR, alternate testing methods approved via EPA's Expedited Method Approval process for TOC and DOC have included EPA Method 415.3 (Rev. 1.2) and SM 5310 B, SM 5310 C and SM 5310 D in the 21st and 22nd editions. SM (APHA, AWWA and WEF, 2012) reports recovery and percent RSD only for SM 5310 D in reagent water. EPA Methods 415.3 (Rev. 1.1) and 415.3 (Rev. 1.2) report percent recovery and percent RSD in fortified environmental waters, thus, no meaningful comparison of relative performance can be made. In addition, EPA Methods 415.3 (Rev. 1.1) and 415.3 (Rev. 1.2) report the same method performance data (DLs, percent recovery and percent RSD), thus, no comparison of relative performance of the two EPA-developed methods can be made.

5.1.4 UV254 and Specific Ultraviolet Light Absorbance (SUVA)

For UV_{254} and specific ultraviolet light absorbance (SUVA), both EPA-developed and non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs, and one EPA-developed method and updated non-EPA methods were approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published.

SUVA is not included in the Stage 1 D/DBPR; however, UV_{254} is included and SM 5910 B (19th ed.) was approved for compliance monitoring. SUVA was introduced in Stage 2 and is determined from UV_{254} and DOC (SUVA = UV_{254} / DOC). SM 5910 B remained approved through the Stage 2 D/DBPR, including the updated version in the 20th edition of *Standard Methods for the Examination of Water and Wastewater*. EPA Method 415.3 (Rev. 1.1) and SM online 5910 B-00 were also approved for compliance monitoring of UV_{254} and the determination of SUVA. Since publication of the Stage 2 D/DBPR, alternate testing methods for UV_{254} and SUVA that have been approved via EPA's Expedited Method Approval process include EPA 415.3 (Rev. 1.2), SM 5910 B in the 21st and 22nd editions and online SM 5910 B-11. SM (APHA, AWWA and WEF, 2012) reports multi-laboratory and single operator percent RSD only for SM 5910 B in reagent water. EPA Methods 415.3 (Rev. 1.1) and 415.3 (Rev. 1.2) report percent recovery and percent RSD in fortified environmental waters, thus, no meaningful comparison of relative performance can be made. EPA Methods 415.3 (Rev. 1.1) and 415.3 (Rev. 1.2) report the same quality control data for DLs, percent recovery and percent RSD, thus, no comparison of relative performance of the two EPA-developed methods can be made either.

5.2 Methods for Disinfection Byproducts

5.2.1 THM

For THMs, only EPA-developed methods were approved in the Stage 1 and Stage 2 D/DBPRs, and only EPA-developed methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published. Since EPA methods are available at no

cost online, the availability of the analytical methods for a comparison of performance metrics is not an issue.

For the Stage 1 D/DBPR, EPA Methods 502.2 (Rev. 2.1), 524.2 (Rev. 4.1) and 551.1 were approved for compliance monitoring. These same methods remained approved under the Stage 2 D/DBPR. Alternate testing methods for THMs approved via EPA's Expedited Method Approval process since Stage 2 include EPA Methods 524.3 and 524.4. Exhibit 5.3 summarizes the available detection limits, LCMRLs, percent recoveries and percent RSDs for the five EPA-developed analytical methods for the THMs. MRLs are from the final Stage 2 D/DBPR.

Exhibit 5.3: Method Performance Metrics for EPA Methods 502.2, 524.2, 524.3, 524.4 and 551.1 – THMs

Method/Analyte	DL/MDL (µg/L)	LCMRL (µg/L)	MRL (µg/L)	Mean % Recovery Range	% RSD Range	Fortifi-cation (µg/L)
502.2	(MDL)		Matrix:	Reagent water		
Bromodichloromethane	0.02-0.10	Not determined	1.0 for each analyte	96-97	2.6-2.9	10
Bromoform	0.09-1.6	Not determined		98-106	4.0-5.2	10
Chloroform	0.01-0.02	Not determined		92-98	2.5-4.2	10
Dibromochloromethane	0.05-0.3	Not determined		99-102	2.0-3.3	10
524.2	(MDL)		Matrix:	Reagent water		
Bromodichloromethane	0.03-0.08	Not determined	1.0 for each analyte	96-100	1.8-1.8	0.2, 2
Bromoform	0.12-0.20	Not determined		89-90	2.2-2.4	0.2, 2
Chloroform	0.02-0.03	Not determined		95-97	2.0-2.1	0.2, 2
Dibromochloromethane	0.05-0.07	Not determined		95-100	2.7-3.0	0.2, 2
524.3	(DL)		Matrices:	Reagent water, chlorinated ground water, chlorinated surface water		
Bromodichloromethane	0.014	0.073	1.0 for each analyte	92.8-102	1.2-8.7	0.5-10
Bromoform	0.040	0.15		78.1-92.6	2.2-8.1	0.5-10
Chloroform	0.025	0.054		80.9-99.4	1.7-8.3	0.5-10
Dibromochloromethane	0.027	0.14		86.1-97.7	1.2-7.9	0.5-10
524.4	(DL)		Matrices:	Reagent water, chlorinated ground water, chlorinated surface water		
Bromodichloromethane	0.011-0.081	0.027-0.19	1.0 for each analyte	87.3-104	1.5-8.5	0.5, 1, 10
Bromoform	0.008-0.14	0.021-0.26		80.6-103	2.4-6.8	0.5, 1, 10
Chloroform	0.015-0.070	0.032-0.16		86-103	1.7-6.1	0.5, 1, 10
Dibromochloromethane	0.006-0.10	0.016-0.23		90.7-102	1.3-5.2	0.5, 1, 10
551.1	(MDL)		Matrices:	Reagent water, fulvic acid enhanced reagent water, high hardness chlorinated ground water		
Bromodichloromethane	0.002-0.068	Not determined	1.0 for each analyte	87-110	1.02-4.07	0.25, 1, 5
Bromoform	0.004-0.020	Not determined		82-104	0.72-2.76	0.25, 1, 5
Chloroform	0.005-0.080	Not determined		92-105	1.20-3.68	0.25, 1, 5
Dibromochloromethane	0.001-0.018	Not determined		85-106	0.71-3.38	0.25, 1, 5

A review of the performance data in Exhibit 5.3 indicates that the more recently approved analytical methods (EPA Methods 524.3 and 524.4) are comparable to the methods that were approved under Stage 1 and Stage 2 in terms of sensitivity, recovery and RSD. All of the methods in Exhibit 5.3 meet the individual method requirements for percent recovery and percent RSD.

5.2.2 HAA5

For HAA5, both EPA-developed methods and non-EPA-developed methods were approved for monitoring during the Stage 1 and Stage 2 D/DBPRs, and both EPA-developed and updated non-EPA methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published. However, performance data are only readily available for the EPA-developed methods and SM 6251 B (22nd ed).

EPA Methods 552.1 and 552.2 were approved for Stage 1 analyses, and EPA Method 552.3 was added under Stage 2. Equivalent methods approved under the Stage 1 and/or Stage 2 D/DBPRs include SM 6251 B (formerly SM 6233 B) in the 19th and 20th editions of *Standard Methods for the Examination of Water and Wastewater* and SM online 6251 B-94. Since the final Stage 2 D/DBPR was published, EPA Method 557, SM 6251 B in the 21st and 22nd editions and SM online 6251 B-07 have been approved via the Expedited Method Approval process.

HAA5 consists of monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA) and dibromoacetic acid (DBAA). EPA Method 552.1 includes these five HAAs along with bromochloroacetic acid (BCAA), which is not regulated. SM 6233 B listed only the HAA5 analytes. When a standard for BCAA became available, SM 6233 B was re-designated SM 6251 B and BCAA was added to the method with the HAA5 analytes.[10] EPA Methods 552.2, 552.3 and 557 were published in 1995, 2003 and 2009, respectively, and include nine HAAs, the five regulated contaminants plus four additional unregulated brominated HAAs.

Exhibit 5.4 summarizes the DLs, LCMRLs, mean percent recovery values and percent RSDs for HAA5 as listed in EPA Methods 552.1, 552.2, 552.3 and 557, along with metrics for SM 6251 B. MRLs are from the final Stage 2 D/DBPR.

Exhibit 5.4: Method Performance Metrics for EPA Methods 552.1, 552.2, 552.3 and 557 and for SM 6251 B – HAA5

Method/ Analyte	DL/MDL (µg/L)	LCMRL (µg/L)	MRL (µg/L)	Mean % Recovery Range	% RSD Range	Fortifi-cation (µg/L)
552.1	(MDL)		Matrices:	Reagent water, dechlorinated tap water, high ionic strength water, high humic content ground water, ozonated river water		
MCAA	0.21	Not determined	2.0	46-109	1.0-15	7.5, 15

[10] 63 FR 69390. 1998. National Primary Drinking Water Regulations: Disinfectants and Disinfection Byproducts, Final Rule, December 16, 1998. Available on the Internet at: http://www.gpo.gov/fdsys/pkg/FR-1998-12-16/pdf/98-32887.pdf

Method/ Analyte	DL/MDL (µg/L)	LCMRL (µg/L)	MRL (µg/L)	Mean % Recovery Range	% RSD Range	Fortifi-cation (µg/L)
MBAA	0.24	Not determined	1.0	5-91	7.9-18	5, 10
DCAA	0.45	Not determined	1.0	59-114	0.1-14	7.5, 15
TCAA	0.07	Not determined	1.0	8-106	0.4-28	2.5, 5
DBAA	0.09	Not determined	1.0	40-103	0.7-22	2.5, 5
552.2	(MDL)		Matrices:	Reagent water, dechlorinated surface water, high ionic strength water, high humic content ground water		
MCAA	0.273	Not determined	2.0	84.3-97	2.8-13	1.5, 3, 6
MBAA	0.204	Not determined	1.0	86.0-109	1.5-11	1, 2, 4
DCAA	0.242	Not determined	1.0	84.7-115	2.5-11	1.5, 3, 6
TCAA	0.079	Not determined	1.0	61.8-93	6.3-15	0.5, 1, 2
DBAA	0.066	Not determined	1.0	71.5-112	2.8-9.2	0.5, 1, 2
552.3	(DL)		Matrices:	Reagent water, chlorinated surface water, chlorinated ground water		
MCAA	0.17-0.20	Not determined	2.0	81.4-131	1.7-9.5	1, 10
MBAA	0.027-0.13	Not determined	1.0	90.7-113	1.1-4.2	1, 10
DCAA	0.020-0.084	Not determined	1.0	93.8-107	0.33-3.8	1, 10
TCAA	0.019-0.024	Not determined	1.0	89.0-107	0.52-2.1	1, 10
DBAA	0.012-0.021	Not determined	1.0	101-111	0.52-5.3	1, 10
557	(DL)		Matrices:	Reagent water, synthetic sample matrix, chlorinated ground water, chlorinated surface water		
MCAA	0.20	0.58	2.0	95.9-109	1.7-5.2	1, 2.5, 8, 10, 15
MBAA	0.064	0.19	1.0	97.2-101	1.4-5.3	1, 2.5, 8, 10, 15
DCAA	0.055	0.13	1.0	79.6-109	1.7-9.3	1, 2.5, 8, 10, 15
TCAA	0.090	0.25	1.0	95.6-107	1.1-5.4	1, 2.5, 8, 10, 15
DBAA	0.015	0.062	1.0	84.5-111	6.0-14	1, 2.5, 8, 10, 15
SM 6251 B (22nd ed.)	(MDL)		Matrices:	Reagent water		
MCAA	0.082	Not determined	2.0	78.9-98.0	3.88-5.92	1, 5
MBAA	0.087	Not determined	1.0	70.6-99.0	2.67-4.76	1, 5
DCAA	0.054	Not determined	1.0	99.0-110	3.11-4.38	1, 5
TCAA	0.054	Not determined	1.0	92.7-101	3.06-5.49	1, 5
DBAA	0.065	Not determined	1.0	99.6-116	2.75-3.11	1, 5

A review of the data in Exhibit 5.4 indicates that the methods show an improvement in percent recovery and percent RSD as the methods evolved from EPA Method 552.1 to 552.2 to 552.3. All three methods include a derivatization step with acidic methanol, wherein the halogenated carboxylic acids are converted to their corresponding methyl esters. EPA Method 557 does not include the derivatization step; hence the issue of the efficiency of the conversion of the carboxylic acids to the corresponding methyl esters is eliminated (however, the instrumentation used in EPA Method 557 is much more costly than the instrumentation used in EPA Methods 552.1, 552.2 and 552.3, so simply switching to EPA Method 557 is not always feasible). How this conversion is accomplished and how the efficacy of the conversion is monitored has changed

as the methods evolved. Since the most marked effect is on the recovery of the unregulated HAAs, the discussion is presented further in Section 5.2.5.1.

EPA Method 552.1 demonstrates high variability in percent recovery. The very low recoveries correspond to matrices of high ionic strength and high humic acid content. Some of the percent RSDs are on the high side (20 percent is a typical high end of the acceptable range, although EPA Method 551.1 requires percent recovery that is within three standard deviations of the mean recovery); however, the percent RSDs do not show the extremes that are seen in the percent recovery data. This suggests that low recoveries can be a problem with this method. EPA Method 552.1 employs a solid phase extraction procedure that may have contributed to the low recoveries. EPA Method 552.2 uses a liquid/liquid extraction procedure, and the recoveries show marked improvement relative to EPA Method 552.1; however, they are still in the low range, especially for DBAA and TCAA in challenging matrices.

The MDLs from SM 6251 B are similar in magnitude to those from the EPA-developed methods. The percent recovery and percent RSD data from SM 6251 B are from fortified reagent water samples only, so a comparison with the EPA method performance data would likely not be meaningful.

5.2.3 Chlorite

For chlorite, both EPA-developed and non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs, and several non-EPA-developed methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published. No meaningful comparison can be made between the Stage 1 and Stage 2-approved methods and those approved since Stage 2 for the Palintest ChlordioX Plus or ASTM methods since performance data are not available on the NEMI website. However, the Palintest ChlordioX Plus amperometric sensor method was approved in the June 2014 Expedited Method Approval Action (USEPA, 2014a) for daily monitoring of chlorite as an alternative to the approved amperometric titration methodology employed in SM 4500-ClO_2 E.

For the Stage 1 D/DBPR, EPA Methods 300.0 (Rev. 2.1) and 300.1 and SM 4500-ClO_2 E (for daily checks only) in the 19th edition of *Standard Methods for the Examination of Water and Wastewater* were approved for compliance monitoring. These same methods remained approved under the Stage 2 D/DBPR. Under Stage 2, EPA Methods 317.0 (Rev. 2.0), 326.0 and 327.0 (Rev. 1.1, for daily checks only), along with SM 4500-ClO_2 E in the 20th edition of *Standard Methods for the Examination of Water and Wastewater* (daily checks only), SM online 4500-ClO_2 E-00 (daily checks only) and ASTM D 6581-00 were also approved for compliance monitoring. Since publication of the Stage 2 D/DBPR, alternate testing methods approved via EPA's Expedited Method Approval process for chlorite include SM 4500-ClO_2 E in the 21st and 22nd editions of *Standard Methods for the Examination of Water and Wastewater* (daily checks only), ASTM D 6581-08 A and B and Palintest ChlordioX Plus (for daily checks only). Exhibit 5.5 summarizes the DLs, LCMRLs, mean percent recovery values and percent RSDs for chlorite as listed in EPA Methods 300.0 (Rev. 2.1), 300.1, 317.0 (Rev. 2.0), 326.0 and 327.0 (Rev. 1.1). Method performance data are not included in SM 4500-ClO_2 E (APHA, AWWA and WEF, 2012). The MRL is from the final Stage 2 D/DBPR.

Exhibit 5.5: Method Performance Metrics for EPA Methods 300.0 (Rev. 2.1), 300.1, 317.0 (Rev. 2.0), 326.0 and 327.0 (Rev. 1.1) –- Chlorite

Method/Analyte	DL/MDL (µg/L)	LCMRL (µg/L)	MRL (µg/L)	Mean % Recovery Range	% RSD Range	Fortifi-cation (µg/L)
300.0 (Rev. 2.1)	(MDL)		Matrices:	Reagent water, drinking water		
Chlorite	10	Not determined	20	76.0-100	N/A	0.05, 0.1, 1, 5
300.1	(MDL)		Matrices:	Reagent water, high ionic strength water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Chlorite	0.45-1.44	Not determined	20	84.4-105	0.41-2.15	100, 500
317.0 (Rev 2.0)	(MDL)		Matrices:	Reagent water, high ionic strength water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Chlorite	0.45-0.89	Not determined	20	84.4-105	0.41-2.15	100, 500
326.0	(DL)		Matrices:	Reagent water, high ionic strength water, high organic content water		
Chlorite	2.0	Not determined	20	99.3-108	0.49-3.0	100, 500
327.0 (Rev. 1.1)	(DL)		Matrices:	Reagent water, chlorinated surface water, chlorinated ground water		
Chlorite	0.078-0.11	Not determined	20	98.5-110	1.4-4.4	1, 2

A review of the performance data in Exhibit 5.5 indicates that EPA Method 327.0 (Rev. 1.1) shows an increase in sensitivity (i.e., in the MDL/DL) relative to the other methods and both EPA Methods 326.0 and 327.0 (Rev. 1.1) show improved recovery relative to the other methods. However, a greater number of potentially challenging matrices were evaluated in EPA Methods 300.0 (Rev. 2.1), 300.1 and 317.0 (Rev. 2.0).

5.2.4 Bromate

For bromate, both EPA-developed and non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs and EPA-developed and ASTM-developed methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published. A comparison of the EPA-developed methods is presented in Exhibit 5.6.

For the Stage 1 D/DBPR, EPA Method 300.1 was approved for compliance monitoring. This method remained approved under the Stage 2 D/DBPR, wherein EPA Methods 317.0 (Rev. 2.0), 321.8 and 326.0, as well as ASTM D 6581-00, were also approved for compliance monitoring. Since publication of the Stage 2 D/DBPR, alternate testing methods for bromate that have been approved via EPA's Expedited Method Approval process include EPA Methods 302.0 and 557, as well as ASTM D 6581-08 A and ASTM D 6581-08 B. Exhibit 5.6 summarizes the DLs, LCMRLs, mean percent recovery values and percent RSDs for bromate as listed in EPA Methods 300.1, 317.0 (Rev. 2.0), 321.8, 326.0, 302.0 and 557. MRLs are from the final Stage 2 D/DBPR.

Exhibit 5.6: Method Performance Metrics for EPA Methods 300.1, 317.0 (Rev. 2.0), 321.8, 326.0, 302.0 and 557 –- Bromate

Method/Analyte	DL/MDL (µg/L)	LCMRL (µg/L)	MRL (µg/L)[11]	Mean % Recovery Range	% RSD Range	Fortifi-cation (µg/L)
300.1	(MDL)		Matrices:	Reagent water, high ionic strength water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Bromate	1.28-1.44	Not Determined	5.0	80.9-106	4.18-19.5	5, 25
317.0 (Rev. 2.0)	(MDL)		Matrices:	Reagent water, high ionic strength water, high organic content water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Bromate	0.12-0.98	Not Determined	1.0	80.9-108	1.87-21.4	0.5, 5, 25
321.8	(DL)		Matrices:	Ozonated drinking water		
Bromate	0.3	Not Determined	1.0	96.0-102	1.4-3.8	25
326.0	(DL)		Matrices:	Reagent water, high ionic strength water, high organic content water		
Bromate	0.17-1.2	Not Determined	1.0	92.9-110	2.0-11	1, 5, 10, 25
302.0	(DL)		Matrices:	Reagent water, synthetic sample matrix, ground water, surface water		
Bromate	0.12	0.18	1.0	89.8-104	0.84-2.6	0.5, 5
557	(DL)		Matrices:	Reagent water, synthetic sample matrix, chlorinated ground water, chlorinated surface water		
Bromate	0.020	0.042	1.0	93.3-117	2.4-11	1, 2.5, 8, 10, 15

A review of the performance data in Exhibit 5.6 indicates that the more recently approved analytical methods (EPA Methods 302.0 and 557) are comparable to the methods that were approved under Stage 1 and Stage 2 in terms of recovery and RSD. However, based on the DL, EPA Method 557 appears to be at least an order of magnitude more sensitive than the other approved analytical methods. Thus, some improvement in method sensitivity might be expected as a result of the approval of this method.

5.2.5 Unregulated DBPs

5.2.5.1 Unregulated Brominated HAAs

Because these contaminants are not currently regulated, there are no methods promulgated for their analysis; however, the four unregulated brominated HAAs that augment HAA5 to HAA9, (BCAA, bromodichloroacetic acid (BDCAA), dibromochloroacetic acid (DBCAA) and tribromoacetic acid (TBAA)) can be quantified by the same methods as those used for HAA5 (with the exception of EPA Method 552.1, which does not include BDCAA, DBCAA, or

[11] An MRL of 1.0 µg/L must be achieved when using EPA Methods 317.0 (Rev. 2.0), 321.8 or 326.0. An MRL of 5.0 µg/L must be achieved when using EPA Method 300.1.

TBAA). Exhibit 5.7 summarizes the DLs, LCMLRs, mean percent recoveries and percent RSDs for the four unregulated HAAs as listed in EPA Methods 552.1, 552.2, 552.3 and 557.

Exhibit 5.7: Method Performance Metrics for EPA Methods 552.1, 552.2, 552.3 and 557 – Unregulated Brominated HAAs

Method/Analyte	DL/MDL (µg/L)	LCMRL (µg/L)	Mean % Recovery Range	% RSD Range	Fortifi-cation (µg/L)
552.1	(MDL)	Matrices:	High ionic strength water, reagent water, dechlorinated tap water, high humic ground water, ozonated river water		
BCAA	0.10	Not determined	85-114	0.7-16	5, 10
BDCAA	Not in method	Not in method	Not in method	Not in method	Not in method
DBCAA	Not in method	Not in method	Not in method	Not in method	Not in method
TBAA	Not in method	Not in method	Not in method	Not in method	Not in method
552.2	(MDL)	Matrices:	Reagent water, dechlorinated tap water, high ionic strength water, high humic ground water,		
BCAA	0.251	Not determined	82.5-108	2.1-9.3	1, 2, 4
BDCAA	0.091	Not determined	96.6-115	8.2-15	1, 2, 4
DBCAA	0.468	Not determined	103-114	4.0-13	2.5, 5, 10
TBAA	0.82	Not determined	96.7-126	7.6-14	5, 10, 20
552.3	(DL)	Matrices:	Reagent water, chlorinated surface water, chlorinated ground water		
BCAA	0.016-0.029	Not determined	99.5-106	0.36-3.8	1, 10
BDCAA	0.031-0.034	Not determined	87.5-117	1.1-6.1	1, 10
DBCAA	0.035-0.054	Not determined	94.4-125	1.5-8.8	1, 10
TBAA	0.097-0.11	Not determined	99.2-128	1.8-8.1	1, 10
557	(DL)	Matrices:	Reagent water, synthetic sample matrix, chlorinated ground water, chlorinated surface water		
BCAA	0.11	0.16	82.8-107	2.9-10	1, 2.5, 8, 10, 15
BDCAA	0.05	0.19	91.0-105	2.0-4.9	1, 2.5, 8, 10, 15
DBCAA	0.041	0.08	90.4-103	3.6-11	1, 2.5, 8, 10, 15
TBAA	0.067	0.27	94.0-103	1.9-5.4	1, 2.5, 8, 10, 15

At the time the Stage 1 D/DBPR was published, analytical standards for BCAA, BDCAA, DBCAA and TBAA were not commercially available (Roberts et al., 2002).

More correctly, standards for the methyl esters of these four HAAs were not commercially available. These methylated standards are important tools for EPA's assessment of the efficiency of the derivatization of the various HAAs to their methyl esters, which would ideally be conducted as part of method development. While the standards were not available at the time EPA Method 552.2 was being developed, the standards were available during the development of EPA Method 552.3. At that time, EPA found that under the conditions specified by EPA Method 552.2, the methylation efficiencies for BCAA, BDCAA, DBCAA and TBAA were low. EPA Method 552.3 uses tert-amyl methyl ether (TAME) as an alternate solvent to methyl tert-butyl ether (MTBE). TAME has a higher boiling point than MTBE, the designated solvent in

EPA Method 552.2. The use of TAME as the extraction solvent results in more efficient derivatization.[12]

As indicated in Section 5.2.2, EPA Method 557 does not include the derivatization step; hence the issue of the efficiency of the conversion of the carboxylic acids to the corresponding methyl esters is eliminated. However, the instrumentation used in EPA Method 557 is of much higher cost than the instrumentation used for EPA Methods 552.1, 552.2 and 552.3, so using EPA Method 557 to avoid issues with derivatization is not always feasible.

5.2.5.2 Nitrosamines

Because the nitrosamines are not currently regulated there are no methods promulgated for them. Only one analytical method for drinking water, EPA Method 521, was approved for nitrosamine monitoring under UCMR 2.

Exhibit 5.8 summarizes the DLs, LCMRLs, MRLs (these MRLs differ from the MRLs presented earlier for other analytes; see footnote), mean percent recovery and percent RSDs for NDMA, NDEA, NDPA, NDBA, NMEA and NPYR. The LCMRLs in Exhibit 5.8 are taken from EPA Method 521 while the MRLs were developed by EPA for use in UCMR 2 (USEPA, 2007a).

Exhibit 5.8: Method Performance Metrics for Six Nitrosamines in EPA Method 521

Analyte	DL (ng/L)	LCMRL (ng/L)	MRL (ng/L)[13]	Mean % Recovery Range[14]	% RSD Range	Fortification (µg/L)
NDMA	0.28	1.6	2	83.7-94.7	3.8-12	2, 4, 10, 20
NDEA	0.26	2.1	5	84.6-95.6	6.5-14	2, 4, 10, 20
NDPA	0.32	1.2	7	77.1-97.0	3.7-10.2	2, 4, 10, 20
NDBA	0.36	1.4	4	79.7-104	2.9-16	2, 4, 10, 20
NMEA	0.28	1.5	3	81.4-91.0	4.5-9.6	2, 4, 10, 20
NPYR	0.35	1.4	2	85.2-102	4.0-12	2, 4, 10, 20

5.2.5.3 Chlorate

Because chlorate is not currently regulated there are no methods promulgated for it; however, there are both EPA-developed methods and non-EPA-developed methods approved for related analytes (e.g., bromide, chlorite and bromate) that are regulated in drinking water and several of these methods can also be used for the analysis of chlorate. These include the approved EPA

[12] E-mail correspondence with Dr. Glynda Smith of EPA's Technical Support Center, February 4, 2015; February 9, 2015; and February 12, 2015. Personal correspondence with Dr. Smith on February 11, 2015.

[13] As determined statistically from LCMRL study data and used in UCMR 2 (USEPA, 2007a).

[14] Percent recovery and percent RSD were obtained for the following matrices: reagent water, chlorinated drinking water from a river, chlorinated drinking water from ground water and chlorinated drinking water from surface water with high TOC.

Methods 300.0 (Rev. 2.1), 300.1, 317.0 (Rev 2.0) and 326. Exhibit 5.9 summarizes the DLs, LCMRLs, mean percent recoveries and percent RSDs for chlorate for the four approved analytical methods that have been developed by EPA, ASTM D6581-08 which was approved for chlorate analysis under UCMR 3 and SM 4110 D (note that the data shown are from the 22nd edition of SM [APHA, AWWA and WEF, 2012], not the 21st, which is the approved edition for chlorate analysis under UCMR 3). LCMRLs and the calculated MRL are only available for EPA Method 300.1 since this was the method designated by EPA for use in UCMR 3 (USEPA, 2012b).

Exhibit 5.9: Method Performance Metrics for Chlorate Using EPA Methods 300.0 (Rev. 2.1), 300.1, 317.0 (Rev. 2.0), 326.0, ASTM D6581-08 and SM 4110 D

Method/Analyte	MDL/DL (µg/L)	LCMRL[1] (µg/L)	MRL[2] (µg/L)	Mean % Recovery Range	% RSD Range	Fortification (µg/L)
300.0 (Rev. 2.1)	(MDL)		Matrices:	Reagent water, drinking water		
Chlorate	3	N/A	N/A	97-121	N/A	0.05, 0.1, 1, 5
300.1	(MDL)		Matrices:	Reagent water, high ionic strength water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Chlorate	0.78-2.55	1.8-14	20	86.1-106	0.47-2.14	100, 500
317.0 (Rev. 2.0)	(MDL)		Matrices:	Reagent water, high ionic strength water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Chlorate	0.62-0.92	N/A	N/A	86.1-106	0.47-2.14	100, 500
326.0	(DL)		Matrices:	Reagent water, high ionic strength water, high organic content water		
Chlorate	1.7	N/A	N/A	99-111	0.66-2.8	100, 500
ASTM D6581-08	(MDL)	N/A	Matrices:	Reagent water, drinking water		
Chlorate	0.32-3.49	N/A	N/A	93-107	N/A	20, 25, 180, 220, 400, 450
SM 4110 D (22nd ed.)	(MDL)	N/A	Matrices:	Reagent water, high ionic strength water, surface water, ground water, chlorinated drinking water, chlorine dioxide-treated drinking water, ozonated drinking water		
Chlorate	2.55	N/A	N/A	86.1-106	0.47-2.14	100, 500

[1] The LCMRLs are not from EPA Method 300.1 but were generated during UCMR 3 development and determination of the MRL for chlorate using EPA Method 300.1.
[2]As determined statistically from LCMRL study data and used in UCMR 3 (USEPA, 2012b).

A review of the performance data in Exhibit 5.9 indicates that the methods are comparable in terms of recovery and RSD; however, EPA Methods 300.1 and 317.0 (Rev. 2.0) may provide an opportunity for better sensitivity relative to EPA Methods 300.0 (Rev. 2.1) and 326.0. Note that, other than some differences in MDLs, the method performance data for EPA Methods 300.1, 317.0 (Rev. 2.0) and SM 4110 D (22nd ed.; APHA, AWWA and WEF, 2012) are identical.

5.3 Methods for Disinfectant Residuals

5.3.1 Chlorine (Free, Combined, Total) and Chloramines

For chlorine, only non-EPA-developed analytical methods were approved for monitoring in the Stage 1 and Stage 2 D/DBPRs, and both EPA-developed and non-EPA-developed analytical methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published.

For the Stage 1 D/DBPR, SM 4500-Cl D (19th ed.), SM 4500-Cl F (19th ed.) and SM 4500-Cl G (19th ed.), ASTM D1253-86 (free, combined, total); SM 4500-Cl E (19th ed.) and SM 4500-Cl I (19th ed.) (total); and SM 4500-Cl H (19th ed.) (free) were approved for compliance monitoring. These same methods remained approved under the Stage 2 D/DBPR. Also under Stage 2, 20th edition versions of the previously cited SMs; ASTM D1253-86(96), ASTM D1253-03, SM online 4500-Cl D-00, SM online 4500-Cl F-00 and 4500-Cl G-00 (free, combined, total); SM online 4500-Cl E-00 and SM online 4500-Cl I-00 (total); and SM online 4500-Cl H-00 (free) were also approved for compliance monitoring. Since publication of the Stage 2 D/DBPR, alternate testing methods for chlorine that have been approved via EPA's Expedited Method Approval process include Hach Method 10260, ASTM D1253-08, SM 4500-Cl D (21st, 22nd ed.), SM 4500-Cl F (21st, 22nd ed.) and SM 4500-Cl G (21st, 22nd ed.) (free, combined, total); EPA Method 334.0, ChloroSense, SM 4500-Cl E (21st, 22nd ed.) and SM 4500-Cl I (21st, 22nd ed.) (total); EPA Method 334.0, ChloroSense, SM 4500-Cl H (21st, 22nd ed.) and Method D99-003 (if approved by state) (free). Since only one EPA method (334.0) has been approved, method performance data are not included in SM 4500-Cl D, F or G (APHA, AWWA and WEF, 2012) and the other non-EPA methods are not available online, no comparison of methods approved in the Stage 1 and Stage 2 D/DBPRs relative to those published since Stage 2 can readily be made.

Additional information about the analytical methods used for measuring the free and total chlorine residuals in distribution system samples is provided in the *Six-Year 3 Review Technical Support Document for Microbial Contaminant Regulations* (USEPA, 2016a). Within the microbial rules, there is a requirement to maintain a detectable concentration of residual in the distribution system, while the D/DBPR includes MRDLs for chlorine and chloramines. There may be additional benefits to providing limits for monochloramine (see, e.g., 59 FR 38683, USEPA 1994a) and analytical methods have been developed that may be able to accommodate such measurements (e.g., an indophenol method that has been shown to be specific for monochloramine). There may be opportunities to consider approaches for realizing these additional benefits that include options that would allow utilities to use either the current methods for free and total chlorine or the newer methods (Wahman and Pressman, 2015).

5.3.2 Chlorine Dioxide

For chlorine dioxide, both EPA-developed and non-EPA-developed analytical methods were approved for monitoring during the Stage 1 and Stage 2 D/DBPRs and non-EPA-developed analytical methods have been approved via EPA's Expedited Method Approval process since the final Stage 2 D/DBPR was published.

For the Stage 1 D/DBPR, SM 4500-ClO_2 D (19^{th} ed.) and SM 4500-ClO_2 E (19^{th} ed.) were approved for compliance monitoring. These same methods remained approved under the Stage 2 D/DBPR, wherein EPA Method 327.0 (Rev. 1.1), SM 4500-ClO_2 D (20^{th} ed.), SM 4500-ClO_2 E (20^{th} ed.) and SM online 4500-ClO_2 E-00 were also approved for compliance monitoring. Since publication of the Stage 2 D/DBPR, alternate testing methods that have been approved via EPA's Expedited Method Approval process for chlorine dioxide have included SM 4500-ClO_2 E (21^{st}, 22^{nd} ed.) and ChlordioX Plus. Since only one EPA method has been approved, method performance data are not included in SM 4500-ClO_2 E (APHA, AWWA and WEF, 2012) and the ChlordioX Plus method is not available online, no comparison of methods approved under Stage 1 and Stage 2 vs. those published since Stage 2 can readily be made.

6 Occurrence and Exposure

This chapter summarizes information relevant to occurrence and exposure to regulated and unregulated disinfection byproducts (DBPs). As with other aspects of the Third Six-Year Review (SYR3), EPA limited its review of occurrence and exposure to information published through 2015. Information published since that time, while informative, was not included in this review.

Section 6.1 provides information related to DBP formation, including what was known at the time of the Stage 2 Disinfectants and Disinfection Byproducts Rule (D/DBPR) and important findings in the literature since the rule was promulgated.

Section 6.2 provides historical and new information related to occurrence of DBP precursors in source water.

Section 6.3 presents historical and new information related to the occurrence of regulated and unregulated DBPs in drinking water.

EPA used multiple data sources to evaluate occurrence and exposure to regulated and unregulated DBPs. The SYR3 Information Collection Rule (ICR) Dataset (USEPA, 2016f), called the "SYR3 ICR dataset," houses public water system (PWS) compliance monitoring data collected between 2006 and 2011 for systems of all sizes. This dataset contains over 47 million records for DBP, microbial, chemical and radiological monitoring data, with over 13 million records passing QA/QC procedures for DBPs and microbial contaminants and indicators (USEPA, 2016f). The SYR3 ICR dataset is regarded as the largest and most comprehensive source of PWS compliance monitoring dataset ever compiled and analyzed by EPA's Drinking Water Program. The SYR3 ICR dataset and general QA/QC procedures are further described in the *Analysis of Regulated Contaminant Occurrence Data from Public Water Systems in Support of the Third Six-Year Review of Existing National Primary Drinking Water Regulations: Chemical Phase Rules and Radionuclides* (USEPA, 2016g) and *The Data Management and Quality Assurance/Quality Control Process for the Third Six-Year Review Information Collection Rule Dataset* (USEPA, 2016i).

In addition to the SYR3 ICR data, information from the DBP ICR dataset (USEPA, 2000e; McGuire et al., 2002) was also further analyzed for understanding changes of DBP occurrence and disinfection practices. The DBP ICR dataset was the main source of occurrence data for development of supporting the Stage 2 D/DBPR and houses monitoring data from large public water systems (PWSs serving a population greater than or equal to 100,000) from an 18-month period (July 1997 to December 1998). Monitoring data for DBPs, plant treatment, source water characteristics and disinfectant type are available within this dataset.

Appendix B provides additional information on several of the topics presented in this chapter. The additional information presented in the appendix addresses DBP formation; precursor occurrence analytical results based on multiple other data sources such as National Rural Water Association (NRWA), ICR Supplemental Survey and Waterstats; discussion of EPA's Surface

Water Analytical Tool (SWAT) developed to predict formation of THM4[15] and HAA5; detailed discussions of the applicability of the DBP ICR and SYR3 ICR datasets; and detailed descriptions of the QA/QC processes undertaken prior to the analysis of the SYR3 ICR data.

6.1 DBP Formation

New research since the promulgation of the Stage 2 D/DBPR has enhanced our understanding of the key factors affecting DBP formation. This section briefly describes what was known at the time of the Stage 2 D/DBPR and presents new information on DBP formation that is relevant to the SYR process.

6.1.1 Summary of Stage 1 and 2 D/DBPR Information

The Stage 2 D/DBPR support documents including the Occurrence Document (USEPA, 2005l), the Economic Analysis (USEPA, 2005g) and the Technology and Costs Document (USEPA, 2005m) summarize what was known at the time regarding DBP formation.

The DBPs regulated by the Stage 2 D/DBPR include total trihalomethanes (THM4) and five haloacetic acids (HAA5). THM4 includes all four regulated trihalomethanes (THMs): chloroform, bromoform, bromodichloromethane (BDCM) and dibromochloromethane (DBCM). HAA5 includes five haloacetic acids for which an adequate analytical method existed at the time of the Stage 2 D/DBPR: monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA) and dibromoacetic acid (DBAA). Other groups of DBPs may also be referred to throughout this document. THM3 refers to THM4 minus chloroform. HAA6 includes all the haloacetic acids (HAAs) included in HAA5 and adds bromochloroacetic acid (BCAA).[16] HAA9 includes all nine HAAs, adding BDCAA, DBCAA and TBAA to those included in HAA6.

Organic DBPs form by the reaction of organic matter and disinfectants (acting as oxidizing agents) added during drinking water treatment. The Stage 2 D/DBPR Occurrence Document (USEPA, 2005l) identifies the following major factors affecting organic DBP formation: disinfection method and dose, contact time, concentration and characteristics of precursors, temperature and water chemistry. Information available at the time of the Stage 2 D/DBPR showed that a variety of DBPs formed from chlorine and natural organic matter (NOM) reactions, however, the amount of regulated organic DBP formation tended to be less upon chloramine disinfection. Research also demonstrated that NOM containing high aromatic content tended to increase DBP levels. Furthermore, DBP levels were found to increase with longer disinfectant contact time and higher temperatures. Upon the understanding of various factors, a water treatment plant model was developed to predict THM4/HAA5 levels at a national level,

[15] THM4 (also referred to as TTHM) is used to recognize the regulated THMs (THM4) vs other THMs (such as iodinated) which could be a part of the total THM mixture.

[16] EPA notes that in the Fourth Unregulated Contaminant Monitoring Rule proposal (USEPA, 2015) HAA6Br includes BCAA, bromodichloroacetic acid (BDCAA), DBAA, dibromochloroacetic acid (DBCAA), MBAA and tribromoacetic acid (TBAA). However, for the purposes of this document, HAA6 includes the regulated species within HAA5 and adds BCAA.

given treatment and water conditions. This model was incorporated into the SWAT, which was used to support economic analysis for the development of the Stage 2 D/DBPR (USEPA, 2005g).

6.1.2 New Information since the Stage 2 D/DBPR

Since the promulgation of the Stage 2 D/DBPR in 2006, considerable research has been done to better understand the formation of DBPs in drinking water, including regulated and unregulated DBPs. Research has further examined the impacts of factors such as source water quality, disinfection practices, treatment operations and distribution system operation and management. There have also been advances in the development of models to predict DBP formation.

6.1.2.1 DBP Types

Numerous studies have evaluated the occurrence of different types of DBPs in PWSs, many of which are unregulated and form after use of disinfectants other than chlorine. Over 600 different DBPs have been identified as forming during the disinfection process and many other DBPs are still unknown (Richardson et al., 2007; Krasner, 2009; Richardson and Postigo, 2011). Exhibit 6.1 summarizes general information about groups of regulated and unregulated DBPs, including examples of specific DBPs within the groups, the levels at which the DBPs occur and the source water and disinfection conditions that lead to DBP formation. These items are discussed further in the following sections. Information is also discussed in Section 6.3 about the occurrence of DBPs. As discussed in Section 6.1.1, EPA has proposed to monitor more brominated acetic acids along with the precursor or precursor indicator (i.e., TOC and bromide) under the Fourth Unregulated Contaminants Monitoring Rule (UCMR 4) (USEPA, 2015).

Exhibit 6.1: Regulated and Unregulated DBPs – General Information

DBP Group	Examples of DBPs	Relative Occurrence[1]	Disinfection Conditions Associated with Formation
Regulated trihalomethanes	Chloroform Bromoform Bromodichloromethane Dibromochloromethane	Chloroform occurs at low to mid µg/L levels; additional three species occur at low µg/L levels (Richardson et al., 2007).	Formed by disinfection with chlorine or chloramines. Formation tends to be less upon chloramine disinfection. Bromoform can also be formed in high-bromide source waters treated with ozone. Disinfection with chlorine dioxide does not result in THMs; however, low THM levels can be present due to chlorine impurities in chlorine dioxide (Richardson et al., 2007; Richardson and Postigo, 2011).
Regulated haloacetic acids	Chloroacetic acid Bromoacetic acid Dichloroacetic acid Dibromoacetic acid Trichloroacetic acid	Chloroacetic and bromoacetic acids occur at sub- to low µg/L levels; dichloroacetic, dibromoacetic and trichloroacetic acids occur at low to mid- µg/L levels (Richardson et al., 2007).	Formed by disinfection with chlorine, chloramines, chlorine dioxide and ozone, although generally formed at highest levels upon chlorination. Dibromoacetic acid can form when source water contains elevated bromide (Glaze et al., 1993; Richardson et al., 2007; Richardson and Postigo, 2011).
Additional haloacetic acids	Tribromoacetic acid Bromochloroacetic acid Bromodichloroacetic acid	Low µg/L levels (Obolensky, 2002; Richardson et al., 2007).	Associated with high-bromide source waters (Obolensky, 2002; Singer, 2006).

DBP Group	Examples of DBPs	Relative Occurrence[1]	Disinfection Conditions Associated with Formation
	Dibromochloroacetic acid		
Iodinated trihalomethanes	Dichloroiodomethane Bromochloroiodomethane Dibromoiodomethane Chlorodiiodomethane Bromodiiodomethane Iodoform	Sub to low µg/L levels (Richardson et al., 2007; Krasner, 2009).	Can form in drinking water treated with chlorine or chloramines when iodide is present in source waters, however, formation is highest when chloramines are used with ammonia added before chlorine (Richardson, 2003; Richardson et al., 2007; Krasner, 2009).
Iodoacids	Monoiodoacetic acid Chloroiodoacetic acid Bromoiodoacetic acid Diiodoacetic acid (E)-3-bromo-3-iodopropenoic acid (Z)-3-bromo-3-iodopropenoic acid (E)-2-iodo-3-methylbutenedioic acid	ng/L to low µg/L levels (Richardson et al., 2007; Kritsch and Weinberg, 2010).	Formed when hypoiodous acid (a result of an iodide and oxidant reaction) reacts with TOC. Presence of strong oxidants such as chlorine or ozone may further oxidize hypoiodous acid to iodate which does not form DBPs. Weaker oxidants like chloramines allow the hypoiodous acid to react with TOC to form iodoacids (Kritsch and Weinberg, 2010).
Haloacetonitriles (HAN)	Dichloroacetonitrile Bromochloroacetonitrile Dibromoacetonitrile Trichloroacetonitrile Tribromoacetonitrile	Sub to low µg/L levels (Richardson et al., 2007).	Formed by treatment with chlorine, chloramines, chlorine dioxide and ozone; highest formation observed in chloraminating plants (Blank et al., 2002; Richardson et al., 2007).
Haloketones (HK)	1-bromo-1,3,3-trichloropropanone 1-bromo-1,1-dichloropropanone	Low µg/L levels (Krasner et al., 2006).	Formed by treatment with chlorine, chloramine, chlorine dioxide and ozone combined with either chlorine or chloramine (Richardson and Postigo, 2011).
Halonitromethanes (HNMs)	Chloropicrin Bromopicrin, Bromodichloronitromethane Dibromochloronitromethane	Sub to low µg/L levels (Richardson et al., 2007)	Some compounds in this group may be associated with use of ozone, chlorine dioxide or UV usage (Richardson et al., 2007; Bull et al., 2011). Formation can be influenced by wastewater effluents and algal blooms (Krasner, 2009; Bull et al., 2011).
Haloacetamides	Dichloroacetamide Dibromoacetamide Trichloroacetamide	Sub to low µg/L levels (Richardson et al., 2007).	Formation associated with use of chlorine or chloramines. There is preliminary indication that formation may be higher upon chloramination (Weinberg et al., 2002; Krasner et al., 2006; Richardson et al., 2007).
Haloacetoaldehydes	Trichloroacetaldehyde (chloral hydrate) Dichloroacetaldehyde	Low µg/L levels for trichloroacetaldehyde; sub to low µg/L levels for dichloroacetaldehyde (Richardson et al., 2007; Jeong et al., 2015).	Associated with use of chlorine, chloramines and ozone (Krasner, 2009).
Cyanogen halides (CNX)	Cyanogen chloride	Low µg/L levels (Bull et al., 2011).	Formation is linked to chloramine use (Bull et al., 2011).

DBP Group	Examples of DBPs	Relative Occurrence[1]	Disinfection Conditions Associated with Formation
Oxyhalides[2]	Chlorate Chlorite Bromate	Sub to low µg/L levels for bromate; high µg/L levels for chlorite and chlorate (Richardson et al., 2007).	Chlorate and chlorite associated with use of chlorine dioxide or hypochlorite; bromate is primarily a byproduct of ozone disinfection, although some studies have shown bromate formation following chlorine dioxide treatment (Richardson et al., 2007; USEPA, 2016e).
Halogenated furanones	3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]furanone (MX) Brominated MX analogs	ng/L to sub µg/L levels (Richardson et al., 2007) can reach µg/L levels with high THM and bromide (Krasner et al., 2006).	Associated with use of chlorine, chloramines and chlorine dioxide.
Halobenzoquinones (HBQ)	2,6-dichlorobenzoquinone 2,6-dibromobenzoquinone	Sub µg/L levels (Bull., 2012).	Formed more in the presence of chloramines than chlorine (Bull et al., 2009).
Nitrosamines[3]	*N*-Nitrosodiethylamine *N*-Nitrosodimethylamine *N*-Nitrosodi-n-propylamine *N*-Nitrosopyrrolidine *N*-Nitrosodi-n-butylamine *N*-Nitrosomethylethylamine *N*-Nitrosomorpholine *N*-Nitrosopiperidine *N*-Nitrosodiphenylamine	ng/L to sub µg/L levels for NDMA; low ng/L levels for other compounds (Richardson et al., 2007; Boyd et al., 2011).	Shown to increase with chloramine use and nitrogenous precursors such as wastewater, pharmaceutical and personal care products and drinking water treatment chemicals (Richardson et al., 2007; Krasner, 2009; USEPA, 2016d).
Halogenated pyrroles	Tribromopyrrole	ng/L level (Richardson et al., 2007)	Information not available.
Aldehydes	Formaldehyde Acetaldehyde Glyoxal Methyl glyoxal	Sub to low µg/L levels (Richardson et al., 2007).	Mostly found with ozone use but also to a lesser extent with chlorine dioxide (Richardson et al., 2007; Richardson and Postigo, 2011).

[1] Section 6.3 provides additional information from the SYR3 ICR dataset about regulated DBPs.
[2] For additional information on chlorate, see USEPA 2016e.
[3] For additional information on nitrosamines, see USEPA 2016d.

6.1.2.2 Disinfection Practices

Unlike most chemical contaminants, DBPs form during treatment (i.e., disinfection or maintenance of disinfectant residual levels). As mentioned earlier, disinfection practices (including disinfectant types, doses and residual levels) can influence the type of DBPs that form, as well as the concentrations at which they occur. This section summarizes information available on the types of DBPs that have been found to occur upon different disinfection conditions, as well as presents information on disinfectant usage at PWSs.

Disinfectant Types and Doses

New research has shown that increased chlorine doses lead to increased DBP formation, although the effect is not uniform across all DBPs. Hua and Reckhow (2008) found that higher chlorine doses led to more trihaloacetic acids (THAA) than dihaloacetic acids (DHAA). Liu and Reckhow (2013) found higher chlorine doses led to more chloroform and DCAA in simulated distribution systems.

Studies have continued to show that chloramines produce less regulated THMs and HAAs than free chlorine (Bougeard et al., 2010; Lee et al., 2007; Hua and Reckhow, 2007; Cimetiere et al., 2010; Tian et al., 2013). Chloramines in particular produce less THM and HAA formation, but are not as effective at producing less DHAA (Krasner, 2014). One study found that using preformed chloramines (when ammonia is added before chlorine) produced between 7 and 18 percent of the total organic halides (TOX) that were produced by chlorination of the same water (Reckhow et al., 2007).

Chloramines can react with nitrogenous organic compounds to form nitrosamines, as described in the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d). While the formation of nitrosamines has been found to be more common with the use of chloramines, nitrosamine formation also can occur with other disinfectants given the proper precursors. Chloramines can also react with nitrogen-containing organic compounds to form additional unregulated DBPs including cyanogen chloride, dichloroacetonitrile (DCAN), dichloroacetamide and chloropicrin (Yang et al., 2010; Huang et al., 2012; Kimura et al., 2013).

New research has shown that chloramines can produce a number of unregulated DBPs, including brominated and iodinated DBPs (Kritsch and Weinberg, 2010; Zhai et al., 2014; Richardson and Ternes, 2014). The formation of iodinated DBPs with chloramines was found to be greater than that with chlorine (Hua and Reckhow, 2007; Kristiana et al., 2009; Criquet et al., 2012; Jones et al., 2012).

Recent research has verified that ozone reactions can create smaller oxygenated molecules such as aldoketoacids, carboxylic acids and aldehydes, which can impact DBP formation when chlorine or chloramines are used downstream (Krasner, 2014). While ozone generally forms fewer DBP species than chlorine alone, ozone has been found to increase THM and HAA levels compared to chlorine when some precursors are present. Bromate is of concern for systems that use ozone with elevated bromide levels in their source water. Use of ozone to oxidize cyanobacterial algae, followed by chlorination, was found to increase THM and HAA concentrations compared to chlorination alone (Coral et al., 2013). DBP concentrations increased with increased ozone dose and were correlated with release of dissolved extracellular organic material on ozonation of the cyanobacteria.

Ozone has also been found to lead to the formation of unregulated DBPs. Researchers found that following ozonation, levels of chloropicrin, trichloroacetaldehyde (TCAL), chloral hydrate, cyanogen bromide, halonitromethanes (HNMs), haloacetonitriles (HANs) and haloketones (HKs) can be elevated (Shah et al., 2012; Yang et al., 2012; Krasner, 2014; Richardson and Ternes, 2014; Xie et al., 2013).

Studies have found that UV disinfection produces very few THMs or HAAs at doses typically used for disinfection (Reckhow et al., 2010; Lyon et al., 2012; Linden et al., 2012). UV has been linked to increases in unregulated DBPs such as chloropicrin, HNM, TCAL, chloral hydrate and cyanogen chloride (Shah et al., 2012; Lyon et al., 2014; Krasner, 2014). Medium pressure lamps with various chlorination strategies were found to increase chloropicrin and bromopicrin formation more than low pressure lamps, with increases between 20 and 50 percent more than chlorine or chloramine alone (Linden et al., 2012).

Research has continued to show that chlorite and chlorate can be present as impurities from chlorine dioxide generation (as well as from decomposition of chlorine dioxide). Chlorite and chlorate have been found to co-occur in hypochlorite solutions. Chlorate may be an impurity in hypochlorite but can also be formed by the disproportionation of hypochlorite into chlorate and chlorite. Longer storage times, higher concentrations and higher temperatures have been found to increase chlorate concentrations in hypochlorite stock solutions (USEPA, 2016e). For more information about the occurrence of chlorate, refer to the *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e). For more information about the co-occurrence of chlorate and chlorite, refer to Section 6.3.4 of this document.

Researchers have found that regulated DBPs may be present as impurities in disinfectants. Emmert et al. (2011) investigated hypochlorite stock solutions at five utilities. Four of those utilities were found to have HAAs in their hypochlorite stock solutions; THMs were also present but in much lower concentrations. Concentrations of HAAs ranged from 56 to 627 µg/L. When added to water during the treatment process, the solution with the highest HAA level was enough to be associated with a concentration of 30 µg/L, or half the maximum contaminant level (MCL), in the finished water. A follow-up study (Emmert et al., 2013) found HAAs in all of 30 bulk hypochlorite samples examined but did not find THMs. The concentrations of HAAs were enough to be associated with concentrations of 4.1 to 16.4 µg/L in finished water and were higher in warmer months.

Disinfectant Usage Trends

As discussed earlier, disinfection practices can be a factor in the types of DBPs formed as well as the levels to which they occur. Characterization of the type(s) of disinfectant(s) used and their changes over time can be helpful for understanding the national occurrence of various DBPs and associated disinfection practices.

The Disinfection Systems Committee under the American Water Works Association (AWWA) has been conducting periodical national surveys (approximately every 10 years) to collect information on disinfection practices. Their most recent survey was published in 2008 and provides insight into disinfectant usage trends. The survey found that between 1998 and 2007, there was a tendency for utilities to switch from using chlorine gas to hypochlorite because of safety concerns. Chloramine usage also rose during that time period from 11 to 30 percent of all plants surveyed, although results should be viewed with caution because there were many more small plants included in the 1998 survey than the 2007 survey. Advanced disinfectants such as ozone, chlorine dioxide and UV light were also found to be increasing in usage, with ozone use rising from 6 to 9 percent, chlorine dioxide use increasing from 4 to 8 percent and UV use from 0 to 2 percent from 1998 to 2007 (AWWA, 2008). As discussed below, these trends continued

after 2007 as systems continued to comply with the Stage 1 D/DBPR/IESWTR and the more recent Stage 2 D/DBPR/LT2ESWTR.

The Third Unregulated Contaminant Monitoring Rule (UCMR 3) dataset provides a comprehensive set of information about disinfectant usage in the United States (USEPA, 2016h). Spanning the period from January 2013 to December 2015,[17] data in the dataset are nationally distributed and demonstrate that systems reporting exclusive use of chloramines, as well as systems that reported using multiple disinfectants (e.g., a system reported chlorine usage in 1 month of the UCMR and ozone in a different month), make up a significant portion of the reporting. Under the UCMR3, disinfectant type is identified for specific monitoring locations (Entry Point (EP) or Maximum Residence (MR)) rather than at the system level. The disinfectant type for a given monitoring period was specific to that monitoring location rather than to the system as a whole. As such, inferences about system-level disinfectant usage may tend to overestimate use of a type of disinfectant in situations where that disinfectant was used only for a portion of the UCMR monitoring program. The *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e) provides further information on disinfectant usage evaluations using the UCMR 3 dataset.

The following 11 disinfectant designation codes are used in the UCMR 3 dataset:

- CLGA (gaseous chlorine),
- CLOF (off-site generated hypochlorite stored as liquid),
- CLON (on-site generated hypochlorite with no storage),
- CAGC (chloramine formed from gaseous chlorine),
- CAOF (chloramine formed from off-site hypochlorite),
- CAON (chloramine formed from on-site hypochlorite),
- CLDO (chlorine dioxide),
- OZON (ozone),
- ULVL (ultraviolet light),
- OTHD (all other types of disinfectant), and
- NODU (no disinfection).

Exhibit 6.2 and Exhibit 6.3 show information about the disinfection types reported in the UCMR 3 dataset (as of July 2016) at the EP and MR distribution system locations, respectively. The results are split by system size and source water type. In both EP and MR locations, more than 30 percent of very large surface water systems (serving >100,000 people) use only chloramines or "chlorine and chloramines," while approximately 50 to 54 percent of very large surface water systems (serving >100,000 people) use chloramines alone or with another disinfectant (i.e., chlorine, chloramines, ozone, chlorine dioxide, UV light and "other disinfectant").

Exhibit 6.4 compares the disinfectant usage data from the DBP ICR and UCMR 3 datasets. A total of 199 systems reported disinfection data in both surveys (i.e., "common systems"). In the

[17] Monitoring was scheduled to occur between 2013 and 2015. Most data were received by EPA during the three-year-long official monitoring period although the reporting of some data continued in 2016.

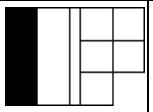
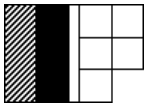
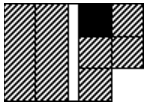
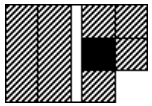
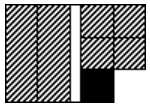
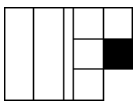
DBP ICR, data from 262 surface water plants were reported from these 199 systems. These results were compared with data from the 342 EP locations and 238 MR locations associated with surface water plants at the 199 systems in the UCMR 3 dataset (as of July 2016). The results show an increase over that time period in the use of chlorine dioxide, ozone, UV and chloramines. Note that although the data were from the same "common systems," the sampling point locations in DBP ICR and UCMR 3 may not have been the same.

As discussed in USEPA (2016e) and Chapter 7 of this document, the information from multiple datasets (i.e., DBP ICR, UCMR 2 and UCMR 3) collectively indicate that:

- The use of disinfectants other than free chlorine (i.e., ozone, chlorine dioxide, chloramines and UV) in treatment plants has increased over time.
- In distribution systems, the use of chloramines has increased over time.
- The use of hypochlorite in lieu of chlorine gas has increased over time.

These trends are important relative to the information about DBP formation and health effects. Chapter 7 presents further discussion of potential implications with these trends, from the treatment perspective.

Exhibit 6.2: Use of Disinfectants by Source Water Type and System Size for UCMR 3 Data in EPs (select categories)

Sampling Location Source Water[1]	System Size (population served)[2]	Number of EPs	Count of EPs Indicating Exclusive Use of Chlorine (% of Total)	Count of EPs Indicating Exclusive Use of Chloramines, OR both Chlorine and Chloramines (% of Total)	Count of EPs Indicating Any Instance of Using Chlorine (% of Total)	Count of EPs Indicating Any Instance of Using Chloramines	Count of EPs Indicating Any Instance of Using Ozone (% of Total)	Count of EPs Indicating Any Instance of Using Chlorine Dioxide (% of Total)	Count of EPs Indicating Any Instance of Using UV Light (% of Total)	Count of EPs Indicating Any Instance of Using "Other Disinfectant" (% of Total)	Count of EPs Indicating "No Disinfectant Used" (% of Total)[3]
											
GW	≤10,000	992	690 (69.6%)	90 (9.1%)	803 (80.9%)	108 (10.9%)	1 (0.1%)	3 (0.3%)	5 (0.5%)	34 (3.4%)	127 (12.8%)
	10,001 - 100,000	6,590	5,244 (79.6%)	602 (9.1%)	5,419 (82.2%)	620 (9.4%)	16 (0.2%)	37 (0.6%)	13 (0.2%)	97 (1.5%)	546 (8.3%)
	>100,000	2,256	1,947 (86.3%)	204 (9.0%)	2,017 (89.4%)	228 (10.1%)	28 (1.2%)	8 (0.4%)	2 (0.1%)	10 (0.4%)	55 (2.4%)
SW	≤10,000	293	155 (52.9%)	75 (25.6%)	256 (87.4%)	101 (34.5%)	19 (6.5%)	33 (11.3%)	12 (4.1%)	8 (2.7%)	0 (0%)
	10,001 - 100,000	2,257	1,240 (54.9%)	591 (26.2%)	1,594 (70.6%)	742 (32.9%)	130 (5.8%)	180 (8.0%)	92 (4.1%)	24 (1.1%)	35 (1.6%)
	>100,000	629	253 (40.2%)	213 (33.9%)	397 (63.1%)	317 (50.4%)	86 (13.7%)	53 (8.4%)	30 (4.8%)	5 (0.8%)	1 (0.2%)

[1] The source water type of the sampling location ("FacilityWaterType" in the UCMR 3 dataset) was used to develop these counts. Note: The "SW" category includes ground water under direct influence of surface water (“GU”) and mixed (“MX”).

[2] The population served by each system reflects the population served at the time of the UCMR 3 sample design. Refer to USEPA 2016e for full detail on UCMR3 data.

[3] The counts in the "no disinfectant used" column includes only those EPs that always specified "no disinfectant used." Furthermore, any surface water facilities identified as using no disinfection (NODU) in UCMR 3 may be a data entry error, as all surface water systems must disinfect.

Note: Based on EP locations with data posted from July 2016.
The disinfection codes used to categorize each sampling point are provided graphically in the table header above each column. The legend to the right indicates what code or set of codes corresponds to each cell. Fully shaded cells show codes that must be present for a sampling point to be assigned to a category and striped cells show codes that may be present. Blank cells show codes that must not be present. Because the categories shown in this table are neither exhaustive nor mutually exclusive, results do not add up to totals.

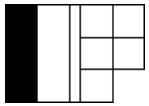
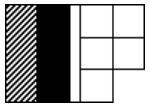
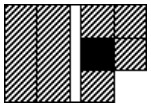
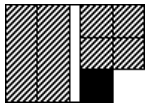
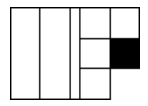
Layout Key

CLGA and/or CLOF and/or CLON	CAGC and/or CAOF and/or CAON		OZON	OTHD
			CLDO	NODU
			UVLV	

Color Key

	Used
	May be used
	Not used

Exhibit 6.3: Use of Disinfectants by Source Water Type and System Size for UCMR 3 Data in MRs (select categories)

Sampling Location Source Water[1]	System Size (population served)[2]	Number of MRs	Count of EPs Indicating Exclusive Use of Chlorine (% of Total)	Count of EPs Indicating Exclusive Use of Chloramines, OR both Chlorine and Chloramines (% of Total)	Count of EPs Indicating Any Instance of Using Chlorine (% of Total)	Count of EPs Indicating Any Instance of Using Chloramines	Count of EPs Indicating Any Instance of Using Ozone (% of Total)	Count of EPs Indicating Any Instance of Using Chlorine Dioxide (% of Total)	Count of EPs Indicating Any Instance of Using UV Light (% of Total)	Count of EPs Indicating Any Instance of Using "Other Disinfectant" (% of Total)	Count of EPs Indicating "No Disinfectant Used" (% of Total)[3]
											
GW	≤10,000	710	535 (75.4%)	67 (9.4%)	596 (83.9%)	69 (9.7%)	1 (0.1%)	4 (0.6%)	5 (0.7%)	20 (2.8%)	75 (10.6%)
	10,001 - 100,000	3,813	3,031 (79.5%)	435 (11.4%)	3,198 (83.9%)	450 (11.8%)	27 (0.7%)	34 (0.9%)	14 (0.4%)	50 (1.3%)	199 (5.2%)
	>100,000	697	555 (79.6%)	113 (16.2%)	596 (85.5%)	120 (17.2%)	13 (1.9%)	0 (0%)	1 (0.1%)	2 (0.3%)	7 (1.0%)
SW	≤10,000	285	153 (53.7%)	74 (26.0%)	250 (87.7%)	99 (34.7%)	16 (5.6%)	30 (10.5%)	11 (3.9%)	9 (3.2%)	0 (0%)
	10,001 - 100,000	2,176	1,163 (53.4%)	604 (27.8%)	1,513 (69.5%)	750 (34.5%)	128 (5.9%)	171 (7.9%)	91 (4.2%)	28 (1.3%)	29 (1.3%)
	>100,000	591	189 (32.0%)	218 (36.9%)	354 (59.9%)	322 (54.5%)	85 (14.4%)	68 (11.5%)	34 (5.8%)	5 (0.8%)	5 (0.8%)

[1] The source water type of the sampling location ("FacilityWaterType" in the UCMR 3 dataset) was used to develop these counts. Note: The "SW" category includes ground water under direct influence of surface water ("GU") and mixed ("MX").

[2] The population served by each system reflects the population served at the time of the UCMR 3 sample design. Refer to USEPA 2016e for full detail on UCMR3 data.

[3] The counts in the "no disinfectant used" column includes only those MRs that always specified "no disinfectant used." Furthermore, any surface water facilities identified as using no disinfection (NODU) in UCMR 3 may be a data entry error, as all surface water systems must disinfect.

Note: Based on MR locations with data posted from July 2016.
The disinfection codes used to categorize each sampling point are provided graphically in the table header above each column. The legend to the right indicates what code or set of codes corresponds to each cell. Fully shaded cells show codes that must be present for a sampling point to be assigned to a category and striped cells show codes that may be present. Blank cells show codes that must not be present. Because the categories shown in this table are neither exhaustive nor mutually exclusive, results do not add up to totals.

Layout Key

CLGA and/or CLOF and/or CLON	CAGC and/or CAOF and/or CAON		OZON	OTHD
			CLDO	NODU
			UVLV	

Color Key

	Used
	May be used
	Not used

Exhibit 6.4: DBP ICR and UCMR 3 Comparison -- Use of Disinfectants (select categories)

Among 199 Common Systems	Total Number of Plants/ EP Locations (surface water only)[3]	Number of Plants / EP Locations with…					Total Number of Plants/ MR Locations (surface water only)	Number of Plants / MR Locations with…
		Exclusive Use of Chlorine	Exclusive Use of Chloramines, OR both Chlorine and Chloramines	Any Instance of Chlorine Dioxide	Any Instance of Ozone	Any Instance of UV Light		Any Instance of Chloramines
DBP ICR[1] (01/1998-12/1998)	262 Plants	149 (56.9%)	75 (28.6%)	24 (9.2%)	14 (5.3%)	0 (0.0%)	262 Plants[4]	113 (43.1%)
UCMR 3[2] (01/2013-05/2016)	342 EP locations	137 (40.15%)	101 (29.5%)	44 (12.9%)	50 (14.6%)	17 (5.0%)	238 MR locations	128 (53.8%)

[1] For DBP ICR, counts were generated as follows: exclusive use of chlorine = plant used no other disinfectant except chlorine (CL2); exclusive use of chloramines, OR both chlorine and chloramines = plant used no other disinfectant except chloramine (CLM) or chloramine & chorine (CL2_CLM); any instance of chlorine dioxide = plant used chlorine dioxide (and may have also used other disinfectants); any instance of ozone = plant used ozone (and may have also used other disinfectants); any instance of UV light = plant used UV (and may have also used other disinfectants); any instance of chloramines = distribution disinfectant type was chloramine with or without other disinfectants.

[2] For UCMR 3, counts were generated as follows: exclusive use of chlorine = EP used no other disinfectant except chlorine (CLGA, CLOF or CLON); exclusive use of chloramines, OR both chlorine and chloramines = EP used no other disinfectant except chloramine (CAGC, CAOF or CAON) or chloramine and chorine. (A plant using both chloramine and chlorine would be counted in this column.); any instance of chlorine dioxide = EP used chlorine dioxide (and may have also used other disinfectants); any instance of ozone = EP used ozone (and may have also used other disinfectants); any instance of UV light = EP used UV (and may have also used other disinfectants); any instance of chloramines = MR used chloramine with or without other disinfectants.

[3] Only DBP ICR plants served by surface water were included. Plants may have multiple EP locations. Furthermore, only UCMR 3 EP and MR locations with source water designation “SW” were included in this analysis; those served by ground water, ground water under the direct influence of surface water (“GU”) or mixed source water (“MX”) were excluded.

[4] To determine the number of plants with any instance of chloramines in MR locations in DBP ICR, the disinfectant type in the distribution system was used.

6.1.2.3 Source Water Quality Research

In this section, considerations related to source water quality that affect DBP formation include the NOM fractions (i.e., hydrophilic and hydrophobic), NOM sources (i.e., terrestrial and aquatic), precursors in wastewater treatment plant effluent, temperature and pH.

NOM Fractions

New research conducted since development of the Stage 2 D/DBPR suggests that both hydrophilic and hydrophobic fractions of NOM serve as DBP precursors and can influence DBP speciation (e.g., Kim and Yu, 2005; Kanokkantapong et al., 2006; Hua and Reckhow, 2007; Karanfil et al., 2011). Hua and Reckhow (2007), Kim and Yu (2005), Panyapinyopol et al. (2005a; 2005b) and Chow et al. (2005) found that hydrophobic fractions of NOM increase the formation potential of THMs, HAAs and TOX more than the hydrophilic portions. Dickenson et al. (2008) reported, however, that, by mass, most of the byproducts of chlorination of β-dicarbonyl acids (i.e., aromatic structures within the hydrophilic fraction of NOM) were THMs and DHAA. Hydrophilic portions of NOM have also been linked to nitrosamine formation (Chuang et al., 2013; Hatt et al., 2013; Krasner et al., 2013; Wang et al., 2013). Chloride and bromide are capable of influencing bromination rates of DBP precursors (Sivey et al., 2015). A recent analysis of more than 30 years of published data on more than 185 NOM compounds, as well as DBP formation reports, found that given the complexities of water quality characteristics, NOM characteristics and DBP speciation, there is unlikely to be any one predictor of DBP formation in drinking water (Bond et al., 2012a). Bond et al. (2012a) recommend that both hydrophobic and hydrophilic components of NOM be removed from raw water to allow for more effective DBP control.

NOM Sources

New research suggests that the source of NOM influences the type of DBPs that are formed. NOM from terrestrial sources forms different types of DBPs than aquatic sources of NOM such as algae, as described below.

Chlorination or chloramination of lignin, a key component of terrestrially derived NOM, has been found to form TCAA and to a lesser extent DCAA (Hua et al., 2014). Aging and biodegradation of terrestrial organic matter yields more HAA, as well as THM, than fresh organic matter (Beggs and Summers, 2011; Reckhow et al., 2004). Terpenoids produced by animals, plants and microorganisms have been found to contribute to THM formation (Joll et al., 2010). Reckhow et al. (2007) found that waters with high humic content, which is indicative of terrestrial sources, tended to form more identifiable DBPs such as THM and HAA, while waters with low humic content formed more unknown DBPs. In a study on seven bacterial cultures commonly found in soil and water, Ng et al. (2015) found bacterial organic matter to also be a potential DBP precursor, as well as reduce disinfection efficiency.

Research since the Stage 2 D/DBPR has found that aquatic sources of NOM, such as algae, can be significant contributors of THM and HAA precursors (Nguyen et al., 2005; Callinan et al., 2013; Lui et al., 2012; Zhang et al., 2012). Callinan et al. (2013) found that THM formation correlated well with trophic indexes of chlorophyll A and total phosphorus, indicating a

dependence of THM precursors on algal growth in lakes. Zhang et al. (2012) observed that odorant compounds released by algae formed chloroform more efficiently than other compounds. Despite accounting for 0.02 percent or less of total organic matter present, algal odorants were responsible for more than 1 percent of the chloroform formed. Nguyen et al. (2005) found that algal-derived dissolved organic carbon (DOC) formed 0.53 µmol chloroform/mg DOC, 0.27 µmol DCAA/mg DOC and 0.14 µmol TCAA/mg DOC. In addition, cyanobacteria (also referred to as blue-green algae) presence has been correlated to precursors for a variety of DBPs including: THMs and HAAs (Wert and Rosario-Ortiz, 2013); HAN, HNM, nitrosamines, CNX and haloacetamides (Bond et al., 2011; Bond et al., 2012b); trichloronitromethane (Fang et al., 2010a; Yang et al., 2011); and NDMA (Fang et al., 2010b; Li et al., 2012; Zamyadi et al., 2012). These findings are important because algae and substances derived from algae tend to have low SUVA values (Henderson et al., 2008; Li et al., 2012; Nguyen et al., 2005). This is contrary to the previous recognition that NOM with high aromatic content tended to increase THM and HAA formation potential (USEPA, 2005l).

Weiss et al. (2013) conducted a study of the New York City water supply to evaluate the extent to which source water selection strategies, based on the amount of NOM, could be used to reduce the concentrations of DBPs in finished drinking water. Reservoir monitoring data indicated wide variability in DBP precursors across time and source waters.

Wastewater Influences

New research has continued to show that wastewater may change the types of DBPs formed and may influence the formation of nitrogenous DBPs. Krasner et al. (2008) suggest that the DBP precursors in wastewater treatment plant effluent may pose more of a risk for downstream drinking water facilities than the actual DBPs in the wastewater effluent. Wastewater treatment facilities that practice nitrification and denitrification generally have lower levels of HAN, haloacetaldehyde and NDMA precursors, as well as lower DOC and dissolved organic nitrogen (DON) concentrations in their effluent than facilities without these practices (Krasner et al., 2008). NOM in treated wastewater effluent may have a higher NDMA formation potential compared to NOM in source drinking water without wastewater influence (Krasner et al., 2013).

Some treatment processes, including those of both wastewater and drinking water, have been found to result in unintended consequences. For instance, while Liu and Li (2010) determined that the biological processes in wastewater treatment plants can lower the quantity of some DBP precursors in wastewater effluent, the wastewater treatment processes can increase formation potential for other DBPs. Yang and Zhang (2014) found that chlorination of saline wastewater effluents used for toilet flushing in coastal cities resulted in brominated DBP formation, specifically halogenated pyrroles (e.g., tetrabromopyrrole, tribromochloropyrrole and tribromopyrrole).

Rice et al. (2013) studied de facto wastewater reuse, the incidental presence of treated wastewater in public water supplies. In 1980, EPA identified PWSs that were influenced by upstream wastewater treatment plant discharges and found that the source water of the top 25 most affected PWSs contained between 2 and 16 percent wastewater discharges from upstream wastewater effluents under average streamflow conditions. Rice et al. (2013) provided an update to the original 1980 study by creating a geospatial dataset of PWSs and water treatment plants

(WTPs) across the United States and using it to determine the degree to which de facto reuse occurs in selected cities. From 1980 to 2008, it was found that de facto reuse increased for 17 of the 25 most heavily influenced PWSs. De facto reuse often made up significant portions of the drinking water supplies (ranging from 7 to 100 percent) under low streamflow conditions. Additionally, Rice and Westerhoff (2014) studied 2,056 surface water intakes from water systems that served approximately 82 percent of the United States' population, finding that 50 percent of the intakes were potentially impacted by upstream wastewater discharges.

Research has provided new insights into the contribution of wastewater-discharged NDMA precursors. In waters impacted by wastewater treatment plants, nitrosamine precursor concentrations (including dimethylamine) ranged from 190 to 1,200 ng/L (Pehlivanoglu-Mantas and Sedlak, 2006). Utilities treating surface waters impacted by wastewater flows generally show higher nitrosamine formation compared to those treating ground water or more pristine surface waters (Padhye et al., 2010). For more information on wastewater influences on nitrosamine formation, see the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d).

Wastewater effluent contains ammonia, which can also influence DBP formation and speciation. Several studies demonstrated a decrease in total DBP formation in the presence of ammonia, most likely due to chloramine formation (Hua and Reckhow, 2008; Yang and Shang, 2004; Fang et al., 2010b; Matamoros et al., 2007). Sun et al. (2009) reported an increase in HAA formation and a decrease in THM formation at elevated levels of ammonia. Research on DBP formation in drinking water from a heavily polluted surface water in Beijing, China, suggests that for some source waters, the presence of ammonia may significantly inhibit formation for certain types of DBPs (including that of THM and HAA) (Tian et al., 2013).

Temperature

New research since the Stage 2 D/DBPR has provided additional insight into the role of temperature in DBP formation. Temperature has been found to generally increase DBP formation, but the effect varies depending on the specific DBP (Toroz and Uyak, 2005; Hua and Reckhow, 2008; Roccaro et al., 2008). Hua and Reckhow (2008) found that THMs increased the most with increasing temperature, followed by DHAA and THAA. Obolensky and Singer (2008) reported that brominated DBPs were less temperature-dependent than chlorinated DBPs. Liu and Reckhow (2015) analyzed DBP levels in hot and cold tap water originating from a municipal water system that used free chlorine as the final disinfectant. They found that levels of THMs, DCAA and chloropicrin were higher in the hot tap water compared to the cold tap water, though there was no difference in the concentrations of TCAA.

Although formation of most DBPs increases with higher temperatures, some DBPs can degrade at higher temperatures, leading to complex behavior. Liu and Reckhow (2013) reported significant decreases in DCAN, 1,1,1-trichloropropanone, chloropicrin and 1,1-dichloropropanone (DCP) following an increase in water temperature for 24 hours, particularly at a higher pH of 8. The decreases in chloropicrin and DCP followed initial increases showing an initial rapid formation followed by rapid degradation. Liu and Reckhow (2015) found that hot tap water contained less DCAN, BDCAA, BCAA and 1,1,1-trichloropropane than cold tap samples.

pH

New research continues to show the linkages between pH and DBP formation during chlorination. General trends indicate increased THM formation at a higher pH, although the influence of pH on THM formation may be more complex than previously thought and depend on disinfectant type, precursor type and reaction time. For example, THM formation increased from chlorine contact with carbohydrates but decreased from chlorine contact with 3-oxopentanedioic acid at pH 8, compared to pH values of 5 and 5.5 (Bond et al., 2012a). Hua and Reckhow (2012) reported initial increases in DBCM and bromoform in chlorinated samples for 5 days with increasing pH, but then decreasing concentrations for the remainder of the 10-day test, when pH levels were adjusted from 7.5 to 8.3 and from 8.3 to 9.6. Based on the results of their study, Hua and Reckhow (2012) suggest that BrTHMs may degrade under high pH levels.

Studies show mixed results on the influence of pH on HAA formation in chlorinated water. Several researchers noted decreased TCAA formation at higher pH and no effect of pH on DCAA formation (Bond et al., 2012a; Hua and Reckhow, 2008; Obolensky and Singer, 2008; Hu et al., 2010; Fang et al., 2010a). Obolensky and Singer (2008) and Chu et al. (2012) found a decrease in DHAA formation at higher pH with chlorine.

Two studies evaluated the impacts of pH on DBP formation during chloramination. Hua and Reckhow (2008) found that TOX formation with chloramination significantly decreased under elevated pH conditions. Both Hua and Reckhow (2008) and Pope et al. (2007) found a decrease in DHAA formation at higher pH when chloramines were used.

6.1.2.4 Distribution System Conditions

As was recognized during the development of the Stage 2 D/DBPR, high THM4 and HAA5 levels do not necessarily occur at the location with the maximum residence time (USEPA, 2005l; USEPA, 2005g). Those factors affecting DBP formation (as discussed earlier) along with the distribution system management practices (including localized treatment, as discussed in Chapter 7 and chlorine burn as discussed in Chapter 8) can affect temporal and spatial variation of DBP levels throughout a distribution system. In addition, some DBPs (as organic contaminants) can be degraded under certain conditions in a distribution system. For instance, biological and inorganic degradation reactions have an effect on where HAA peaks occur in the distribution system. New studies have examined the conditions under which degradation occurs. Researchers found that monohaloacetic acids degrade most quickly, followed by DHAAs and THAAs, which degrade slowly or not at all (Baribeau et al., 2005; Bayless and Andrews, 2008). Speight and Singer (2005) found that degradation only occurs when no chlorine residual is present. According to research by Baribeau et al. (2005) and Speight and Singer (2005), degradation of HAAs proceeds more quickly at higher temperatures. Some bacterial species responsible for HAA degradation have been identified, including *Afipia* and *Methylobacterium* (Zhang et al., 2009a). Reaction of HAA with iron pipe walls in the distribution system has also been found to be a mechanism for HAA degradation (Zhang et al., 2004; Arnold et al., 2010).

6.1.2.5 DBP Formation Modeling

Since promulgation of the Stage 2 D/DBPR, numerous studies have been done to develop predictive models for DBP formation. Chowdhury et al. (2009) provided an overview of more than 100 models for predicting DBP concentrations. While a few models have used kinetic equations to predict DBP formation, most rely on empirical methods (Chowdhury et al., 2009). Most models use DOC, disinfectant dose, pH, temperature and contact time as variables and use empirical fits of DBP formation to data. Many of these models are very similar in form to the ones used in SWAT to predict DBP formation (additional information on the SWAT model is available in Appendix B, as well as in Chapter 7. Some models have introduced higher order terms, such as time squared, or other variables, such as fulvic acid instead of DOC (Chowdhury et al., 2009). Many of these models have not been calibrated using independent datasets. Generally, models based on laboratory data can be better controlled and may be more widely applicable, while models based on field data are more site-specific, but can show better predictability and distribution system effects.

New DBP modelling efforts have included precursor inputs to study possible effects on DBP formation potential (Boyer, 2015; Roccaro et al., 2015; Tang et al., 2015). Roccaro et al. (2015) modeled the formation of THMs, HAAs and HANs in two chlorinating PWSs. DBP species as well as NOM transformation reactions were evaluated and the authors noted formation changes when bromide was present. Tang et al. (2015) modeled DBPs in swimming pools, in which DBP formation was found to be caused by the continuous introduction of anthropogenic contaminants as well as the number of pool users. Boyer (2015) evaluated previously developed THM formation models to determine if they could be used at PWSs to predict DBP formation. The models that contained bromide as a variable tended to under-predict THM4 concentrations; however, the most statistically-robust models were believed to be appropriate for use at water utilities.

In addition to models of DBP formation in water distribution systems, Chen and Westerhoff (2010) constructed a model based on samples from wastewater treatment plants for both HAA and THM formation. Chowdhury et al. (2011) constructed a model to predict DBP concentrations in residential plumbing. Hao et al. (2012) used three-dimensional excitation and emission fluorescence spectroscopy to develop a predictive model for THM and HAA formation.

As described in Chapter 3, EPA regulated HAA5, not HAA9, due to a lack of analytical standards at that time for four species (BDCAA, DBCAA, TBAA and BCAA) (Shoaf and Singer, 2007). To further inform an understanding of HAA9, EPA reviewed the literature on methodologies for estimating unreported HAAs based on the reported HAA5 (or HAA6) and THM4 concentrations. This included the review of six articles, with five papers by the "Singer group" (Cowman and Singer, 1996; Roberts et al., 2002; Shoaf and Singer, 2007; Obolensky et al., 2007; Obolensky and Singer, 2008) and a paper by Francis et al. (2009).

Exhibit 6.5 presents the predictive models developed by the "Singer group" for estimating the four unregulated HAAs based on the assumption that these HAAs would form in the same proportion as the corresponding BrTHM species in relation to chloroform on a molar basis.

Exhibit 6.5: Singer Group Models for Estimating Unreported HAAs as a Function of Reported HAAs and THMs

Equation		Roberts et al. (2002)	Shoaf and Singer (2007)	Obolensky and Singer (2008)
1	$[BrCl_2AA] = C_0 + C_1 \times ([Cl_3AA] \times ([CHBr_2Cl] \div [CHCl_3]))$	**$C_0 = 0$** **$C_1 = 1$** n=1,844	**$C_0 = 0$** **$C_1 = 1$**	**$C_0 = 0.422$** **$C_1 = 0.804$** **n=3,943 r^2=0.88**
2	$[Br_2ClAA] = C_0 + C_1 \times ([Cl_3AA] \times ([CHBr_2Cl] \div [CHCl_3]))$	**$C_0 = 0$** **$C_1 = 1$** n=1,707	**$C_0 = 0$** **$C_1 = 1$**	**$C_0 = 0.770$** **$C_1 = 0.418$** **n=3,600 r^2=0.67**
3	$[Br_3AA] = C_0 + C_1 \times ([Cl_3AA] \times ([CHBr_3] \div [CHBr_3]))$	**$C_0 = 0$** **$C_1 = 1$** n=unknown	**$C_0 = 0$** **$C_1 = 1$**	**$C_0 = 1.014$** **$C_1 = 0.270$** **n=2,663 r^2=0.23**
4	$[BrClAA] = C0 + C1 \times ([Cl_2AA] \times (([CHBrCl_2] + [CHBr_2]) \div (2 \times [CHCl_3])))$	N/A	**$C_0 = 0$** **$C_1 = 1$**	N/A

N/A: model not available.
[…] indicates µM concentration.
$BrCl_2AA$ = dichlorobromoacetic acid, Br_2ClAA = dibromochloroacetic acid, Br_3AA = tribromoacetic acid, BrClAA = bromochloroacetic acid, Cl_3AA = trichloroacetic acid, $CHBr_3$ = bromoform, $CHCl_3$ = chloroform, $CHBr_2Cl$ = dibromochloromethane, $CHBrCl_2$ = bromodichloromethane, Cl_2AA = dichloroacetic acid.

Cowman and Singer (1996) examined the impact of pH and bromide concentration on the mole fraction of total HAA subject to chlorination and chloramination, which laid a foundation for the subsequent model developmental work. Roberts et al. (2002) developed a three-equation model for predicting three unreported HAAs (the sum of these three species is called HAA3) using the first 12 months of the 1997-98 DBP ICR dataset for facilities that reported all nine HAAs. (Note: all DBP ICR plants reported HAA6; approximately 30 percent of plants reported HAA9.) Obolensky and Singer (2008) calibrated the Roberts et al. (2002) three-equation model using the full 18-month ICR dataset after data screening described by Obolensky et al. (2007) and applied their model to the remaining ICR data for plants that only reported HAA6 to estimate HAA3 and HAA9. They found that on average, HAA3 represents 13 percent of HAA9 on a molar basis (Obolensky and Singer, 2008). Furthermore, Shoaf and Singer (2007) extended the Roberts et al. (2002) approach by adding a fourth equation to estimate BCAA (Exhibit 6.5). A sixth paper by Francis et al. (2009) proposed a multivariate normal model and data augmentation methods for characterizing the distribution of groups of DBPs using datasets with left-censored and missing data. Censored data were treated via a Bayesian Markov Chain Monte Carlo approach.

More recently, EPA proposed a data collection effort under UCMR 4 that would help to further inform an understanding of the extent to which these unregulated HAAs are present in drinking water (refer to 40 FR 76897, USEPA, 2015, for further information about the UCMR 4 proposal).

6.2 Occurrence of DBP Precursors

This section summarizes occurrence information for organic and inorganic DBP precursors. It focuses on specific water quality indicators for these precursors, such as TOC as an indicator for organic precursors.

6.2.1 Organic Precursors

6.2.1.1 Summary of Stage 1 and 2 D/DBPR Information

Prior to the development of the Stage 2 D/DBPR, the available national organic precursor occurrence information consisted primarily of data collected as part of the DBP ICR (for systems serving 100,000 or more people). Specifically, the DBP ICR dataset contained data for UV_{254}, alkalinity and TOC in surface and ground waters. The DBP ICR supplemental survey following the DBP ICR collected precursor occurrence data from systems serving less than 100,000 (USEPA, 2005l). During the development of the Stage 2 D/DBPR, TOC was considered a surrogate for the amount of NOM and potential precursors, UV_{254} was considered a measure of the aromaticity of the TOC and alkalinity was recognized as affecting TOC removal through coagulation/sedimentation and DBP formation. During rule development for Stage 2, for large water systems (serving at least 100,000), EPA generated summary-level information on the concentration of these parameters as a function of source water type. Additionally, EPA used multiple other data sources (NRWA; ICR Supplemental Survey; and Waterstats) to characterize precursor occurrence for small and medium-sized systems. These results are presented in Appendix B. The Occurrence Assessment for the Final Stage 2 D/DBPR also presents a national distribution of bromide and TOC occurrence in source water (USEPA, 2005l).

The Stage 1 D/DBPR requires all surface water systems (including systems using ground water under the direct influence of surface water (GWUDI)) using conventional filtration or precipitative softening to reduce DBP precursors.

6.2.1.2 New Information since the Stage 2 D/DBPR

For the purposes of SYR3, EPA evaluated data collected from the SYR3 ICR dataset and new literature published since 2006. Additionally, EPA compared the DBP ICR TOC data (pre-Stage 1 D/DBPR; see introduction) to the SYR3 ICR TOC data to evaluate changes in DBP precursor occurrence over time. EPA evaluated available TOC data on the plant-level. TOC reductions in the context of the treatment technique (TT) requirement are discussed in Chapter 7. For additional details on the TT requirement and how available data relate to that requirement, please see Chapter 7.

The SYR3 ICR dataset contains TOC data for 33 states and surface water systems of all sizes. Additionally, 34 states and primacy agencies submitted data for alkalinity. EPA excluded all data that did not pass through its general and analyte-specific QA/QC processes to ensure that the data were high quality; for more details on the QA/QC steps, please see Appendix B. After data management and quality checks on the dataset were conducted, approximately 446,000 TOC and alkalinity records from January 2006 to December 2011 were available.

It is important to note that both CWSs and non-community water systems (NCWSs) were included in all analyses (presented in this chapter) using the SYR3 ICR precursor data.

Precursor Inventory Analyses

The results of system and population inventories of the SYR3 ICR TOC dataset in 2011 (the most recent and complete year of data) are included below in Exhibit 6.6 through Exhibit 6.8. For inventory information in all years (2006-2011), see Appendix B. Exhibit 6.6 depicts the distribution of systems and population among the different system types and Exhibit 6.7 includes the same information but distributed based on source water type. The source types are split by ground water (includes purchasing systems), surface water (includes purchasing systems) and GWUDI and includes purchased systems as well. Exhibit 6.8 depicts the distribution of systems and population by both source water type, system type and aggregated by population size. Overall, the results indicate the majority of the systems with TOC data are surface water CWSs, serving between 3,300 and 50,000 people.

Exhibit 6.6: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset with TOC Records, by System Type (2011)

Year	System Type	Systems		Population	
		Number	Percent	Number	Percent
2011	Community	1,775	93.9%	62,322,706	99.9%
	Non-transient Non-community	116	6.1%	65,806	0.1%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**1,891**	**100.0%**	**62,388,512**	**100.0%**

Exhibit 6.7: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset with TOC Records, by Source Water Type (2011)

Year	Source Water Type	Systems		Population	
		Number	Percent	Number	Percent
2011	Ground Water	179	9.5%	5,068,752	8.12%
	GWUDI	63	3.3%	528,104	0.85%
	Surface Water	1,649	87.2%	56,791,656	91.03%
	Total	**1,891**	**100.0%**	**62,388,512**	**100.0%**

Exhibit 6.8: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset with TOC Records, by System Size and System Type (2011)

Year	System Size (Population Served by the System)	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
Community Water Systems							
2011	< 101	16	970	74	2,185	90	3,155
	101 – 500	22	5,997	89	25,863	111	31,860
	501 – 1,000	16	13,015	98	76,394	114	89,409
	1,001 – 3,300	22	42,194	339	710,311	361	752,505
	3,301 – 10,000	14	92,891	430	2,622,616	444	2,715,507
	10,001 – 50,000	20	506,456	415	9,634,912	435	10,141,368
	50,001 – 100,000	8	630,238	92	6,482,543	100	7,112,781
	100,001 – 1 million	18	3,763,850	98	26,250,976	116	30,014,826
	> 1 million	0	0	4	11,461,295	4	11,461,295
	Total	**136**	**5,055,611**	**1,639**	**57,267,095**	**1,775**	**62,322,706**
Non-Transient Non-Community Water Systems							
2011	< 101	21	977	14	769	35	1,746
	101 – 500	18	3,869	22	6,368	40	10,237
	501 – 1,000	2	1,244	21	16,973	23	18,217
	1,001 – 3,300	1	1,051	15	24,755	16	25,806
	3,301 – 10,000	1	6,000	1	3,800	2	9,800
	10,001 – 50,000	0	0	0	0	0	0
	50,001 – 100,000	0	0	0	0	0	0
	100,001 – 1 million	0	0	0	0	0	0
	> 1 million	0	0	0	0	0	0
	Total	**43**	**13,141**	**73**	**52,665**	**116**	**65,806**

Note: GWUDI systems are included in SW and purchased systems are included in each category as well.

Representativeness of SYR3 ICR Precursor Data

There were nearly 36,000 records for TOC reported in 2011 by 1,639 surface water CWSs in the SYR3 ICR data. Overall, these systems serve approximately 57 million people. When comparing the 2011 SYR3 data to inventory data in EPA's Safe Drinking Water Information System (SDWIS)[18] in 2011, the SYR3 total count of systems that submitted TOC data represents

[18] SDWIS contains information about PWSs and their violations of EPA's drinking water regulations, as reported to EPA by the states.

approximately 14 percent of the total SDWIS system count for surface water CWSs.[19] Despite these differences, the population served by the SYR3 ICR systems that reported TOC data in 2011 is approximately 28 percent of the entire retail population served by SDWIS surface water CWSs in 2011, implying that the SYR3 ICR TOC data encompasses a considerable portion of drinking water consumers from surface water CWSs. Recognizing these findings, EPA believes that the TOC data in the SYR3 ICR are useful for informing a perspective on the national occurrence of TOC for SYR.

While these data are helpful for informing an understanding of TOC and alkalinity occurrence on a national level, it is important to note that there may be gaps in the available information that could potentially lead to misrepresentation of TOC and alkalinity occurrence. For example, the SYR3 TOC dataset does not include any surface water CWSs from some states (e.g., Texas) that, based on data from the DBP ICR, have historically exhibited elevated levels of organic precursors. It is also important to recognize that surface water systems not using conventional treatment were not required to collect TOC removal data and such systems (e.g., those using slow sand or direct filtration) would in general have lower TOC concentrations.

State-level inventory information and record counts for 2006-2011 are presented in Appendix B for both raw and finished water. For alkalinity inventory data in all years of the SYR3 ICR data, please see Appendix B.

National TOC Occurrence for 2011

EPA reviewed the entire SYR3 ICR TOC dataset to evaluate plant-level means for TOC in raw and finished waters for given system size categories. These results, shown in Exhibit 6.9, represent the most recent and complete year of the SYR3 ICR data (2011); information in all years is provided in Appendix B. Additionally, EPA included only those plants from systems that had "paired" data (i.e., data for raw water TOC, finished water TOC and alkalinity collected during the same month) in the analyses below. The average plant TOC levels are shown as cumulative distributions in Exhibit 6.10. These results do not estimate TOC removal; thus, the reader should not construe the difference between raw and finished water TOC values to be indicative of compliance. Please see Chapter 7 for an evaluation of TOC removal.

Exhibit 6.9: Raw and Finished Water Plant Means from the SYR3 ICR TOC Dataset; Surface Water Systems (2011)

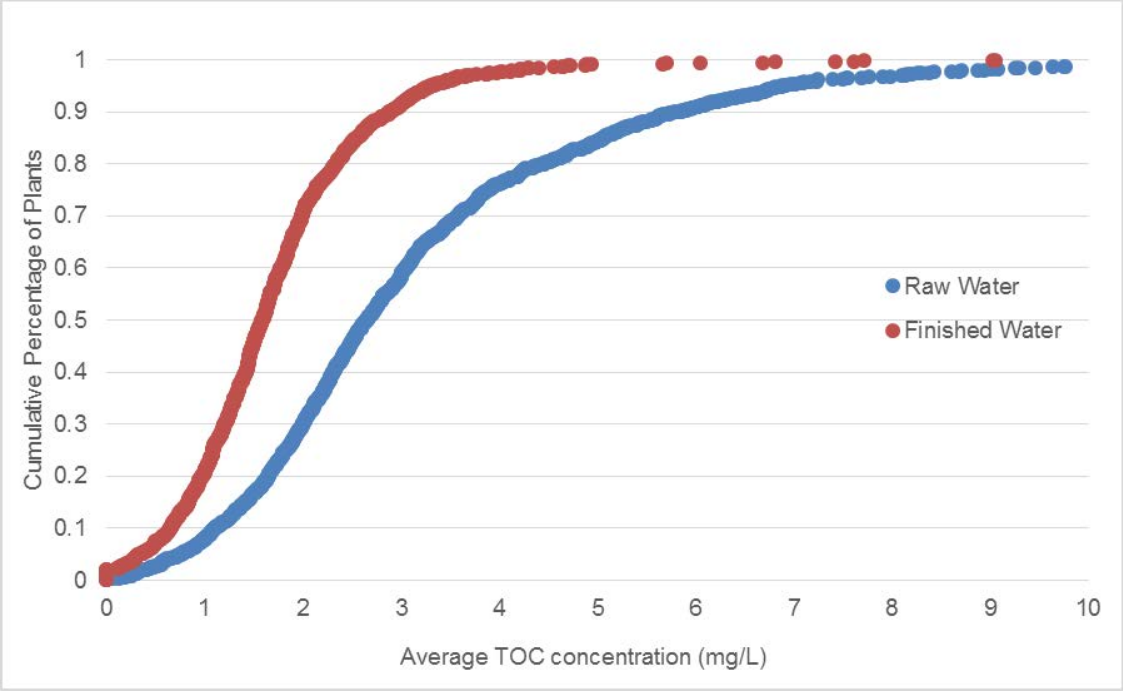
System Size	Year	Count of Plants	Median (mg/L)	Mean (mg/L)	90%ile (mg/L)	95%ile (mg/L)	% Plant Means > 2 mg/L	% Plant Means > 3 mg/L
Raw Water								
Serving <10,000	2011	682	2.54	3.07	5.77	6.79	66%	40%
Serving 10,000 - <100,000	2011	415	2.68	3.19	5.61	6.93	74%	40%

[19] To evaluate the completeness of the SYR3 ICR TOC dataset, EPA compared the number of SW CWSs and their associated population served in each state that submitted TOC data for the year 2011 to the number of active SW CWSs and their associated population served according EPA's SDWIS/Fed dataset in 2011. For more details on this comparison, refer to Appendix B.

System Size	Year	Count of Plants	Median (mg/L)	Mean (mg/L)	90%ile (mg/L)	95%ile (mg/L)	% Plant Means > 2 mg/L	% Plant Means > 3 mg/L
Serving ≥100,000	2011	120	3.06	3.63	6.15	7.04	80%	52%
All	2011	1,217	2.65	3.16	5.79	6.88	70%	41%
Finished Water								
Serving <10,000	2011	682	1.53	1.70	3.04	3.47	30%	10%
Serving 10,000 - <100,000	2011	415	1.60	1.69	2.61	3.02	28%	6%
Serving ≥100,000	2011	120	1.72	1.79	2.78	3.24	26%	8%
All	2011	1,217	1.59	1.71	2.88	3.30	29%	8%

The 2 mg/L TOC level represents the level below which TOC removal is not required in the Stage 2 D/DBPR. There could be one or more plants per system.

Exhibit 6.10: Cumulative Distribution of Raw Water and Finished Water Means in SYR3 ICR TOC Dataset; Surface Water Plants (2011)



Note that the x-axis is cut-off at 10 mg/L; 15 raw water plant-level means were greater than 10 mg/L and are, therefore, not shown here. While only raw and finished water data from plants providing both raw and finished water data were used, the respective raw and finished water distributions for a given cumulative percentage are not paired.

Raw water data show that between 40 and 52 percent of surface water plants have average TOC values greater than 3 mg/L depending on the system size category. Raw water data are fairly consistent across the three size categories, with slightly higher results across the large size category (serving 100,000 people or more).

In finished water, the data show slightly higher plant mean TOC values at the upper end of the distribution for small systems serving less than 10,000 people compared to systems in the 2

larger size categories. For example, the percent of plant-average finished water TOC values greater than 3 mg/L is 10 percent for small systems compared to 6 percent and 8 percent for medium and large systems, respectively. The difference can also be seen in the percent of plant-average TOC values greater than 2 mg/L, with 30 percent greater than 2 mg/L for small systems, compared to 28 percent and 26 percent greater than 2 mg/L for medium and large systems, respectively. Differences in finished water data could indicate that small systems are removing less TOC compared to medium and large systems. Please refer to Chapter 7 for information on TOC reductions in the context of the TT requirement.

Changes in TOC Occurrence

EPA evaluated the changes in TOC occurrence over time, using data from both the DBP ICR and SYR3 ICR datasets. EPA used 1998 data from the DBP ICR dataset and 2011 data from the SYR3 ICR dataset, including only data from systems that were found in both datasets (referred to as "common systems"). As mentioned earlier, the DBP ICR only contains information from large surface water systems serving 100,000 or more people. Thus, the common systems between the two datasets are limited to large surface water systems.

Exhibit 6.11 below presents TOC raw and finished water plant-level summary statistics for common systems in the DBP ICR and SYR3 ICR. The common systems were distributed across 14 states (Alabama, Alaska, Illinois, Indiana, Iowa, Kentucky, Nevada, New Jersey, North Carolina, Oklahoma, Pennsylvania, South Carolina, Virginia and West Virginia).

Exhibit 6.11: Raw and Finished Water Plant Mean TOC from the DBP ICR (1998) and SYR3 ICR (2011); Common Surface Water Systems

Data Source	Year	Count[1]	Median (mg/L)	Mean (mg/L)	90%ile (mg/L)	95%ile (mg/L)	% Means > 2 mg/L	% Means > 3 mg/L
Raw Water								
DBP ICR	1998	100	2.84	2.96	5.08	6.39	67%	44%
SYR3 ICR	2011	105	3.01	3.35	5.64	6.58	79%	50%
Finished Water								
DBP ICR	1998	101	1.78	1.77	2.82	3.21	36%	7%
SYR3 ICR	2011	105	1.73	1.74	2.68	3.23	26%	7%

[1] The 61 common water systems for raw water TOC represent 100 plants in the DBP ICR and 105 plants in the SYR3 ICR datasets and the 61 common water systems for finished water TOC represent 101 plants in the DBP ICR and 105 in the SYR3 ICR datasets.

Exhibit 6.11 demonstrates that, when looking at data from 1998 and 2011, there was an increase in raw water TOC levels for large surface water supplies. Large system raw water TOC averaged 2.96 and 3.35 mg/L in DBP ICR and SYR3 ICR data, respectively. The finished water data showed more variability across distribution of values, with slightly lower averages with the SYR3 ICR data. A possible explanation for instances where there is minimal difference across years is that even though the Stage 1 D/DBPR implementation did not begin until 2002, many systems may have already been in the process of addressing the TOC requirements since they were initially included with the 1994 proposed D/DBPR (see Chapter 3 for background

information on the regulation). Other possible explanations for minimal difference across years could be that for many systems the treatment they already had in place may have been able to remove TOC.

TOC Data from DBP ICR

The DBP ICR dataset contains TOC information spanning 18 months (July 1997-December 1998) of the pre-Stage 1 D/DBPR time period. For SYR3, EPA looked at DBP ICR data for calendar year 1998 to minimize seasonal bias. EPA evaluated the finished water TOC data for conventional plants (further differentiated into conventional with softening and conventional without softening categories) and non-conventional plants (including direct filtration, slow sand and unfiltered plants) in systems serving at least 100,000 people. For those instances where 90th percentiles were based on less than 10 plant means and where 95th percentiles were based on less than 20 plant means, EPA chose not to include these results because they were not believed to be reliable estimates.

Exhibit 6.12 and Exhibit 6.13 provide a summary of raw water and finished water plant mean TOC values for surface water plants, respectively. Results are shown separately for seven surface water plant types as indicated in the DBP ICR.

Exhibit 6.12: Raw Water Plant Mean TOC Data from Surface Water Plants in the DBP ICR (1998, Systems Serving > 100,000 People)[1]

Plant Type[2]	Plant Type Code	Number of Surface Water Plants[3]	Percentage of Total	Mean of Plant Mean TOC, mg/L	90%ile of Plant Mean TOC, mg/L	95%ile of Plant Mean TOC, mg/L	% Plant Mean TOC > 2 mg/L	% Plant Mean TOC > 3 mg/L
Conventional (No Softening)	CONV	258	75%	3.2	5.1	6.1	79%	45%
Conventional (Softening)	SOFT	38	11%	4.7	7.3	7.9	95%	84%
Direct Filtration	DF	23	7%	2.4	3.2	3.8	65%	22%
In-Line Filtration	ILF	6	2%	1.4	-	-	17%	17%
Slow Sand Filtration	SSF	2	1%	1.6	-	-	50%	0%
Unfiltered	UNFILT/SW	14	4%	1.6	2.5	-	29%	0%
Other	OTHER	4	1%	2.2	-	-	75%	0%
Total	**--**	**345**	**100%**	**3.2**	**5.3**	**6.4**	**77%**	**45%**

[1] If more than one TOC value was provided for a given month, EPA calculated the monthly average before calculating the yearly average (also to minimize seasonal bias).
[2] The plants with the treatment plant type code of "DIS/GW" or "MEMBRANE" (one each) were excluded. The "Conventional (Softening)" category includes plant type codes: CMPLX/SOFT, CS/SOFT, SOFT, SPLIT/SOFT and TS/SOFT.
[3] All SW plants were included in this analysis, not just those with at least 9 months of data.

Exhibit 6.13: Finished Water Plant Mean TOC Data from Surface Water Plants in the DBP ICR (1998, Systems Serving > 100,000 People)[1]

Plant Type[2]	Plant Type Code	Number of Surface Water Plants[3]	Percentage of Total	Mean of Plant Mean TOC, mg/L	90%ile of Plant Mean TOC, mg/L	95%ile of Plant Mean TOC, mg/L	% Plant Mean TOC > 2 mg/L	% Plant Mean TOC > 3 mg/L
Conventional (No Softening)	CONV	263	75%	2.1	3.1	3.5	46%	13%
Conventional (Softening)	SOFT	39	11%	2.6	3.7	3.9	77%	33%
Direct Filtration	DF	23	7%	1.9	2.6	2.7	48%	4%
In-Line Filtration	ILF	6	2%	1.0	-	-	0%	0%
Slow Sand Filtration	SSF	2	1%	1.2	-	-	0%	0%
Unfiltered	UNFILT/SW	14	4%	1.5	2.4	-	21%	0%
Other	OTHER	4	1%	1.3	-	-	25%	0%
Total	--	351	100%	2.1	3.2	3.7	48%	13%

[1] If more than one TOC value was provided for a given month, EPA calculated the monthly average before calculating the yearly average (also to minimize seasonal bias).
[2] The plants with the treatment plant type code of "DIS/GW" or "MEMBRANE" (one each) were excluded. The "Conventional (Softening)" category includes plant type codes: CMPLX/SOFT, CS/SOFT, SOFT, SPLIT/SOFT and TS/SOFT.
[3] All SW plants were included in this analysis, not just those with at least 9 months of data.

Conventional treatment plants without softening were the most common type of surface water plant included in this dataset, representing approximately 75 percent of the surface water plants. Conventional plants with softening, as well as direct filtration plants, were also common (approximately 11 percent and 7 percent, respectively). These three plant types had higher levels of TOC overall than the other types of treatment plants evaluated.

Exhibit 6.14 and Exhibit 6.15 provide a summary of raw water and finished water plant mean TOC values for ground water (GW) plants, respectively. Results are shown separately for five GW plant types as indicated in the DBP ICR.

Exhibit 6.14: Raw Water Plant Mean TOC Data from Ground Water Plants in the DBP ICR (1998, Systems Serving > 100,000 People)[1]

Plant Type[2]	Plant Type Code	Number of GW Plants[3]	Percentage of Total	Mean of Plant Mean TOC, mg/L	90%ile of Plant Mean TOC, mg/L	95%ile of Plant Mean TOC, mg/L	% Plant Mean TOC > 2 mg/L	% Plant Mean TOC > 3 mg/L
Conventional (No Softening)	CONV	2	2%	9.4	-	-	100%	50%
Conventional (Softening)	SOFT	23	18%	5.8	11.7	12.6	83%	61%

Plant Type[2]	Plant Type Code	Number of GW Plants[3]	Percentage of Total	Mean of Plant Mean TOC, mg/L	90%ile of Plant Mean TOC, mg/L	95%ile of Plant Mean TOC, mg/L	% Plant Mean TOC > 2 mg/L	% Plant Mean TOC > 3 mg/L
Disinfecting / GW	DIS/GW	63	50%	0.3	0.9	1.2	3%	2%
Other / GW	OTHER/GW	34	27%	0.9	2.3	3.4	12%	9%
Other	OTHER	4	3%	3.1	-	-	25%	25%
Total	**--**	**126**	**100%**	**1.7**	**4.2**	**10.3**	**22%**	**16%**

[1] If more than one TOC value was provided for a given month, EPA calculated the monthly average before calculating the yearly average (also to minimize seasonal bias).
[2] The one plant with the treatment plant type code of "MEMBRANE" was excluded. The "Conventional (Softening)" category includes plant type codes: CMPLX/SOFT, CS/SOFT, SOFT, SPLIT/SOFT and TS/SOFT.
[3] All GW plants were included in this analysis, not just those with at least 9 months of data.

Exhibit 6.15: Finished Water Plant Mean TOC Data from Ground Water Plants in the DBP ICR (1998, Systems Serving > 100,000 People)[1]

Plant Type[2]	Plant Type Code	Number of GW Plants[3]	Percentage of Total	Mean of Plant Mean TOC, mg/L	90%ile of Plant Mean TOC, mg/L	95%ile of Plant Mean TOC, mg/L	% Plant Mean TOC > 2 mg/L	% Plant Mean TOC > 3 mg/L
Conventional (No Softening)	CONV	2	2%	6.2	-	-	100%	50%
Conventional (Softening)	SOFT	23	18%	4.1	8.7	10.0	70%	43%
Disinfecting / GW	DIS/GW	63	50%	0.3	1.2	1.7	3%	0%
Other / GW	OTHER/GW	34	27%	0.9	2.3	3.4	12%	9%
Other	OTHER	4	3%	1.1	-	-	25%	0%
Total	**--**	**126**	**100%**	**1.3**	**3.4**	**6.8**	**20%**	**11%**

[1] If more than one TOC value was provided for a given month, EPA calculated the monthly average before calculating the yearly average (also to minimize seasonal bias).
[2] The one plant with the treatment plant type code of "MEMBRANE" was excluded. The "Conventional (Softening)" category includes plant type codes: CMPLX/SOFT, CS/SOFT, SOFT, SPLIT/SOFT and TS/SOFT.
[3] All GW plants were included in this analysis, not just those with at least 9 months of data.

Ground water plants that disinfect ("Disinfecting / GW") were the most common type of GW plant included in this dataset, representing approximately 50 percent of the GW plants. Other / GW plants, as well as conventional softening plants, were also common (approximately 27 percent and 18 percent, respectively).

Literature Information on Organic Precursor Occurrence

In addition to the DBP ICR and SYR3 ICR data, information is available about organic precursor data for individual and small groups of PWSs. For example, Potter and Wimsatt (2012) measured TOC, DOC, UV_{254} and SUVA in seven source waters in Ohio, California, Minnesota and Indiana to demonstrate compliance with quality control requirements and procedures outlined in the

approved Stage 2 D/DBPR method. The source water UV_{254} measurements of 0.0726 to 1.0507 cm^{-1} were similar to DBP ICR UV_{254} data that ranged from ND (non-detection) to 0.88 cm^{-1}. TOC measurements were in the same range as DBP ICR data with mean values ranging from 0.42 to 3.64 mg/L. Mean values for DOC ranged from 0.42 to 3.38 mg/L and the mean SUVA values ranged from 1.95 to 3.37 L/mg-m. It is unclear how many samples were collected for these source waters.

Selbes et al. (2015) studied nine different amino acids under different oxidation conditions and found that the presence of amino acids in source waters can contribute to the formation of some halogenated DBPs. However, amino acids in source waters were not determined to affect nitrogenous DBP formation.

Since the promulgation of the Stage 2 D/DBPR, studies have demonstrated that changing climate and weather conditions are contributing to changes in organic DBP precursor occurrence. For example, Samson et al. (2013) demonstrated a significant correlation between climate change variables (e.g., precipitation and temperature) and source water TOC levels using three case study utilities that exceeded monthly TOC thresholds. In the Rocky Mountains, the mountain pine beetle epidemic, which was sustained by warmer winter temperatures and drought conditions, caused large scale tree die-off in one million acres of pine forest and resulted in changes in organic precursors in drinking water sources (Mikkelson et al., 2013). Based on data collected from 2009 to 2011, Mikkelson et al. reported a mean TOC concentration of 2.7 mg/L in water samples from affected areas, compared to a mean TOC concentration of 0.62 mg/L in control watersheds. Researchers have also observed increased source water DOC levels downstream of watersheds impacted by wildfires, particularly during thunderstorms (Writer et al., 2014) and other periods of increased flow or an increased degree of disturbance (Emelko et al., 2013). Impacts on DBP precursors can, however, be mixed. In a controlled laboratory study, Majidzadeh et al. (2015) observed decreased chloroform formation but increased nitrogenous DBP formation after plant burns. In a controlled field study, Tsai et al. (2015) observed reductions in dissolved organic matter, THMs, HANs and chloral hydrate after burn. Within burned areas, the large loss of organic matter from the forest floor can reduce the available DBP precursors and associated DBP formation potential, as documented by Wang et al. (2015a).

6.2.2 Inorganic Precursors

6.2.2.1 Summary of Stage 1 and 2 D/DBPR Information

Inorganic precursors relevant to DBP formation include bromide and iodide. During development of the Stage 2 D/DBPR, EPA had occurrence information about bromide for large, medium and small systems. These data were available in the DBP ICR for large systems; for systems serving fewer than 100,000 people, data were available from the NRWA and ICR Supplemental Surveys. Summary-level information about the inorganic precursor data are included in Appendix B as well as presented in the Occurrence Document for the Stage 2 D/DBPR (USEPA, 2005l). Iodide was not measured as part of ICR monitoring; thus, national-level occurrence data for iodide was not reviewed during the development of the Stage 2 D/DBPR.

6.2.2.2 New Information since the Stage 2 D/DBPR

This section includes new information on the occurrence of bromide and iodide that has been identified since the Stage 2 D/DBPR was promulgated in 2006.

Bromide Occurrence and Influence on DBP Formation

Since the Stage 2 D/DBPR was promulgated, new information has become available both on the occurrence of bromide and how it influences DBP formation.

Several studies have indicated that both natural and man-made factors have contributed to increases in bromide in many source waters. Since the Stage 2 D/DBPR was promulgated, several studies have documented how wastewater from hydraulic fracturing activities can contribute to increased source water bromide concentrations. The research has primarily assessed high-total dissolved solids (TDS) wastewaters with elevated bromide concentrations that originate from the significantly increased natural gas production in the Marcellus Shale (mainly in Pennsylvania). Moreover, hydraulic fracturing operators in Pennsylvania have discontinued the practice of sending wastewater from hydraulic fracturing operations to wastewater treatment plants (States et al., 2013) and have been shifting towards treatment of those wastewaters for reuse rather than discharging to surface water bodies (Hammer and VanBriesen, 2012).

Recent findings demonstrated that upstream increases in bromide resulted in increased THM4 and HAA5 concentrations, leading some plants to exceed the Stage 2 MCLs (Hladik et al., 2014; Parker et al., 2014; States et al., 2013; Warner et al., 2013; McTigue et al., 2014; Xu et al., 2008). Most drinking water treatment plants are not designed to address high concentrations of TDS (which can include bromide and iodide), limiting their options for restricting the formation of brominated and iodinated DBPs. Tighter restrictions in Pennsylvania on TDS in effluent from wastewater treatment plants and centralized waste treatment facilities have led to a reduction in in-stream bromide concentrations (Wilson and Van Briesen, 2013).

New research shows that bromide in source water is also being affected by air quality regulations (e.g., Mercury and Air Toxic Standards; USEPA, 2011b) that are intended to reduce metals (including mercury), acid gases, particulates, nitrogen oxides and sulfur dioxide emissions from coal and oil-fired electrical generating units larger than 25 megawatts. McTigue et al. (2014) reported that the new regulations have led to an increase of the use of calcium bromide in power plant wet scrubbers. The bromide from the coal and coal additives is discharged to receiving streams along with the wet scrubber wastewater. McTigue et al. (2014) linked the Stage 2 D/DBPR violations at surface water treatment plants with upstream coal-fired power plants that had installed wet scrubbers. Of 96 water treatment plants evaluated, 17 have had DBP violations since the wet scrubbers were installed and 6 of the 17 had violations within 1 year of the scrubber installation. One power plant installed a wet scrubber in 2007 and led to a downstream WTP exceeding the THM4 MCL six times between 2008 and 2012. For this same water treatment plant, data for the period 2006 to 2013 demonstrated the increased concentration of bromoform and BDCM following installation of the wet scrubber.

Gruchlik et al. (2015) evaluated the impact of high bromide concentrations in Western Australian drinking water sources. A survey of bromide concentrations was conducted through their study,

in which they found concentrations ranging from 400 µg/L to 8,450 µg/L. Bromide occurred in both ground and surface water sources.

Increased bromide concentrations have been found to not only affect the amount of DBPs formed but also their speciation. New research supports the previous understanding that higher source water bromide leads to higher THM and HAA concentrations following chlorination (Yang and Shang, 2004; Hua et al., 2006; Matamoros et al., 2007; Reckhow et al., 2007; Navalon et al., 2008; Singer, 2010; Wert and Rosario-Ortiz, 2013). New studies have shown that bromide can increase DBP formation when disinfectants in addition to chlorine are used. Hu et al. (2010) reported that as source water bromide increased, THMs also increased when ozone was used followed by chlorine. Shah et al. (2012) concluded that NDMA formation can increase during disinfection with chloramine with high source water bromide concentrations (e.g., >500 µg/L). Regli et al. (2015) estimated increased THM levels as a function of hypothetical increased source water bromide levels. They estimated that on average across large plants in the United States, THM levels could increase by roughly 1 µg/L for every 10 µg/L bromide in source water, with increases varying greatly across plants depending on site-specific conditions.

In addition to increasing the amount of DBPs formed, new research supports the understanding that increased bromide causes a shift toward more brominated species (Reckhow et al., 2007; Obolensky and Singer, 2008; Pan and Zhang, 2012; Zha et al., 2014). As the bromine-to-chlorine ratio increases, Yang and Shang (2004) and Hua et al. (2006) showed that the bromine incorporation factor (i.e., the number of bromines substituted in each DBP) increases. High chlorine dose, lower temperature and shorter reaction times have been found to increase the amount of bromine incorporation into DBPs (Hua and Reckhow, 2012). Reckhow et al. (2007) found that bromine substitution relative to chlorine substitution is not uniform across all regulated and unregulated DBPs. Some DBPs form bromine-substituted forms more easily than others. Bromine substitution was highest with dihaloacetonitrile followed by THM and DHAA, with THAA having the least bromine substitution. Cornwell (2014) points out that because bromine is heavier than chlorine, the same number of molecules of DBPs will have higher mass concentrations as bromide increases. This could result in cases where plants near the THM4 and/or HAA5 MCL could exceed the MCL as DBPs shift to more brominated species with higher bromide source waters.

Increased bromide incorporation in DBPs can result in an increase in HAA9 (as described in Section 6.1.1) but result in no change or a decrease in the regulated group HAA5. Hua et al. (2006) found that while increased bromide led to an increase in total HAAs produced, it led to a slight decrease in the regulated HAA5. Reckhow et al. (2007) found that increasing bromide concentrations from 0 to 30 µmol/L led to a decrease in HAA5 but an increase in HAA9. The unregulated HAAs were a significant portion of HAA9 at 2 µmol/L bromide and were greater than the HAA5 contribution at 10 µmol/L bromide. Singer (2010) found that the bromine incorporation factor was similar between THMs and HAAs, but the HAA9 concentrations were significantly higher than HAA5, indicating a substantial influence of brominated HAAs.

A similar trend can occur for THMs. As described above, McTigue et al. (2014) observed a marked shift in speciation from chloroform to BrTHMs, sometimes resulting in THM4 levels above the MCL.

Iodide Occurrence and Influence on DBP Formation

Increased iodide can lead to iodinated DBPs (e.g., monoiodoacetic acid, iodobromoacetic acid, iodobromopropenoic acid and 2-iodo-3-methylbutenedioic acid) upon disinfection. A study (Gruchlik et al., 2015) on iodide in two Western Australian drinking water sources (ground and surface waters) was conducted to better understand the impact and occurrence of high concentrations of iodide in source waters. Concentrations of iodide were measured, ranging from 5 µg/L to 593 µg/L. In addition to inorganic iodide, organic iodine can also be a source of precursors. For instance, iodinated x-ray contrast media have also been found to be a potential precursor of iodinated DBPs. These iodinated media are non-toxic and are designed to pass through the body following the x-ray procedure. Iodinated x-ray contrast media are not well removed at wastewater treatment plants (Duirk et al., 2011). Laboratory experiments found that reactions between iopimadol (an iodinated x-ray contrast medium), chlorine or chloramine and NOM produced up to 212 nM (44.6 µg/L) dichloroiodomethane and up to 3 nM (558 ng/L) monoiodoacetic acid (Duirk et al., 2011).

Research has led to improved understanding of the reactions of disinfectants with iodide and other precursors to form iodinated DBPs. Compared to chlorine, chloramines appear to favor formation of iodinated DBPs (Hua and Reckhow, 2007; Kristiana et al., 2009; Criquet et al., 2012; Jones et al., 2012). Criquet et al. (2012) found that an increase in the bromide-to-iodide ratio in source water, as well as exposure to free chlorine and ammonia, reduced the formation of iodo-THMs in finished water. Hua et al. (2006) found that chlorine could oxidize iodine resulting in less iodine incorporation at higher doses. Under chlorination, higher iodide concentrations in source water can actually lead to lower TOX concentrations (Reckhow et al., 2007). Zha et al. (2014) observed an increase in HAA formation in the presence of iodide followed by a decrease in chlorinated and brominated HAA concentrations, indicating both an increased rate of HAA formation and a shift to more iodinated HAAs.

6.3 DBP Occurrence and Exposure

For the purposes of SYR3, EPA assessed the occurrence of regulated and unregulated DBPs. As was discussed previously, the main source of information was the SYR3 ICR dataset, which contains PWS compliance monitoring data for THMs, HAAs, bromate and chlorite from 2006 to 2011.

This section summarizes what was known at the time of the Stage 2 D/DBPR on organic and inorganic DBP occurrence, presents the results of new occurrence analyses using the SYR3 ICR data for regulated DBPs and discusses new occurrence information available for unregulated DBPs. EPA excluded all data in the SYR3 ICR dataset that did not pass through its general and analyte-specific QA/QC processes. See Appendix B for additional details on the QA/QC steps.

Compliance with the Stage 1 D/DBPR for systems monitoring for THM4 and HAA5 is based on a running annual average (RAA); the annual average of sample results for each treatment plant within a given system. A key finding that led to the development of the Stage 2 D/DBPR was that elevated concentrations of THM4 and/or HAA5 above the MCL were present at specific locations in distribution systems and not accurately reflected by plant-wide averages (USEPA, 2006a). Systems are required under the Stage 2 D/DBPR to report the RAA at each monitoring

location, also known as the locational running annual average (LRAA). Locations with elevated levels of DBP occurrence within treatment plants and distribution systems (e.g., maximum residence locations where organic matter has more time to react with disinfectants) were identified by the systems and the states in an initial distribution system evaluation (IDSE). Systems disinfecting with ozone or chlorine dioxide are required to monitor for bromate and chlorite, respectively. Compliance with the bromate MCL is based on monthly entry point monitoring and compliance with the chlorite MCL is based on daily entry point and monthly distribution system monitoring.

The timeframe of the SYR3 ICR data (2006 through 2011) covers post-Stage 1 D/DBPR occurrence. Compliance monitoring for the Stage 2 D/DBPR did not begin until 2012, or later, for some PWSs. As such, the SYR3 ICR dataset primarily reflects occurrence information for systems following the effective date of the Stage 1 D/DBPR, but prior to the effective date of the Stage 2 D/DBPR. However, some systems may have started to make operational adjustments in anticipation of the Stage 2 requirements before their respective compliance monitoring deadlines. In addition, for many small systems, the LRAA and RAA sampling locations will be identical (for example, for systems with only one sampling location in the distribution system). In these cases, the SYR3 ICR DBP dataset may be reflective of post-Stage 2 occurrence.

Exposure is characterized in the DBP analyses below by summing the population served by systems with detections ("Phase 1" analyses) and averages ("Phase 2" analyses) above thresholds of interest (i.e., minimum reporting levels (MRLs) and MCLs). The population served by water from distribution system locations in which DBP levels exceeded the thresholds mentioned above would be needed to more accurately estimate exposure; however, the population served associated with specific sampling locations is often difficult to know and is not reported along with other SYR3 ICR compliance monitoring records. Additionally, since non-community water systems are included in the estimates below, the population counts may not accurately represent the number of people who are served from non-community water systems (e.g., a campground) where the actual number of consumers may fluctuate over a given period of time. These caveats should be considered when reviewing the population information below, where further information on exposure estimates is included.

In a separate effort, the American Water Work Association (AWWA) (Samson, 2015), conducted a survey of post-Stage 2 D/DBPR occurrence for systems that serve more than 100,000 people. This survey provides a summary of the data they collected for approximately 400 systems across 44 states, covering a time period from 1980 to early 2015 (Samson, 2015).

6.3.1 Overview of DBP Inventory Analyses

The results of system and population inventory information of the entire SYR3 ICR DBP dataset in 2011 (the most recent and complete year of ICR data) are included below in Exhibit 6.16 through Exhibit 6.18. (Inventory information from all years of the SYR3 ICR dataset (2006-2011) is provided in Appendix B.) Exhibit 6.16 depicts the distribution of systems and population among the different system types and Exhibit 6.17 includes the same information but distributed based on source water type. The source types are split by ground water (includes purchasing systems), surface water (includes purchasing systems) and purchased and non-purchased GWUDI systems. Exhibit 6.18 depicts the distribution of systems and population by

both source water type and aggregated by population size. Overall, the results indicate that many of the systems represented in the dataset are very small ground water systems. Nearly all systems in the dataset are CWSs. These results are expected, based on the general system characteristics of those that are expected to comply with the DBP regulations.

Exhibit 6.16: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset (2011) with DBP Records, by System Type

Year	System Type	Systems		Population	
		Number	Percent	Number	Percent
2011	Community	17,484	81.3%	199,318,093	99.0%
	Non-transient Non-community	4,015	18.7%	1,917,482	1.0%
	Transient Non-community	8	0.0%	910	0.0%
	Unknown	0	0.0%	0	0.0%
	Total	**21,507**	**100.0%**	**201,236,485**	**100.0%**

Exhibit 6.17: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset (2011) with DBP Records, by Source Water Type

Year	Source Water Type	Systems		Population	
		Number	Percent	Number	Percent
2011	Ground Water	14,558	67.7%	52,559,785	26.1%
	GWUDI	380	1.8%	1,755,985	0.9%
	Surface Water	6,569	30.5%	146,920,715	73.0%
	Total	**21,507**	**100.0%**	**201,236,485**	**100.0%**

Exhibit 6.18: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset (2011) with DBP Records, by System Size and System Type

Year	System Size (Population Served by the System)	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
Community Water Systems							
2011	< 101	2,222	137,751	397	18,611	2,619	156,362
	101 – 500	3,267	836,532	932	265,835	4,199	1,102,367

Year	System Size (Population Served by the System)	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	501 – 1,000	1,342	996,958	643	487,084	1,985	1,484,042
	1,001 – 3,300	1,843	3,465,602	1,528	3,072,766	3,371	6,538,368
	3,301 – 10,000	1,186	6,812,788	1,369	8,369,480	2,555	15,182,268
	10,001 – 50,000	849	17,725,805	1,255	28,285,116	2,104	46,010,921
	50,001 – 100,000	119	7,876,457	228	15,813,961	347	23,690,418
	100,001 – 1 million	57	11,279,556	231	58,785,307	288	70,064,863
	> 1 million	1	2,100,000	15	32,988,484	16	35,088,484
	Total	**10,886**	**51,231,449**	**6,598**	**148,086,644**	**17,484**	**199,318,093**
Non-Community Water Systems							
2011	< 101	1,693	92,862	93	4,604	1,786	97,466
	101 – 500	1,370	339,302	136	33,874	1,506	373,176
	501 – 1,000	355	255,289	56	42,555	411	297,844
	1,001 – 3,300	219	368,505	45	82,485	264	450,990
	3,301 – 10,000	31	170,278	15	89,903	46	260,181
	10,001 – 50,000	4	102,100	4	61,297	8	163,397
	50,001 – 100,000	0	0	1	71,963	1	71,963
	100,001 – 1 million	0	0	1	203,375	1	203,375
	> 1 million	0	0	0	0	0	0
	Total	**3,672**	**1,328,336**	**351**	**590,056**	**4,023**	**1,918,392**

Note: There is one water system with data in 2006 and 2008 that has an unknown system type. That system is not counted in this table. In addition, GWUDI systems are included in SW and purchased systems are included in each category.

6.3.2 Regulated Organic DBPs

6.3.2.1 Summary of Stage 1 and 2 D/DBPR Information

The primary source of national-level occurrence data used for the Stage 1 and Stage 2 D/DBPRs was the DBP ICR dataset (as presented in the introduction). In addition to the information summarized below, an evaluation of the DBP ICR dataset, including THM4 and HAA5 occurrence information, is available in USEPA (2005l) and McGuire et al. (2002). Additional discussions related to the analyses in McGuire et al. (2002), as well as other sources of data (particularly for systems serving fewer than 100,000 people), are available in USEPA (2005l).

Chapter 4 of McGuire et al. (2002) (McGuire and Graziano, 2002) specifically discusses the occurrence of THMs in U.S. drinking water based on the DBP ICR dataset. Analyses of THM4 records, as well as records for the four individual species, are included, along with analyses of

variations in THM4 as a function of source water type, time of year, sampling location, treatment, geographical location and source water quality parameters like TOC and bromide. The results were used to estimate the Stage 1 baseline for the Stage 2 D/DBPR as described in the Stage 2 D/DBPR Economic Analysis (USEPA, 2005g).

Chapter 5 of McGuire et al. (2002) (Obolensky, 2002) discusses the occurrence of HAAs in U.S. drinking water based on the DBP ICR dataset. Unlike THMs, which have been the subject of research for decades, this was the first comprehensive resource on HAA occurrence at the national level. The chapter included results for the five species now regulated as part of HAA5, as well as four other unregulated HAA species.

Chapter 6 in McGuire et al. (2002) (McClain et al., 2002) included information about the impact of bromide on THM speciation. Overall, McClain et al. (2002) found that there was a shift to brominated species as the bromide influent concentration increased.

6.3.2.2 Analysis of SYR3 ICR THM/HAA Data

Occurrence information was collected for both THM4 and HAA5 as part of the SYR3 ICR, along with information for four individual species of THMs and five individual species of HAAs. The information is based on data submitted by 45 states for THMs and 44 states for HAAs, as well as several other primacy agencies, and represents systems of all sizes. Approximately 70 percent of the systems with SYR3 ICR THM data (about 29,500) submitted analytical results for THM4 and (4) individual THMs and approximately 74 percent of the systems with SYR3 ICR HAA data (around 25,000) submitted analytical results for HAA5 and all HAA5 species. After data management and quality checks on the dataset were conducted, approximately 2.3 million THM (including results for both THM4 and individual species) records and 1.9 million HAA (including results for both HAA5 and individual species) records from January 2006 to December 2011 were available.

It is important to note that both community and non-community water systems were included in all analyses (presented in this chapter) using the SYR3 ICR THM and HAA data.

Representativeness of SYR3 ICR THM and HAA Data

Inventory information and record counts for the SYR3 ICR data from 2006 to 2011 are presented in Appendix B. These analyses indicate that the SYR3 ICR data for THMs and HAAs are generally useful for informing an understanding of the national occurrence of those contaminants in drinking water. The datasets for THMs and HAAs both represent a large percentage of the total population served as compared to SDWIS 2011 data,[20] systems of various sizes and source water types and most geographical areas within the United States.

There were nearly 310,000 THM records reported in 2011 from CWSs, with the majority having been reported by surface water CWSs. More than 17,000 CWSs are included, of which about

[20] To evaluate the completeness of the SYR3 ICR DBP dataset, EPA compared the number of CWSs and their associated population served in each state that submitted trihalomethane and haloacetic acid data for the year 2011 to the number of active CWSs and their associated population served according EPA's SDWIS/Fed dataset in 2011. For more details on this comparison, refer to Appendix B.

two-thirds are GW systems. Overall, these systems serve close to 200 million people. When comparing the 2011 SDWIS inventory information with 2011 SYR3 inventory information for systems reporting THM data, the SYR3 total CWS count represents approximately 35 percent of the total SDWIS CWS count. Despite these differences, the population served by the SYR3 CWS that reported THM data in 2011 is approximately 67 percent of the entire retail population served by active SDWIS CWSs in 2011, indicating that the SYR3 ICR THM data encompasses a large portion of drinking water consumers. Note that although all SW systems must monitor for THM4 and HAA5, not all GW systems disinfect and non-disinfecting GW systems are not required to monitor for DBPs (though non-disinfecting GW systems were included in the total SDWIS CWS counts).

The HAA dataset is comparable with the THM dataset in terms of geographic areas, system sizes and system types represented. However, about 3,000 fewer CWSs reported HAAs than THMs in general; the difference came from ground water CWSs as the number of surface water CWSs reporting THM and HAA records in 2011 is very close. Even so, the population served by systems reporting HAA data makes up a large portion (approximately 60 percent) of the SDWIS population served by CWSs.

Without knowing the number of SDWIS systems that are required to monitor for DBPs, it is fair to conclude that the counts are likely biased in favor of SDWIS and that not all SDWIS systems are regulated under the Stage 1 and Stage 2 D/DBPRs. It is also important to note that some systems/states did provide THM and/or HAA data or their data did not pass the QA/QC review and are, therefore, not included in the inventory tables included in this chapter and the appendix (see Appendix B for more details on QA/QC processes). Notwithstanding, the SYR3 ICR THM and HAA datasets are highly comprehensive, represent a variety of system sizes and types and cover many geographic areas. Based on the outcomes of the inventory analyses, it is clear that the SYR3 ICR is one of the largest data sources available for THM and HAA compliance monitoring results.

The analyses presented below used the SYR3 ICR DBP dataset to assess the number of systems (and population served by those systems) with detections and averages above thresholds of interest (known as the Phase 1 and Phase 2 analyses, respectively – performed in the same manner as the Stage 1 and Stage 2 analyses for the chemical phase rules [see USEPA, 2016g for further information about occurrence analyses for the chemical phase rules]). Other analyses included below evaluate the differences in average DBP concentrations based on source water type and system size (cumulative distribution analyses).

Phase 1 - Comparisons of Individual Measurements Relative to the Minimum Reporting Level (MRL) and MCL

The Phase 1 analysis uses the SYR3 ICR data to identify only systems with detection records, which were compared to the MRL and MCL as analytical concentration thresholds. All non-detection records were excluded from the Phase 1 analyses. The number of systems with detections greater than the MRL and MCL varied by DBP group, with THM4 having a greater number of systems with detections above the thresholds than HAA5. As mentioned previously, the timeframe of the SYR3 ICR data corresponds to the period prior to full implementation of the Stage 2 D/DBPR. Thus, the Stage 1 D/DBPR, where THM4 and HAA5 compliance was

determined as an RAA of all samples for each treatment plant, was in effect. Since the Phase 1 analyses represent counts of systems with at least one detection greater than the MCL and not calculations of the RAA, detections above the MCL are not equivalent to violations of the MCL.

The population served is likely an overestimation of the true population exposed because of the way this estimate was derived. In this estimate, the entire retail population served by a system was counted, even if there was only one sample location where the concentration of THM4 or HAA5 was greater than 80 or 60 µg/L, respectively. In these cases, the true population exposed to such elevated concentrations would more appropriately be considered as those consumers associated with the specific sampling locations where the elevated levels were measured. However, the population served associated with specific sampling locations is often difficult to know and is not reported along with other SYR3 ICR compliance monitoring records. Given these constraints, this evaluation considered the total retail population as an upper-bound for potential exposure to these contaminants.

Exhibit 6.19 through Exhibit 6.22 below show the Phase 1 analyses relative to the MRL and MCL for THM4 and HAA5, respectively. The results are provided for each year of the SYR3 ICR data (2006–2011) and are split by ground water (includes purchasing systems) and surface water (includes purchasing and GWUDI systems). The number and percentage of systems with detections greater than or equal to the MRL (or MCL) and the population and percentage of the population served by those systems is presented.

Exhibit 6.19: SYR3 ICR Comparison of Individual THM4 Measurements to the MRL[1]

Year	Systems with at Least One Detection ≥ MRL (0.5 µg/L)						Population Served by Systems with at Least One Detection ≥ MRL (0.5 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	14,319	81.6%	7,619	71.2%	6,700	97.8%	177,017,643	96.0%	40,948,355	87.4%	136,069,288	98.9%
2007	16,670	75.1%	9,818	64.7%	6,852	97.6%	181,767,765	95.9%	45,563,542	87.2%	136,204,223	99.2%
2008	14,115	78.9%	7,484	67.3%	6,631	98.2%	184,748,156	96.8%	42,891,929	89.4%	141,856,227	99.3%
2009	14,717	83.1%	8,062	73.7%	6,655	98.1%	188,431,430	96.7%	43,683,995	90.7%	144,747,435	98.7%
2010	17,479	77.2%	10,759	68.2%	6,720	98.0%	188,438,743	95.7%	46,435,543	87.7%	142,003,200	98.6%
2011	14,286	80.2%	7,621	69.1%	6,665	98.4%	185,903,996	96.4%	42,948,738	89.0%	142,955,258	98.9%
Average	**15,264**	**79.4%**	**8,561**	**69.0%**	**6,704**	**98.0%**	**184,384,622**	**96.3%**	**43,745,350**	**88.6%**	**140,639,272**	**98.9%**

Note: Percentages are based on the total number of systems providing at least one record for THM4.
[1] Within the SYR3 ICR dataset, multiple MRLs were used for the THM4 data. However, the national modal MRL (i.e., mode of all state modal values) for THM4 was equal to 0.5 µg/L.

As shown in Exhibit 6.19, averaging across the yearly results shows that almost all surface water systems detected THM4 (approximately 98 percent), as did a majority of ground water systems (approximately 69 percent). The population served by those systems represented almost the entire population of systems that provided THM4 data; for surface water systems, the average

across all years is nearly 99 percent. The average percentage of all systems (both surface and ground water) with detections greater than the MRL is close to 80 percent, indicating that the majority of all systems that submitted THM4 data detected the analyte in any given year over the SYR3 ICR timeframe.

Exhibit 6.20: SYR3 ICR Comparison of Individual THM4 Measurements to the MCL (80 µg/L)

Year	Systems with at Least One Detection > MCL (80 µg/L)						Population Served by Systems with at Least One Detection > MCL (80 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	2,932	16.7%	652	6.1%	2,280	34.0%	59,662,823	32.4%	4,278,313	9.1%	55,384,510	40.3%
2007	2,958	13.3%	634	4.2%	2,324	33.9%	51,971,584	27.4%	4,398,346	8.4%	47,573,238	34.6%
2008	2,779	15.5%	555	5.0%	2,224	33.5%	52,505,549	27.5%	5,904,068	12.3%	46,601,481	32.6%
2009	2,583	14.6%	556	5.1%	2,027	30.5%	44,801,789	23.0%	5,568,723	11.6%	39,233,066	26.7%
2010	2,539	11.2%	579	3.7%	1,960	29.2%	51,097,106	25.9%	5,924,733	11.2%	45,172,373	31.4%
2011	2,419	13.6%	497	4.5%	1,922	28.4%	50,706,736	26.3%	3,742,539	7.8%	46,964,197	32.5%
Average	**2,702**	**14.2%**	**579**	**4.8%**	**2,123**	**31.6%**	**51,790,931**	**27.1%**	**4,969,454**	**10.1%**	**46,821,478**	**33.0%**

Note: Percentages are based on the total number of systems providing at least one record for THM4.

The Phase 1 analyses relative to the MCL for THM4 demonstrate that there is a larger percent of at least one-time detections above 80 µg/L in surface water systems than ground water systems; averaging across years, nearly 5 percent of ground water systems had at least one detection over the MCL as compared to approximately 32 percent of surface water systems across all years. By reviewing the results across the ICR time period, one can see that there have been slight reductions in the number of systems with detections greater than the MCL. This could be a result of a number of factors, including system treatment changes made to more easily comply with the Stage 1 D/DBPR and/or early system adjustments made in anticipation of more easily complying with the Stage 2 D/DBPR when that rule would become effective.

Exhibit 6.21: SYR3 ICR Comparison of Individual HAA5 Measurements to the MRL[1]

Year	Systems with at Least One Detection ≥ MRL (1 µg/L)						Population Served by Systems with at Least One Detection ≥ MRL (1 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	12,001	72.8%	5,711	57.9%	6,290	95.1%	156,393,504	91.2%	33,529,612	77.6%	122,863,892	95.7%
2007	12,823	62.7%	6,460	47.2%	6,363	94.1%	157,486,222	89.0%	34,061,983	70.9%	123,424,239	95.7%
2008	11,727	70.4%	5,481	54.1%	6,246	95.6%	162,606,241	91.0%	33,561,768	75.6%	129,044,473	96.1%
2009	12,323	74.8%	6,011	60.6%	6,312	96.3%	166,767,736	92.1%	34,953,708	79.7%	131,814,028	96.0%

Year	Systems with at Least One Detection ≥ MRL (1 µg/L)						Population Served by Systems with at Least One Detection ≥ MRL (1 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2010	13,558	64.9%	7,234	50.8%	6,324	95.3%	165,355,659	91.8%	35,222,970	73.0%	130,132,689	98.7%
2011	11,650	71.1%	5,377	54.7%	6,273	95.6%	163,206,005	93.1%	33,215,768	76.6%	129,990,237	98.5%
Average	**12,347**	**69.4%**	**6,046**	**54.2%**	**6,301**	**95.3%**	**161,969,228**	**91.4%**	**34,090,968**	**75.6%**	**127,878,260**	**96.8%**

Note: Percentages are based on the total number of systems providing at least one record for HAA5.

[1] Within the SYR3 ICR dataset, multiple MRLs were used for the HAA5 data. However, the national modal MRL (i.e., mode of all state modal values) for HAA5 was equal to 1 µg/L.

As demonstrated in Exhibit 6.21, averaging across years shows that almost all surface water systems (approximately 95 percent) had detections of HAA5, as did a majority of ground water systems (approximately 54 percent). The average across years shows that close to 70 percent of systems detected HAA5 in any given year. The total population served by both ground and surface water systems represented almost the entire population of systems that provided HAA5 data (approximately 91 percent).

Exhibit 6.22: SYR3 ICR Comparison of Individual HAA5 Measurements to the MCL (60 µg/L)

Year	Systems with at Least One Detection > MCL (60 µg/L)						Population Served by Systems with at Least One Detection > MCL (60 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	1,678	10.2%	284	2.9%	1,394	21.1%	35,687,934	20.8%	1,172,846	2.7%	34,515,088	26.9%
2007	1,741	8.5%	317	2.3%	1,424	21.1%	36,451,893	20.6%	1,326,211	2.8%	35,125,682	27.2%
2008	1,535	9.2%	239	2.4%	1,296	19.8%	34,983,415	19.6%	2,971,772	6.7%	32,011,643	23.8%
2009	1,491	9.0%	240	2.4%	1,251	19.1%	31,998,268	17.7%	3,098,387	7.1%	28,899,881	21.1%
2010	1,305	6.3%	213	1.5%	1,092	16.5%	29,866,868	16.6%	957,186	2.0%	28,909,682	21.9%
2011	1,151	7.0%	163	1.7%	988	15.0%	30,375,448	17.3%	2,773,616	6.4%	27,601,832	20.9%
Average	**1,484**	**8.4%**	**243**	**2.2%**	**1,241**	**18.8%**	**33,227,304**	**18.8%**	**2,050,003**	**4.6%**	**31,177,301**	**23.6%**

Note: Percentages are based on the total number of systems providing at least one record for HAA5.

As demonstrated in the Phase 1 analysis for THM4, HAA5 average results show that the amount of systems with detections greater than the MCL of 60 µg/L is more prevalent in surface water systems (approximately 19 percent) than ground water systems (approximately 2 percent). Additionally, a slight downward trend in population exposed can be observed for surface water systems (and less notably for ground water systems); in 2006 there were approximately 34.5 million people exposed to HAA5 levels above the MCL, greater than approximately 27.6 million people in 2011. Comparatively speaking, THM4 occurred in more systems and at higher levels than HAA5; on average, 1,200 more systems had detections above the MCLs for THM4 than for HAA5.

Phase 2 - Comparisons of Average THM4 and HAA5 Concentrations to the MCL

For Phase 2 analyses of THM4 and HAA5 data, EPA compared system mean concentrations to the respective MCLs. The Phase 2 analyses include systems with both detection and non-detection records; all non-detection records were set equal to zero for the calculation of system mean concentrations. The results of the Phase 2 analyses show similarities to the Phase 1 analyses, as the number of surface water systems with averages above the MCLs is greater than the number of GW systems. As with the Phase 1 analyses, the timeframe of the SYR3 ICR data corresponds to the Stage 1 D/DBPR, where compliance is determined as an RAA of all samples for each treatment plant. Since the Phase 2 analyses calculate system-wide averages, results should not be construed as compliance under the Stage 1 D/DBPR.

Exhibit 6.23 and Exhibit 6.24 below show the Phase 2 analyses compared to the MCL for THM4 and HAA5, respectively. The summary results are provided for each year of the SYR3 ICR dataset (2006–2011) and are split by ground water (includes purchasing systems) and surface water (includes purchasing surface water and GWUDI systems). The number and percentage of systems with average concentrations greater than the MCL and the population and percentage of the population served by those systems is presented.

Exhibit 6.23: SYR3 ICR Comparison of System Mean THM4 Measurements to the MCL (80 µg/L)

Year	Systems with Averages > MCL (80 µg/L)						Population Served by Systems with Averages > MCL (80 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	933	5.3%	308	2.9%	625	9.1%	2,347,404	1.3%	436,534	0.9%	1,910,870	1.4%
2007	931	4.2%	278	1.8%	653	9.3%	2,683,938	1.4%	476,678	0.9%	2,207,260	1.6%
2008	724	4.0%	223	2.0%	501	7.4%	1,981,252	1.0%	274,524	0.6%	1,706,728	1.2%
2009	619	3.5%	197	1.8%	422	6.2%	1,476,721	0.8%	315,561	0.7%	1,161,160	0.8%
2010	633	2.8%	246	1.6%	387	5.6%	1,381,043	0.7%	266,555	0.5%	1,114,488	0.8%
2011	560	3.1%	197	1.8%	363	5.4%	1,185,915	0.6%	273,336	0.6%	912,579	0.6%
Average	**733**	**3.8%**	**242**	**2.0%**	**492**	**7.2%**	**1,842,712**	**1.0%**	**340,531**	**0.7%**	**1,502,181**	**1.1%**

Note: Percentages are based on the total number of systems providing at least one record for THM4.
It is important to note that system-level averages above the MCLs are not equivalent to violations of the MCLs.

Overall, the THM4 Phase 2 averages across yearly results show that approximately 1 percent of the population of systems that reported THM4 in the SYR3 ICR dataset is served by a system with an average THM4 concentration greater than 80 µg/L. There are a greater percentage of surface water systems (approximately 7 percent) that had averages greater than the MCL than GW systems (approximately 2 percent). Population exposure estimates indicate that there are slight downward trends in the population served with high THM4 levels for both ground water and surface water systems.

Exhibit 6.24: SYR3 ICR Comparison of System Mean HAA5 Measurements to the MCL (60 µg/L)

Year	Systems with Averages > MCL (60 µg/L)						Population Served by Systems with Averages > MCL (60 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	520	3.2%	145	1.5%	375	5.7%	1,257,533	0.7%	151,190	0.3%	1,106,343	0.9%
2007	494	2.4%	153	1.1%	341	5.0%	1,485,755	0.8%	119,015	0.2%	1,366,740	1.1%
2008	378	2.3%	109	1.1%	269	4.1%	826,524	0.5%	85,383	0.2%	741,141	0.6%
2009	327	2.0%	91	0.9%	236	3.6%	767,476	0.4%	81,778	0.2%	685,698	0.5%
2010	274	1.3%	92	0.6%	182	2.7%	708,673	0.4%	98,900	0.2%	609,773	0.5%
2011	216	1.3%	65	0.7%	151	2.3%	1,674,622	1.0%	99,559	0.2%	1,575,063	1.2%
Average	**368**	**2.1%**	**109**	**1.0%**	**259**	**3.9%**	**1,120,097**	**0.6%**	**105,971**	**0.2%**	**1,014,126**	**0.8%**

Note: Percentages are based on the total number of systems providing at least one record for HAA5.
It is important to note that system-level averages above the MCLs are not equivalent to violations of the MCLs.

The Phase 2 averages across yearly results for HAA5 show that the number of ground water systems with averages greater than the MCL of 60 µg/L decreased from 145 systems in 2006 to 65 systems in 2011. Similarly, the number of surface water systems with averages greater than the MCL decreased from 375 systems in 2006 to 151 systems in 2011. However, despite the reductions in the number of systems with averages above the MCL, there is variation across years in the population served by systems with averages above the MCL (the total population served by systems with detections greater than the MCL ranged from 708,673 in 2010 to 1,674,622 in 2011). Interestingly, the population served by systems with average concentrations of HAA5 greater than the MCL is less than the ground water, surface water and total categories than the population served by systems with average concentrations of THM4 greater than the MCL. This indicates that overall exposure from drinking water above the MCLs may not be the same for both groups of regulated organic DBPs.

The Phase 2 analyses indicate that THM4 and HAA5 average concentrations are above the MCLs in some systems, but in general are dropping over time. It is important to note that system-level detections and averages above the MCLs are not equivalent to violations of the MCLs.

Cumulative Distributions of Average Concentrations for THM4 and HAA5

Using the SYR3 ICR THM4 and HAA5 data, EPA compared the occurrence of the regulated DBP groups in systems of different sizes and source water types, using the monitoring records from 2011, the most complete and recent year reflected in the SYR3 ICR DBP dataset. In this analysis, an average THM4 and HAA5 concentration was calculated for each system for the calendar year of 2011. Summary results are presented in Exhibit 6.25 for THM4 and Exhibit 6.26 for HAA5. Cumulative distributions of the average concentration per system are presented in

Exhibit 6.27 for THM4 and Exhibit 6.28 for HAA5. As with the Phase 2 analyses, EPA substituted non-detections with zero for the calculation of system mean concentration.

The resulting curves indicate that average concentrations for THM4 and HAA5 in several ground water systems are less than those in surface water systems. For example, the THM4 cumulative distribution plot demonstrates that approximately 50 percent of surface water systems serving less than or equal to 10,000 people have THM4 average concentrations below 42 µg/L. In contrast, 50 percent of ground water systems in this same size category people have average THM4 concentrations below 5 µg/L. Average HAA5 concentrations at this size category are lower; for example, about 50 percent of surface water systems serving less than or equal to 10,000 people have average HAA5 concentrations that approximately fall below 25 µg/L. About 50 percent of ground water systems in this same size category have averages around 2 µg/L.

Exhibit 6.25: System Means from the SYR3 ICR THM4 Data (2011)

System Size	Year	Count of Systems	Mean	90%ile	95%ile	% System Means > 80 µg/L
Ground Water Systems						
<=10,000	2011	10,052	14.5	44.4	61.6	1.9%
>10,000	2011	982	17.6	46.8	57.4	0.3%
Surface Water Systems						
<=10,000	2011	5,067	43.58	73.0	85.6	6.9%
>10,000	2011	1,707	35.23	58.9	65.2	0.9%

Exhibit 6.26: System Means from the SYR3 ICR HAA5 Data (2011)

System Size	Year	Count of Systems	Mean	90%ile	95%ile	% System Means > 60 µg/L
Ground Water Systems						
<=10,000	2011	8,931	6.4	17.5	29.5	0.7%
>10,000	2011	899	7.2	21.8	28.3	0.2%
Surface Water Systems						
<=10,000	2011	4,943	23.7	44.0	52.6	2.7%
>10,000	2011	1,622	21.1	38.8	46.0	1.0%

Exhibit 6.27: SYR3 ICR Data Showing Cumulative Distribution of System Mean Concentrations for THM4 by System Size and Source Water Type (2011)

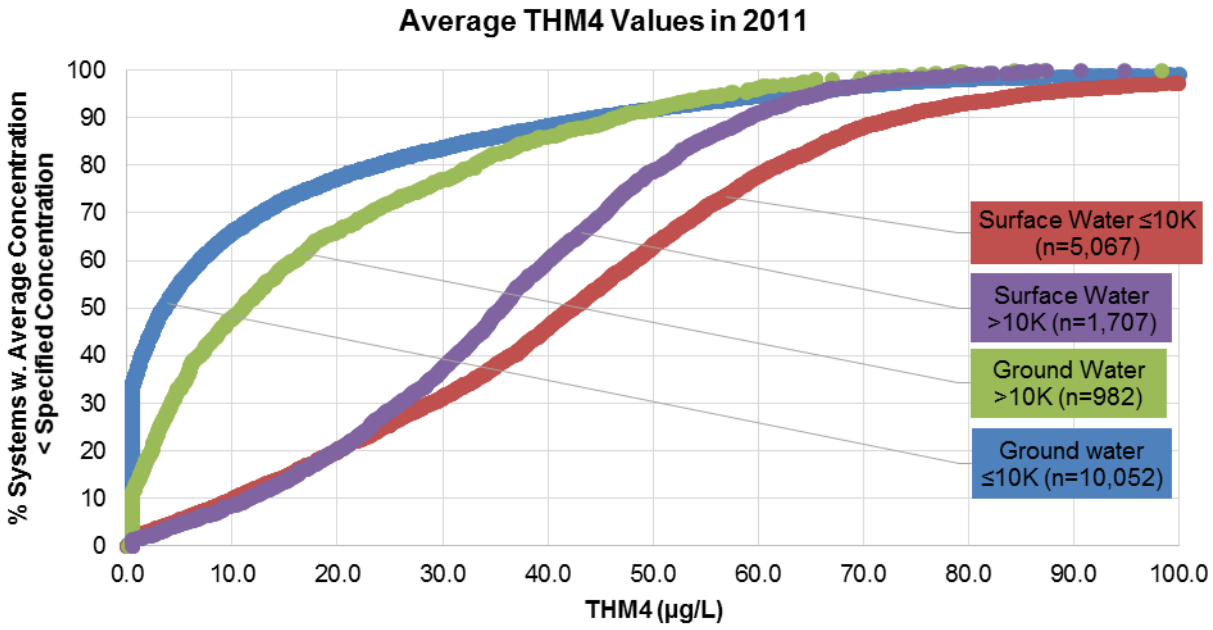
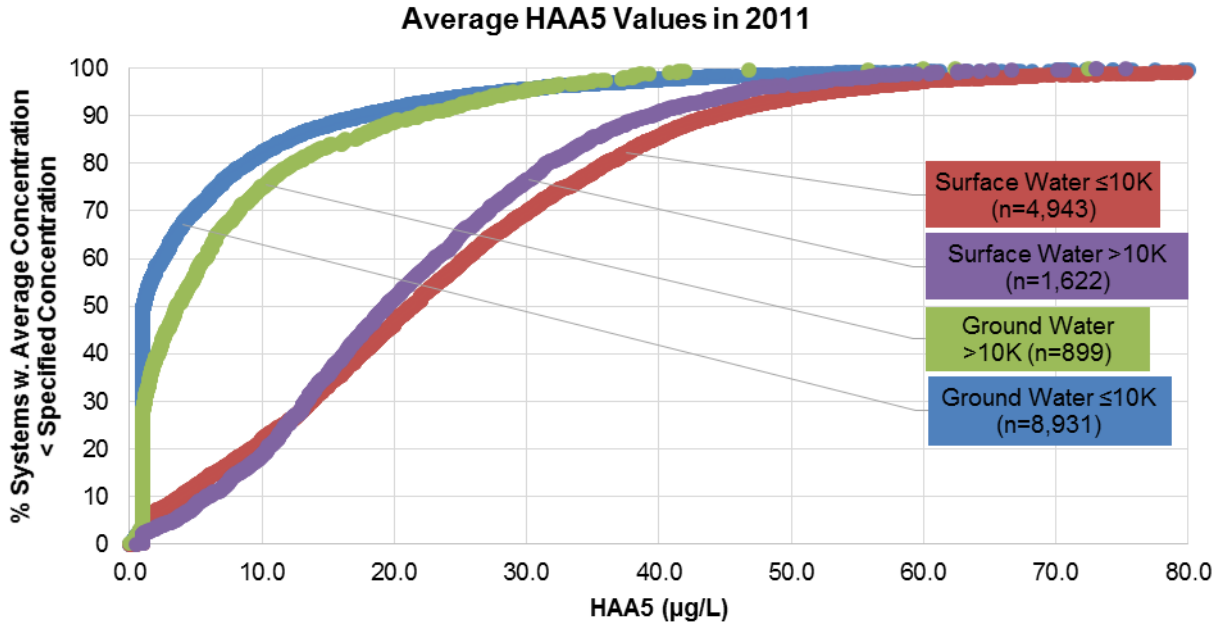


Exhibit 6.28: SYR3 ICR Data Showing Cumulative Distribution of System Mean Concentrations for HAA5 by System Size and Source Water Type in 2011



The differences between the surface water and ground water system mean concentrations could have resulted from a variety of factors, such as influent water quality. Given that systems using ground water tend to have lower TOC levels than systems using surface water (as demonstrated

by DBP ICR TOC data presented in Section 6.2), these figures further support the understanding that higher levels of precursors can, in general, result in greater levels of DBPs.

Effects from Stage 2 D/DBPR

While the SYR3 ICR did not collect information about post-Stage 2 D/DBPR occurrence, EPA believes that the DBP occurrence estimates for THM4 and HAA5 presented in this document can be expected to drop for those systems needing to make treatment changes to comply with the Stage 2 D/DBPR. Samson (2015) is collecting information pertaining to post-Stage 2 D/DBPR compliance. Samson is focused on collecting post-Stage 2 D/DBPR regulated DBP occurrence information from systems serving more than 100,000 people. The data collected through this project and resulting analyses may be able to serve as a comparison with the DBP ICR data from pre-Stage 1 D/DBPR and the post-Stage 1 D/DBPR time period using the SYR3 ICR data. Such a comparative analysis would need to consider the effects of different sampling locations required under the Stage 2 D/DBPR.

6.3.3 Regulated Inorganic DBPs

This section summarizes occurrence and exposure information for bromate and chlorite, which are the inorganic DBPs regulated under the Stage 1 D/DBPR. Systems were required to comply with the regulations under the Stage 1 D/DBPR by 2004, so the timeframe in the SYR3 ICR dataset (2006 through 2011) covers the post-Stage 1 D/DBPR occurrence.

Routine monitoring requirements for bromate require both community and non-transient non-community water systems (NTNCWSs) using ozone for disinfection or oxidation to take one sample per month at the entry point to the distribution system for each treatment plant using ozone. A system is in violation of the bromate MCL if the average of samples covering any consecutive four quarter period exceeds 10 µg/L. Additionally, community and non-community (includes non-transient non-community and transient non-community) water systems using chlorine dioxide for disinfection or oxidation must monitor for chlorite daily at the entrance to the distribution system as well as monthly in the distribution system. For any daily sample that exceeds the chlorite MCL, the system must take additional samples in the distribution system the following day. A system that has an average of any three sample sets exceeding 1,000 µg/L is in violation of the chlorite MCL. Further information on the Stage 1 D/DBPR requirements for these contaminants is available in Chapter 3.

6.3.3.1 Summary of Stage 1 and 2 D/DBPR Information

The DBP ICR dataset contains occurrence information on bromate and chlorite occurrence and analyses of the data are available in McGuire et al. (2002) and USEPA (2005l).

Chapter 9 of McGuire et al. (2002) (Moll and Krasner, 2002) specifically discusses the occurrence of bromate in U.S. drinking water among systems using ozone and includes the results from the DBP ICR survey. Correlations between bromate concentrations and other parameters, such as ozone contact time, were analyzed, but no association was found. Moll and Krasner (2002) also discussed other surveys that examined bromate occurrence levels. One study in particular included a utility that also participated in the DBP ICR and Moll and Krasner (2002)

found that source water bromide loading appeared to be a significant contributor to the occurrence of bromate in finished water samples among systems using ozone.

6.3.3.2 Analysis of SYR3 ICR Bromate and Chlorite Data

Occurrence information was collected for both bromate and chlorite as part of the SYR3 ICR and consists of data from 29 states for bromate and 28 states for chlorite, as well as from other primacy agencies, and represents systems of all sizes. After data management and quality checks on the dataset were conducted, approximately 8,900 bromate records and 26,000 chlorite records from January 2006 to December 2011 were available. As mentioned earlier in the chapter, all information on contaminant-specific QA/QC steps is provided in Appendix B.

The SYR3 ICR data are illustrative of bromate and chlorite occurrence following implementation of the Stage 1 D/DBPR. Note that the methods used to calculate compliance for bromate and chlorite did not change with the Stage 2 D/DBPR. Thus, although post-Stage 2 bromate and chlorite occurrence data are not currently available, EPA believes that any changes in occurrence due to implementation of the Stage 2 D/DBPR may not be significant.

Representativeness of SYR3 ICR Bromate and Chlorite Data

Inventory information (i.e., the number of records, the number of systems with data and the population served by those systems) of SYR3 ICR bromate and chlorite data from 2006-2011 are presented in Appendix B.

An important consideration for understanding the representativeness of the SYR3 ICR bromate and chlorite data is the monitoring requirements for both analytes. As mentioned previously (background information on the Stage 1 and Stage 2 D/DBPRs in Chapter 3), systems are only required to monitor for bromate or chlorite if they disinfect using ozone or chlorine dioxide, respectively. Overall, the percentage of systems using these two disinfectants in the United States is unknown but thought to be small. Through the Stage 2 D/DBPR Economic Analysis (USEPA, 2005g), EPA predicted baseline pre-and-post D/DBPR conditions and projected that the majority of plants would disinfect using free chlorine or chloramines, with far fewer plants disinfecting with ozone or chlorine dioxide. Additionally, EPA summarized the use of disinfectants using UCMR 3 data for entry points and maximum residence time locations (presented earlier in Section 6.1), the results of which can be characterized as post-Stage 2 D/DBPR conditions, as the monitoring took place from January 2013 to December 2015.[21] Using the UCMR 3 data, EPA found that disinfectant usage varied across source water type and system size; with a range of 0.2 to 14.8 percent of entry points using ozone and between 0.4 and 10.3 percent of entry points using chlorine dioxide. It is important to note that although systems that disinfect with chlorine dioxide and ozone must monitor for chlorite and bromate, respectively, the disinfectant usage for the systems that reported these data below is unknown.

[21] UCMR 3 monitoring was scheduled to occur from January 2013 through December of 2015. Some monitoring data continued to be reported to EPA through 2016. The UCMR 3 occurrence analyses presented in this report are based on data collected through May 2016 (released online in July 2016). The complete dataset is anticipated to become available in early 2017.

Compared to THMs and HAAs, there are fewer bromate records because only systems that use ozone as a primary disinfectant are required to monitor for bromate. Altogether, there are 8,884 bromate records, with more than 7,000 records from surface water systems. Over 200 systems are represented, of which about two-thirds are surface water systems. More than 23 million people are served water by these systems, almost all of them from surface water systems. All analyses using bromate data evaluated records at both entry point and distribution system locations. Approximately 46 percent of the bromate records that passed QA/QC procedures are samples taken within distribution system locations. Although systems disinfecting with ozone are not federally required to monitor for bromate in distribution system locations, EPA chose to include these records in analyses due to the large percentage of distribution system samples and the possibility that some states may require distribution system monitoring for bromate.

There are fewer chlorite records (compared to THM and HAA records) because only systems that use chlorine dioxide as a primary disinfectant are required to monitor for chlorite. Altogether, there are almost 26,000 chlorite records, with the vast majority of records from surface water systems. Over 200 systems are represented, of which almost 90 percent are surface water. Over 13 million people are served water by these systems, almost entirely from surface water systems. The chlorite dataset and analyses within this document contain records from both entry point and distribution system monitoring locations. Overall, these results are similar to those for bromate and indicate that the systems that provided chlorite data for the SYR3 ICR are almost entirely surface water systems.

Taking the proportion of systems that use alternative disinfectants into account, EPA expects that far fewer systems would report bromate and chlorite records as opposed to their organic counterparts. This is consistent with the results of the inventory analyses for bromate and chlorite throughout all years of the SYR3 ICR data.

Analysis Background

Similar types of inventory and occurrence analyses (except for cumulative distribution and highest concentration analyses) were conducted for bromate and chlorite as for the organic DBPs (discussed in Section 6.3.2.2).

Phase 1 - Comparisons of Individual Measurements Relative to the MRL and MCL

The Phase 1 analyses for regulated inorganic DBPs follow the same methodology as the Phase 1 analyses for regulated organic DBPs presented earlier. Exhibit 6.29 through Exhibit 6.32 below show the Phase 1 analysis relative to the MRL and MCL for bromate and chlorite, respectively. The results are provided for each year covered by the SYR3 ICR dataset and are split by ground water (includes purchasing systems) and surface water (includes purchasing and GWUDI systems). The number and percentage of systems with detections greater than or equal to the MRL (or greater than the MCL) and the population and percentage of the population served by those systems are presented.

The population served may be an overestimation of the true population exposed at a given time because of the way this estimate was derived. In this estimate, the retail population served by a system was counted, even if there was only one sample location where the concentration of

bromate or chlorite was greater than 10 or 1,000 µg/L, respectively. To the extent that bromate concentration at the tap is conserved throughout the system (which is assumed for the regulation with no distribution sampling required), occurrence at the tap should generally reflect occurrence within the distribution system. However, exceptions to this generalization apply such as a system blending its distribution system water from multiple plants, not all of which may be using ozone. Regarding chlorite, systems using chlorine dioxide must monitor daily and if only one of such measurements exceeds the MRL and MCL, the total population served by that system would be counted in Exhibit 6.31 and Exhibit 6.32, respectively. Also, for chlorite, the concentration measured at a given location may be greater or less if measured at point-of-entry or within the distribution system at different locations due to chemical reactions that can occur.

Exhibit 6.29: SYR3 ICR Comparison of Individual Bromate Measurements to the MRL[1]

Year	Systems with at Least One Detection ≥ MRL (5 µg/L)						Population Served by Systems with at Least One Detection ≥ MRL (5 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	38	33.0%	7	26.9%	31	34.8%	2,006,305	28.9%	8,359	5.5%	1,997,946	29.5%
2007	28	22.8%	7	25.9%	21	21.9%	6,363,954	45.9%	7,200	9.7%	6,356,754	46.1%
2008	48	31.6%	14	30.4%	34	32.1%	8,249,902	45.2%	12,653	12.1%	8,237,249	45.4%
2009	55	36.2%	13	34.2%	42	36.8%	9,137,433	47.3%	20,179	16.3%	9,117,254	47.5%
2010	62	41.3%	12	30.8%	50	45.0%	10,159,216	62.7%	19,839	12.4%	10,139,377	63.2%
2011	57	38.5%	15	36.6%	42	39.3%	12,985,200	61.5%	34,085	28.3%	12,951,115	61.6%
Average	**48**	**33.9%**	**11**	**30.8%**	**37**	**35.0%**	**8,150,335**	**48.6%**	**17,053**	**14.0%**	**8,133,283**	**48.9%**

Note: Percentages are based on the total number of systems providing at least one record for bromate.

[1] Within the SYR3 ICR dataset, multiple MRLs were used for the bromate data. However, the national modal MRL (i.e., mode of all state modal values) for bromate was equal to 5 µg/L.

Exhibit 6.30: SYR3 ICR Comparison of Individual Bromate Measurements to the MCL (10 µg/L)

Year	Systems with at Least One Detection > MCL (10 µg/L)						Population Served by Systems with at Least One Detection > MCL (10 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	15	13.0%	5	19.2%	10	11.2%	661,798	9.5%	2,489	1.6%	659,309	9.7%
2007	9	7.3%	3	11.1%	6	6.3%	511,583	3.7%	935	1.3%	510,648	3.7%
2008	13	8.6%	6	13.0%	7	6.6%	1,589,208	8.7%	2,314	2.2%	1,586,894	8.7%
2009	16	10.5%	4	10.5%	12	10.5%	5,189,830	26.8%	1,230	1.0%	5,188,600	27.0%
2010	9	6.0%	2	5.1%	7	6.3%	2,396,741	14.8%	1,170	0.7%	2,395,571	14.9%

Year	Systems with at Least One Detection > MCL (10 µg/L)						Population Served by Systems with at Least One Detection > MCL (10 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2011	14	9.5%	9	22.0%	5	4.7%	498,547	2.4%	9,415	7.8%	489,132	2.3%
Average	**13**	**9.1%**	**5**	**13.5%**	**8**	**7.6%**	**1,807,951**	**11.0%**	**2,926**	**2.4%**	**1,805,026**	**11.1%**

Note: Percentages are based on the total number of systems providing at least one record for bromate.

Exhibit 6.31: SYR3 ICR Comparison of Individual Chlorite Measurements to the MRL[1]

Year	Systems with at Least One Detection ≥ MRL (20 µg/L)						Population Served by Systems with at Least One Detection ≥ MRL (20 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	93	90.3%	4	80.0%	89	90.8%	3,228,368	81.4%	63,841	56.1%	3,164,527	82.2%
2007	94	88.7%	5	71.4%	89	89.9%	3,135,052	56.1%	82,506	61.7%	3,052,546	56.0%
2008	103	77.4%	8	47.1%	95	81.9%	5,141,427	59.6%	89,445	61.7%	5,051,982	59.6%
2009	124	85.5%	7	87.5%	117	85.4%	5,506,619	77.5%	90,414	100.0%	5,416,205	77.2%
2010	133	89.3%	7	77.8%	126	90.0%	6,378,381	76.8%	63,377	98.8%	6,315,004	76.6%
2011	148	90.8%	7	77.8%	141	91.6%	7,514,795	82.4%	94,459	97.0%	7,420,336	82.3%
Average	**116**	**87.0%**	**6**	**73.6%**	**110**	**88.3%**	**5,150,774**	**72.3%**	**80,674**	**79.2%**	**5,070,100**	**72.3%**

Note: Percentages are based on the total number of systems providing at least one record for chlorite.
[1] Within the SYR3 ICR dataset, multiple MRLs were used for the chlorite data. However, the national modal MRL (i.e., mode of all state modal values) for chlorite was equal to 20 µg/L.

Exhibit 6.32: SYR3 ICR Comparison of Individual Chlorite Measurements to the MCL (1,000 µg/L)

Year	Systems with at Least One Detection > MCL (1,000 µg/L)						Population Served by Systems with at Least One Detection > MCL (1,000 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	3	2.9%	0	0.0%	3	3.1%	174,198	4.4%	0	0.0%	174,198	4.5%
2007	4	3.8%	1	14.3%	3	3.0%	67,132	1.2%	178	0.1%	66,954	1.2%
2008	5	3.8%	0	0.0%	5	4.3%	156,392	1.8%	0	0.0%	156,392	1.8%
2009	7	4.8%	0	0.0%	7	5.1%	230,807	3.2%	0	0.0%	230,807	3.3%
2010	8	5.4%	0	0.0%	8	5.7%	284,914	3.4%	0	0.0%	284,914	3.5%
2011	10	6.1%	0	0.0%	10	6.5%	114,129	1.3%	0	0.0%	114,129	1.3%
Average	**6**	**4.5%**	**0**	**2.4%**	**6**	**4.6%**	**171,262**	**2.6%**	**30**	**0.0%**	**171,232**	**2.6%**

Note: Percentages are based on the total number of systems providing at least one record for chlorite.

The Phase 1 analyses for the regulated inorganic DBPs indicate that the average population (across all years from 2006-2011) served by systems with detections greater than the MCL for bromate (approximately 1.8 million) was significantly greater than the average population served by systems with detections above the MCL for chlorite (approximately 171,262). This is likely because the systems that use ozone to disinfect have a larger population (approximately 23.2 million) than the population served by systems that use chlorine dioxide (approximately 13.5 million), as demonstrated by the inventory tables. For the Stage 1 D/DBPR, compliance is determined based on an average of samples for each treatment plant. Since the Phase 1 analyses represent counts of systems with at least one detection above the MCL rather than counts of system averages, they should not be used to estimate compliance with the Stage 1 D/DBPR.

Phase 2 - Comparisons of Average Measurements to the MCL

The Phase 2 analysis for bromate follows the same methodology as the Phase 2 analyses for regulated organic DBPs, as presented in Section 6.3.2.2. Exhibit 6.33 below shows the Phase 2 analysis relative to the MCL for bromate. The results are provided for each year of the SYR3 ICR data and are split by ground water (includes purchasing systems) and surface water (includes purchasing and GWUDI systems). The table presents the number and percentage of systems with system means greater than the MCL and the population and percentage of the population served by those systems.

Exhibit 6.33: SYR3 ICR Comparison of System Mean Bromate Measurements to the MCL (10 µg/L)

Year	Systems with Average > MCL (10 µg/L)						Population Served by Systems with Average > MCL (10 µg/L)					
	Total		Ground Water		Surface Water		Total		Ground Water		Surface Water	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
2006	4	3.5%	3	11.5%	1	1.1%	10,392	0.1%	2,300	1.5%	8,092	0.1%
2007	2	1.6%	2	7.4%	0	0.0%	135	0.0%	135	0.2%	0	0.0%
2008	2	1.3%	2	4.3%	0	0.0%	137	0.0%	137	0.1%	0	0.0%
2009	2	1.3%	2	5.3%	0	0.0%	80	0.0%	80	0.1%	0	0.0%
2010	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
2011	3	2.0%	3	7.3%	0	0.0%	150	0.0%	150	0.1%	0	0.0%
Average	**2**	**1.6%**	**2**	**6.0%**	**0**	**0.2%**	**1,816**	**0.0%**	**467**	**0.3%**	**1,349**	**0.0%**

Note: Percentages are based on the total number of systems providing at least one record for bromate.

The results of the Phase 2 analysis for bromate shows that very few systems have average concentrations above the MCL across all years of the SYR3 ICR dataset and that, relative to the MCL, there is a lower risk of exposure than for organic DBPs. As described above for the Phase 1 analyses, compliance with bromate and chlorite MCLs under the Stage 1 D/DBPR is determined as an average concentration for each treatment plant. Since the Phase 2 analyses calculate system means, results should not be considered indicative of compliance under the Stage 1 D/DBPR.

Overall, the available new occurrence information for bromate and chlorite indicates that the contaminants do occur at PWSs that have to monitor for them and detections above the MCL occur as well. The Phase 2 analyses indicate that very few, if any, systems experienced prolonged levels of bromate or chlorite above the MCL. Again, these occurrence estimates should not be construed as indicative of compliance with the Stage 1 and 2 D/DBPRs.

6.3.4 Additional Considerations

EPA understands that the regulated contaminants represent only a portion of the entire universe of DBPs and serve as proxies for the many other unregulated DBPs. Since the Stage 1 and 2 D/DBPRs, new information has become available on the relative toxicity (see Chapter 4) and occurrence of some unregulated DBPs, including brominated and iodinated species, chlorate, nitrogenous DBPs and halobenzoquinones.

6.3.4.1 Chlorate

Similar to nitrosamines, chlorate was included on CCL 3 and evaluated as part of Regulatory Determinations for CCL 3. Occurrence data for chlorate were collected as part of UCMR 3, which took place from 2013 through 2015. Detailed information on the occurrence analyses conducted using UCMR 3 data are available in the *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e).

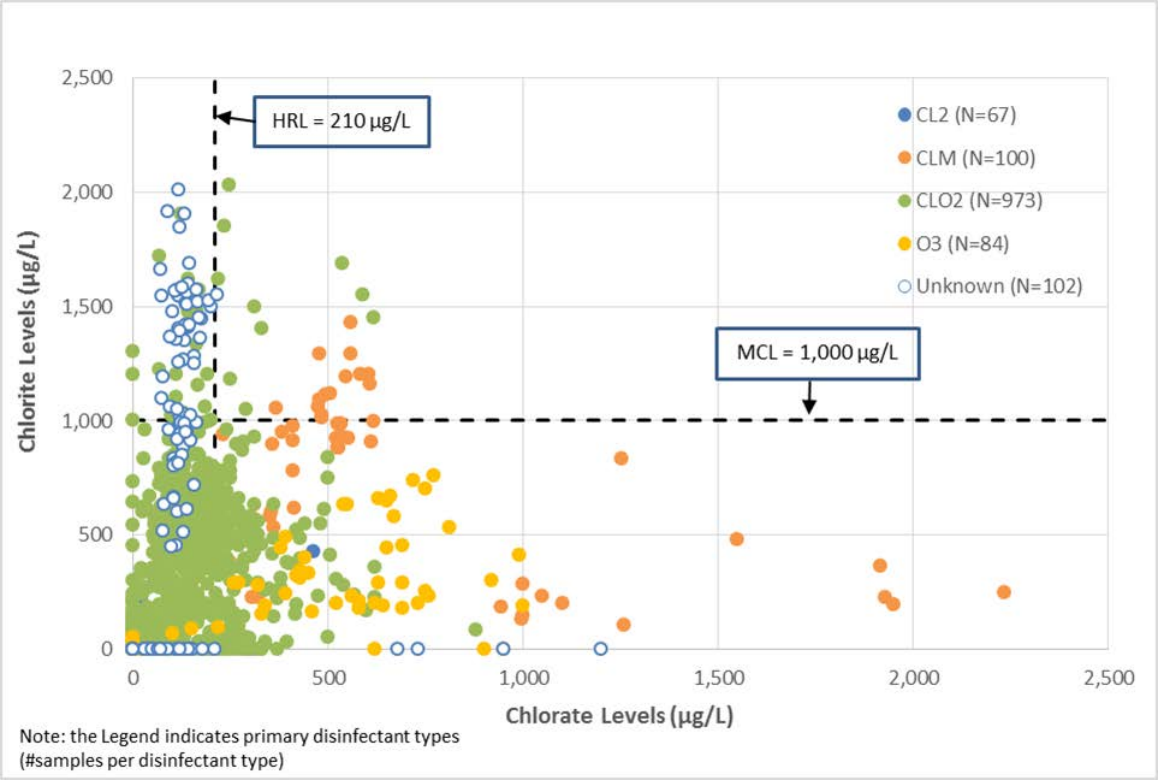
Chlorate and chlorite are two different oxidation states of chlorine and are chemically inter-convertible in water. While the potential common health effects of chlorate and chlorite are discussed in Chapter 4, the co-occurrence of chlorate and chlorite in U.S. drinking water is discussed in this section.

The data sources used to evaluate co-occurrence of chlorate and chlorite include: DBP ICR, the Environmental Working Group (EWG) National Drinking Water Dataset and UCMR 3 data for chlorate and SYR3 ICR data for chlorite.

DBP ICR

Under the DBP ICR, all systems serving 100,000 or more people and using chlorine dioxide or hypochlorite solution were required to monitor chlorite and chlorate in finished water on a monthly basis between January 1997 and June 1998 (USEPA, 2000e; McGuire et al., 2002). The resulting dataset includes data from systems with a variety of primary disinfectants. EPA used the dataset to extract 1,326 paired sets of monthly chlorite and chlorate monitoring results. The samples in each pair were taken at the same time and at the same location, either at the entry point to the distribution system or at a location in distribution system. A plot of the contaminant concentrations in the paired samples, grouped by primary disinfectant type, is shown in Exhibit 6.34. In this analysis, non-detections are assigned a value of zero.

Exhibit 6.34: DBP ICR Data: Paired Monitoring Results for Chlorate and Chlorite



The results show that there was simultaneous exceedance of the lowest chlorate Health Reference Level (HRL) of 210 µg/L and the chlorite MCL of 1,000 µg/L at systems using chloramines (in many cases presumably formed with use of hypochlorite solution) and systems using chlorine dioxide. Note that an HRL is defined as a risk derived concentration against which to compare the occurrence data from PWSs to determine if chlorate occurs with a frequency and at levels of public health concern. Chlorate and chlorite also co-occurred at relatively high levels (above the chlorate HRL of 210 µg/L and above one half the chlorite MCL or greater than 500 µg/L) when ozone was used as the primary disinfectant.

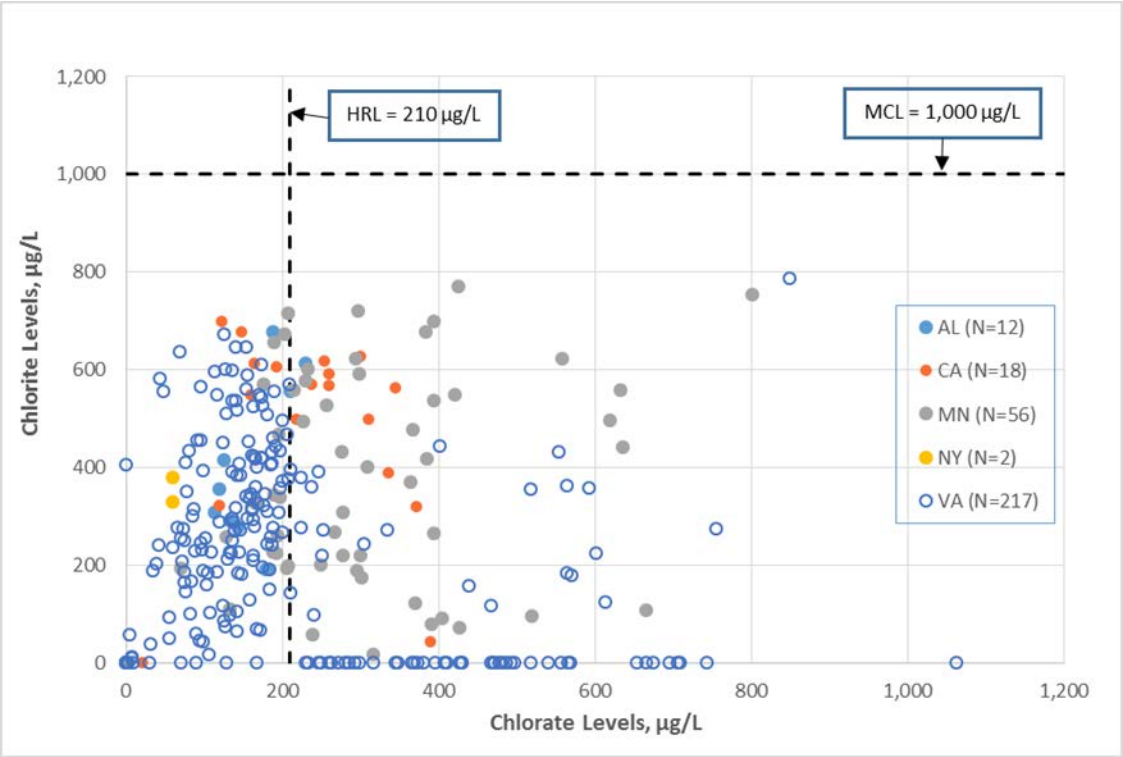
Note that the assignment of systems to primary disinfection categories was based on limited data included in the DBP ICR dataset. Some systems (labelled "unknown") could not be categorized. Some labelled as using chlorine, chloramines, chlorine dioxide or ozone as the primary disinfectant may in fact have made use of a combination of disinfectants.

EWG National Drinking Water Dataset

The EWG National Drinking Water Dataset, posted online (http://www.ewg.org/tap-water/chemical-contaminants/), includes a selection of water sampling data, covering the period 2004-2009, obtained from state water officials by EWG staff. From the EWG dataset, EPA was able to extract 305 paired chlorate/chlorite records. These paired records are from 14 systems (with customer bases ranging in size from 6,525 people to 289,000 people) in 5 states: Alabama, California, Minnesota, New York and Virginia. Each pair represents a single day's average daily chlorate concentration and average daily chlorite concentration at the system, as calculated and

reported by EWG (EWG included non-detections when calculating daily averages, assigning them a value of zero. No information is reported by EWG about disinfection practices or sampling locations in the distribution system. It is possible that the bulk of the EWG data may be from systems that use chlorine dioxide that were monitoring for chlorite in compliance with the MDBP rules. A plot of the paired concentrations, grouped by state, is shown in Exhibit 6.35.

Exhibit 6.35: EWG Data: Paired System Daily Averages for Chlorate and Chlorite



The data show no daily average chlorite levels in excess of the MCL of 1,000 µg/L, which could be attributable to compliance with the MCL under the Stage 1 D/DBPR. The distribution of daily average chlorite levels is fairly wide (from non-detection to approximately 800 µg/L), regardless of whether daily average chlorate levels exceed or fall below 210 µg/L.

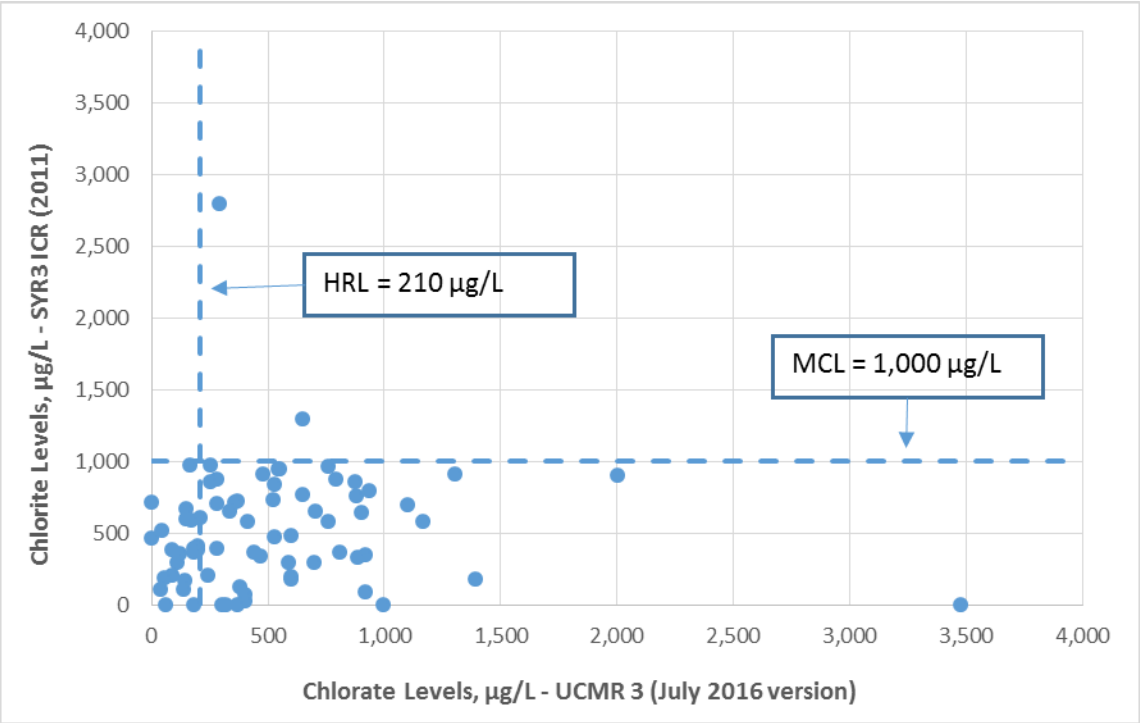
The EWG National Drinking Water Dataset has several limitations. It is a compilation of data that EWG acquired from multiple sources; it is not a complete national dataset and cannot be assumed to be representative of the nation's drinking water. The use of daily average concentrations obscures some variability in the data. As noted above, there is no information about sampling locations or disinfection practices associated with data in the dataset.

UCMR 3 (chlorate) and SYR3 ICR Dataset (chlorite)

The most robust and recent monitoring data on chlorate and chlorite occurrence are in the UCMR 3 and SYR3 ICR dataset, respectively. EPA identified 73 systems that each had at least one record in each dataset for both chlorate and chlorite. All of the SYR3 chlorite records were from 2011. The UCMR 3 chlorate records were from 2013-2016. It is expected that most of the 73 systems employ chlorine dioxide as a primary disinfectant, as those are the systems required

to sample for chlorite. The highest chlorate and chlorite concentrations from each system are plotted in Exhibit 6.36 below. Non-detections are assigned a value of zero. This analysis indicates that systems reporting chlorite records below the MCL of 1,000 µg/L may have chlorate in concentrations significantly higher than the HRL of 210 µg/L.

Exhibit 6.36: System Highest Chlorate and Chlorite Levels in UCMR 3 and SYR3 ICR Datasets (N = 73)



It is important to acknowledge that there are several limitations to this analysis. Only samples with the highest respective concentrations of chlorite and chlorate were selected for inclusion in the analysis. Those samples were gathered in different timeframes (the SYR3 chlorite records were from 2011, while the UCMR 3 chlorate records were from 2013-2016) and were not necessarily taken at the same sampling point. These data provide only a crude picture of potential co-occurrence of chlorate and chlorite in the 73 systems. Also, the 73 systems that each had at least 1 record for both chlorate and chlorite cannot be considered nationally representative.

6.3.4.2 Nitrosamines

Five nitrosamines were included on the Third Contaminant Candidate List (CCL 3). Four nitrosamines from CCL 3, as well as two other nitrosamines that were not on CCL 3, were later part of the Second UCMR (UCMR 2) data collection effort and considered as part of Regulatory Determinations for CCL 3 as candidates for a potential NPDWR. Detailed information on the occurrence analyses conducted using UCMR 2 data are available in the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d).

6.3.4.3 Disinfectant Residuals

In a separate but related effort, EPA evaluated disinfectant residual records (that were taken during the same time and at the same locations as coliform samples) from the SYR3 ICR dataset to understand what disinfectant types/levels are present upon coliform occurrence. This information is available in the *Six-Year Review 3 Technical Support Document for Microbial Contaminant Regulations* (USEPA, 2016a). Overall, analysis of the disinfectant residual data indicated that very few records for both free and total chlorine exceeded the Maximum Residual Disinfectant Level requirement of 4.0 mg/L.

7 Treatment

7.1 Introduction

This chapter discusses information about treatment to remove DBP precursors and DBPs that has become available since the development of the Stage 2 D/DBPR. As with other aspects of the SYR3, EPA limited its review to treatment information published through December 2015.

During the development of the Stage 1 and Stage 2 D/DBPRs, a variety of technologies were evaluated for their effectiveness, applicability and unintended consequences relative to achieving compliance with the treatment technique (TT) requirements and Maximum Contaminant Levels (MCLs), as well as providing a basis for the Best Available Technology (BATs) (USEPA, 1998b. 2005g 2005n, 2006a, 2007).

Since the Stage 2 D/DBPR, the Agency has identified information that improves its understanding of technologies available for lowering occurrence of and exposure to regulated and unregulated DBPs. The information addresses the full spectrum of drinking water system operations, including removal of organic precursors to DBPs, disinfection practices, source water management and localized treatment. As discussed in Chapter 6, one new information source is the SYR3 Information Collection Request (ICR) dataset. For Chapter 7, EPA analyzed this dataset to inform the extent to which total organic carbon (TOC, as an organic precursor surrogate) was removed from source water per the TT requirement under the Stage 1 D/DBPR. These TOC results, along with new literature on treatment technologies, could help improve the understanding of not only the technologies that were considered during the development of the Stage 2 D/DBPR (i.e., enhanced coagulation, use of alternative disinfectants, granular activated carbon (GAC) and membranes), but also those technologies not included before (e.g., biofiltration, localized post-treatment and source water management). EPA analyzed this new information to assess the applicability, effectiveness and unintended consequences of these individual treatment technologies. Overall, the information collectively indicates that: (1) greater removals of DBP precursors are being achieved than were achieved prior to the Stage 1 D/DBPR; and (2) occurrence of DBPs can be further controlled.

This chapter is organized as follows:

Section 7.2, “Background on Treatment Technologies Considered for the Stage 1 and Stage 2 D/DBPRs,” provides a brief overview of the existing TT requirement included in the Stage 1 D/DBPR for removal of TOC. This section also summarizes the treatment technologies considered during the development of the Stage 1 D/DBPR and Stage 2 D/DBPR, respectively.

Section 7.3, “Information on Reducing DBP Formation Potentials in Treatment Plants,” includes an analysis of SYR3 ICR data on TOC removal. It also discusses the information reviewed during the SYR3 process on: 1) conventional treatment, 2) non-conventional treatment and 3) potential add-on physical unit processes.

Section 7.4, “Information on Source Water Management,” covers literature on potential approaches for lowering DBP formation potential in source water (e.g., source water management, bank filtration, pre-sedimentation or pre-oxidation).

Section 7.5, "Information on Changing Disinfection Practices in Treatment Plants and Distribution Systems," focuses on formation and occurrence of different DBP groups with use of different disinfection practices (including different disinfectant types) and discusses potential implications of changes in disinfectant types.

Section 7.6, "Information on Removing DBPs after Formation in Treatment Plants and/or Distribution Systems," provides information on methods for removal of DBPs after their formation. These methods (e.g., aeration) may be applicable in treatment plants or in distribution systems.

Appendix C provides additional information on several of the topics presented in this chapter.

7.2 Background on Treatment Technologies Considered for the Stage 1 and Stage 2 D/DBPRs

The main purpose of the Stage 1 and Stage 2 D/DBPRs is to reduce exposure to DBPs while maintaining protection against microbial risks in public water systems (PWSs). During the development of the Stage 1 D/DBPR, EPA determined that it was necessary to control for organic matter in source water through a TT requirement. This TT requirement complemented the MCLs and was designed to help remove DBP precursor material to help reduce the risks posed by DBPs. This section briefly describes the TT requirement and the treatment technologies considered during development of the Stage 1 D/DBPR and the Stage 2 D/DBPR, respectively.

7.2.1 Treatment Technique Requirements for TOC Removal

As described in Chapter 6, under the Stage 1 D/DBPR, PWSs using surface water or ground water under the direct influence of surface water (GWUDI) sources and using conventional treatment (i.e., "a series of processes including coagulation, flocculation, sedimentation and filtration resulting in substantial particulate removal") are required to remove specified percentages of TOC from the source water. TOC removal is achieved with enhanced coagulation or enhanced softening unless a system meets one of several alternative compliance criteria. This TT applies to community and non-transient non-community water systems (NTNCWSs) of all sizes.

The TT requirement identifies the minimum percentage of TOC a conventional plant must remove based on the raw water TOC and alkalinity levels, which are divided into three ranges, respectively. These criteria are referred to as the "3x3 matrix" and are shown in Exhibit 7.1 (USEPA, 1998b).

Exhibit 7.1: Required TOC Removal for Conventional Treatment Plants Using Surface Water or GWUDI[1,2,3]

Source water TOC, mg/L	Source water alkalinity, mg/L as $CaCO_3$		
	0–60	60–120	>120[4]
>2.0–4.0	35.0%	25.0%	15.0%
>4.0–8.0	45.0%	35.0%	25.0%
>8.0	50.0%	40.0%	30.0%

Notes:
[1] Plants meeting at least one of the alternative compliance criteria are not required to operate with enhanced coagulation.
[2] Softening plants meeting one of the alternative compliance criteria are not required to operate with enhanced softening.
[3] Compliance with the TOC removal requirement is based on a running annual average, computed quarterly.
[4] Plants practicing softening must also meet the TOC removal requirements in this column.

EPA developed the 3x3 matrix recognizing that systems would have a greater challenge removing TOC from source waters with high alkalinity. Some types of water may not be amenable to effective TOC removal by coagulation or softening. Alternative compliance criteria included in the Stage 1 D/DBPR provide flexibility for complying with the TT requirements. Those alternative criteria are described in EPA's Enhanced Coagulation Guidance Manual (USEPA, 1999b).

7.2.2 Treatment Technologies Considered During Rule Development

Exhibit 7.2 collectively lists the treatment technologies included in the Stage 1 D/DBPR Regulatory Impact Analysis (RIA), along with those used in the Stage 2 D/DBPR Economic Analysis (EA). The Stage 2 D/DBPR EA (USEPA, 2005g) and its appendices (USEPA, 2005n), along with the Technologies and Costs Document for the Stage 2 D/DBPR (USEPA, 2005m) and the Simultaneous Compliance Guidance Manual for LT2ESWTR and Stage 2 D/DBPR (USEPA, 2007b) present a detailed description of these technologies, including their effectiveness, applicability and unintended consequences. Water Research Foundation (WRF) studies published since promulgation of the Stage 2 D/DBPR contain similar lists of technologies (Schendel et al., 2009 and Becker et al., 2013).

Exhibit 7.2: Treatment Technologies Considered for the Stage 1 and Stage 2 D/DBPRs[1]

Stage 1 D/DBPR RIA Treatment Technologies	Stage 2 D/DBPR EA Treatment Technologies
Chlorine/Chloramine	Adjust Primary Disinfection Move Points of Disinfection with Chloramines
Enhanced Coagulation	Enhanced Coagulation with Chlorine Turbo Coagulation with Chlorine
Enhanced Coagulation with Chloramines	Enhanced Coagulation with Chloramines Turbo Coagulation with Chloramines

Stage 1 D/DBPR RIA Treatment Technologies	Stage 2 D/DBPR EA Treatment Technologies
Chlorine Dioxide	Chlorine Dioxide with Chlorine
	Chlorine Dioxide with Chloramines
Ozone with Chloramines	Ozone with Chlorine
	Ozone with Chloramines
GAC10	GAC10 with Chlorine
	GAC10 with Chloramines
	GAC10 + Chlorine Dioxide with Chlorine
	GAC10 + Chlorine Dioxide with Chloramines
	GAC10 + UV (Small Systems)
GAC20	GAC20 with Chlorine
	GAC20 with Chloramines
	GAC20 + Chlorine Dioxide with Chlorine (Large and Medium Systems)
	GAC20 + Chlorine Dioxide with Chloramines (Large and Medium Systems)
	GAC20 + Ozone with Chlorine (Small Systems)
	GAC20 + Ozone with Chloramines (Small Systems)
	GAC20 + UV (Small Systems)
Membranes	Microfiltration/Ultrafiltration with Chlorine
	Microfiltration/Ultrafiltration with Chloramines
	Integrated Membranes with Chlorine (Surface Water Systems)
	Integrated Membranes with Chloramines (Surface Water Systems)
	Nanofiltration with Chlorine (Ground Water Systems)
	Nanofiltration with Chloramines (Ground Water Systems)

[1] Source: Exhibit A.7 in Appendix A of the Stage 2 D/DBPR EA (USEPA, 2005n).

7.3 Information on Reducing DBP Formation Potentials in Treatment Plants

The treatment technologies listed in Exhibit 7.2 include enhanced coagulation, granular activated carbon (GAC) and membranes; they are intended to reduce DBP formation in treatment plants. Enhanced coagulation is an enhanced mode of operation that assumes possible adjustments in coagulant application and pH to achieve the minimum target TOC levels through a combination of coagulation and sedimentation basins followed by filtration.

Exhibit 7.3 shows the percent TOC removal by surface water filtration treatment plant types from source to filter effluent. It is based on paired TOC data from the DBP ICR dataset. As indicated in Exhibit 7.3, prior to the Stage 1 D/DBPR, a conventional treatment train was the most common type of treatment for surface water systems serving 100,000 or more people. Systems with direct filtration, in-line filtration and slow sand filtration tended to have much lower TOC levels in their source water and were not subject to the TT requirement under the Stage 1 D/DBPR.

Exhibit 7.3: Percent TOC Removal from Source to Filter Effluent by Surface Water Filtration Treatment Plant Types Based on DBP ICR Dataset

Plant Type	Plant Type Code	Number of Plants	Mean Plant Average Raw Water Turbidity, NTU	Mean Plant Average Raw Water TOC, mg/L	Mean Plant Average Filtered Water TOC, mg/L	Mean Plant Average %TOC Removal[1]
Conventional/ Softening[2]	CONV/ SOFT[2]	272	3.5	3.5	2.2	31.2%[3]
Direct Filtration	DF	22	2.1	2.5	2.0	17.6%
In-Line Filtration	ILF	5	1.3	1.7	1.3	11.4%
Slow Sand Filtration	SSF	2	1.1	1.7	1.2	28.8%

Notes:
[1] %TOC removal from source water to filter effluent.
[2] "Conventional/Softening" includes plant type codes in the DBP ICR database: Conv; CMPLX/SOFT; CS/SOFT; SOFT; SPLIT/SOFT; and TS/SOFT.
[3] About 24% and 8% on average came from coagulation/sedimentation and filtration, respectively.

The TOC monitoring data in the SYR3 ICR dataset enables EPA to evaluate TOC removal relative to the 3x3 matrix criteria. This section contains analytical results on TOC removal using SYR3 ICR data, followed by discussion of the information available since the Stage 2 D/DBPR on conventional treatment, non-conventional treatment and potential add-on physical removal unit processes, for reducing DBP formation potentials. Since the information presented and discussed in this section is relatively lengthy, a summary for this section is provided below.

The analytical results from the SYR3 ICR dataset indicate a wide range of percent TOC removal observed for each cell of the 3x3 matrix, as was anticipated when the requirements were promulgated. The mean removal in each category of the 3x3 matrix was 6 to 19 percent higher than the TT requirement, indicating that greater removals of DBP precursors were commonly being achieved compared to the TT requirement. These observations are consistent with the notion that "since the Stage 1 D/DBPR does not require that all coagulable dissolved organic matter be removed, there is a potential for additional removal of organic matter beyond that required by the 3x3 matrix." (McGuire et al., 2014).

Some of the TOC removal observed greater than the minimal TOC removal requirement may reflect operational optimization of conventional treatment, including use of innovative coagulants/coagulant aids and/or use of biofiltration. Application of biofiltration recently has become a key research area in the water industry and there are several ongoing studies (e.g., the biofiltration-related projects listed on the WRF website, including project numbers 4496, 4525, 4555, 4559 and 4620) that could further inform the applicability, effectiveness and unintended consequences for use of biofiltration. Studies have shown that biological filtration can also reduce precursors of DBPs other than THM4/HAA5 in many, though not all cases (Mitch et al., 2009; Liao et al., 2014; Krasner et al., 2015). As noted by McGuire et al. (2014), if the removal of precursors for DBPs other than THM4/HAA5 becomes part of the treatment goals, then performance parameters in addition to TOC may also be needed (e.g., parameters indicating both vulnerability and nitrosamine formation potential).

As was known during development of the Stage 1 and the Stage 2 D/DBPRs, GAC and membranes can be added to existing treatment trains to achieve additional reductions of DBP formation potential. One longstanding issue has been the extent to which organic precursor removal may cause a shift of chlorinated species to more brominated species when the bromide level is relatively high in source water (Summers et al., 1993; Symons et al., 1993). The ICR Treatment Study database (USEPA, 2000f) provides extensive bench- and pilot-scale data by which to evaluate the effects of GAC and membrane removal of TOC and resulting shifts in BrTHMs. EPA's recent analysis of these data generally shows increased percent reduction of BrTHMs as TOC removal by GAC increases (e.g., from a target effluent level of 2 mg/L to 1 mg/L) for source waters with high bromide concentrations. It also shows that bromoform formation increases as bromide concentrations increase and that bromoform becomes the dominating species when source water bromide concentrations exceed 200 µg/L.

7.3.1 Analysis of SYR3 ICR Data for TOC Removal

This section presents analytical results of the SYR3 ICR data within the context of the 3x3 matrix. Appendix C of this document contains the background/inventory information, supplemental analytical results of the paired SYR3 ICR TOC dataset and details on the creation of the "paired TOC dataset." The main observations from the analytical results are summarized below:

- The data show a wide range of percent TOC removal for each combination of raw water TOC and alkalinity levels provided in the Stage 1 D/DBPR TT requirement. The data also indicate that the mean removal for each element of the 3x3 matrix was 6 to 19 percent greater than the requirement.

- In the context of the 3x3 matrix, although TOC removal generally increased as the raw water TOC levels increased, the treated water TOC levels generally still increased as the raw water TOC levels increased. When the raw water TOC levels were greater than 8 mg/L, nearly all the plants had mean treated water TOC levels above 2 mg/L and it was not uncommon to see the treated water TOC levels greater than 4 mg/L.

- Regarding system sizes, while the levels of raw water TOC and alkalinity appeared essentially no different (i.e., were independent of system size), percent TOC removals among small systems (those serving <10,000 people) were slightly lower than in medium systems (serving between 10,000 and 100,000) and large systems (serving ≥100,000) (41 percent mean removal in small systems versus 44 percent and 45 percent in medium and large systems, respectively).

7.3.1.1 Analytical Approach

Under the existing TT requirements, some systems may take more than one pair of TOC samples per month and compute an average of the monitoring results each month for compliance calculation. Compliance with the TOC removal requirements is based on a running annual average, computed quarterly. Changes in raw water TOC and/or alkalinity levels from month to month will cause some plants to move from one category to another in the 3x3 matrix (see Exhibit 7.1). The required TOC removal, therefore, may change on a month-to-month basis.

Such a regulatory construct makes the monthly-level analysis of the SYR3 ICR paired TOC data more complex. To simplify the data analysis, annual averages per plant (i.e., facility in the dataset) per calendar year were calculated, using the monthly average values for raw water TOC, raw water alkalinity and treated water TOC. Annual average removals (percentages) of TOC were calculated with the annual average values of raw water TOC and treated water TOC per facility.

7.3.1.2 Summary Statistics for 3x3 Matrix

To maximize the number of records included in the data analysis, all years of data were included. In this context, the term "Facility Years" (i.e., facilities x years) was used. It should be noted that the use of multiple years rather than the most recent single year (i.e., 2011) can lead to an underestimate of the levels of TOC removal achieved by the implementation of Stage 1, as 2011 shows the higher percent removal (on average) and also likely reflects the highest degree of Stage 1 implementation (See Appendix C for more discussion). The summary statistics associated with each TOC/alkalinity category of the 3x3 matrix are shown in Exhibit 7.4. These statistics (based on an annual average per facility year) include the following analytical endpoints:

(1) The count of facility years (i.e., #Facility Years),

(2) Percentages of facility years with percentage of TOC removal less than that required for each of the TOC/alkalinity categories in the 3x3 matrix (i.e., %Facility Years with % Removal < Required),

(3) The mean, median and 90th percentile of TOC removal (i.e., Mean/Median and 90th Percentile Removal),

(4) Percentage of facility years with treated water TOC levels greater than 2 mg/L (i.e., %Facility Years with Treated TOC > 2 mg/L), and

(5) The mean of the treated water TOC levels (i.e., Mean Treated TOC, mg/L).

These analytical endpoints were selected to represent the distribution and variation of TOC removals in each category of the 3x3 matrix for facility years when the annual average raw water TOC levels were greater than 2 mg/L. All facility years included in the dataset were associated with surface water systems. Appendix C of this document shows a similar analysis for annual average raw TOC levels ≤ 2 mg/L (for which 99 percent of facility years included in the dataset were associated with surface water systems).

Exhibit 7.4: Evaluation of TOC Compliance Monitoring Data from SYR3 ICR Dataset Relative to 3x3 Matrix (Based on Paired TOC Data from 2006-2011)

Raw Water TOC, mg/L	Summary[1] (Total #Facility Years = 4,793)	Raw Water Alkalinity, mg $CaCO_3$/L		
		0-60	>60 to 120	>120
2.0 < TOC ≤ 4.0	#Facility Years	1,735	915	510
	%Facility Years with %Removal < Required	27.8%	16.4%	9.0%
	Mean Removal	41.7%	35.2%	30.4%
	Median Removal	41.6%	35.1%	30.1%
	90th Percentile Removal	56.2%	49.2%	47.2%
	%Facility Years with Treated TOC > 2 mg/L	14.3%	26.0%	44.3%
	Mean Treated TOC, mg/L	1.6	1.8	2.0
4.0 < TOC ≤ 8.0	#Facility Years	739	322	366
	%Facility Years with %Removal < Required	15.6%	12.1%	4.9%
	Mean Removal	54.7%	46.8%	44.1%
	Median Removal	54.3%	46.3%	43.9%
	90th Percentile Removal	70.0%	58.3%	61.8%
	%Facility Years with Treated TOC > 2 mg/L	77.4%	91.9%	91.8%
	Mean Treated TOC, mg/L	2.5	2.9	3.0
TOC > 8.0	#Facility Years	129	35	38
	%Facility Years with %Removal < Required	7.0%	25.7%	2.6%
	Mean Removal	66.2%	46.3%	46.9%
	Median Removal	66.4%	44.2%	47.8%
	90th Percentile Removal	82.2%	67.3%	63.9%
	%Facility Years with Treated TOC > 2 mg/L	85.3%	100.0%	100.0%
	Mean Treated TOC, mg/L	3.5	5.6	6.2

Note: Facility Years = number of facilities x number of years for the paired TOC data between 2006 and 2011.

As described in Section 7.2.1, some systems could be using some of the alternative criteria; thus, the values of "%Facility Years with %Removal < Required" cannot be assumed to be equivalent to the percentage of facility years with a TT violation. For instance, "%Facility Years with %Removal < Required" is 27.8 percent (i.e., 482 facility years). This can be attributable to a significant number of the facility years (i.e., 302) among these 482 facility years that have treated water TOC levels less than 2 mg/L or might have elected to meet alternative criteria and be exempted from meeting the removals specified in 3x3 matrix. The extent to which the facilities with treated water TOC levels less than 2 mg/L actually used the alternative criteria is unknown. Because of this uncertainty, the analytical results in the upper three boxes of the 3x3 matrix (i.e., for 2.0 < TOC ≤ 4.0 mg/L) were not included in the remainder of this discussion.

A wide range of TOC removal was observed in each TOC/alkalinity category of the 3x3 matrix, from removal percentages below the requirement to some achieving 25 percent more than the requirement. Overall, the means and medians of removal are 6 to 19 percent more than that required in each category included in the 3x3 matrix (refer to mean and median removals in Exhibit 7.4 versus required removals in Exhibit 7.1). For example, in looking at the category where TOC is in the range of 4.0 to < = 8.0 mg/L, with alkalinity of 0-60 mg/L, Exhibit 7.4 shows mean and median removals of about 54 percent, while Exhibit 7.1 shows a required removal of 45 percent, corresponding to 9 percent more than the requirement for that category. In addition, a comparison between the value of "90th percentile Removal" and the removal required in each of the middle and bottom boxes indicates some facilities achieved significantly higher removal than required (e.g., 70 percent vs 45 percent).

These observations are consistent with the notion that "since the Stage 1 D/DBPR does not require that all coagulable dissolved organic matter be removed, there is a potential for additional removal of organic matter beyond that required by the 3x3 matrix." (McGuire et al., 2014). As discussed later, a TOC removal in some plants for a given category of the 3x3 matrix can be attributable to the treatability of the water and/or an operational optimization of the conventional treatment trains. This can be achieved with operation in a "turbo" enhanced coagulation mode (as defined in the Economic Analysis of Stage 2 D/DBPR, USEPA, 2005g) or by following enhanced coagulation with biofiltration.

7.3.1.3 TOC Removal by System Size

The SYR3 ICR data enables EPA for the first time to evaluate TOC removal at a national scale among systems of different sizes. For this purpose, the systems with the paired TOC data were grouped into three population size categories: < 10,000, 10,000-100,000 and ≥ 100,000. As indicated by Exhibit 7.5, small systems (< 10,000) removed slightly less TOC than medium (10,000 -100,000) and large (≥ 100,000) systems—the mean removal for small systems was 41 percent versus 44 percent and 45 percent for medium and large systems, respectively. However, the top 20 percent of performers across all system size categories achieved greater than 50 percent removal. The distributions of raw water TOC and alkalinity levels by system size are included in Appendix C of this document; the difference in raw water values between systems of different sizes is relatively small.

Exhibit 7.5: TOC Removal by System Size from SYR3 ICR Dataset (Based on Paired TOC Data from 2006-2011)

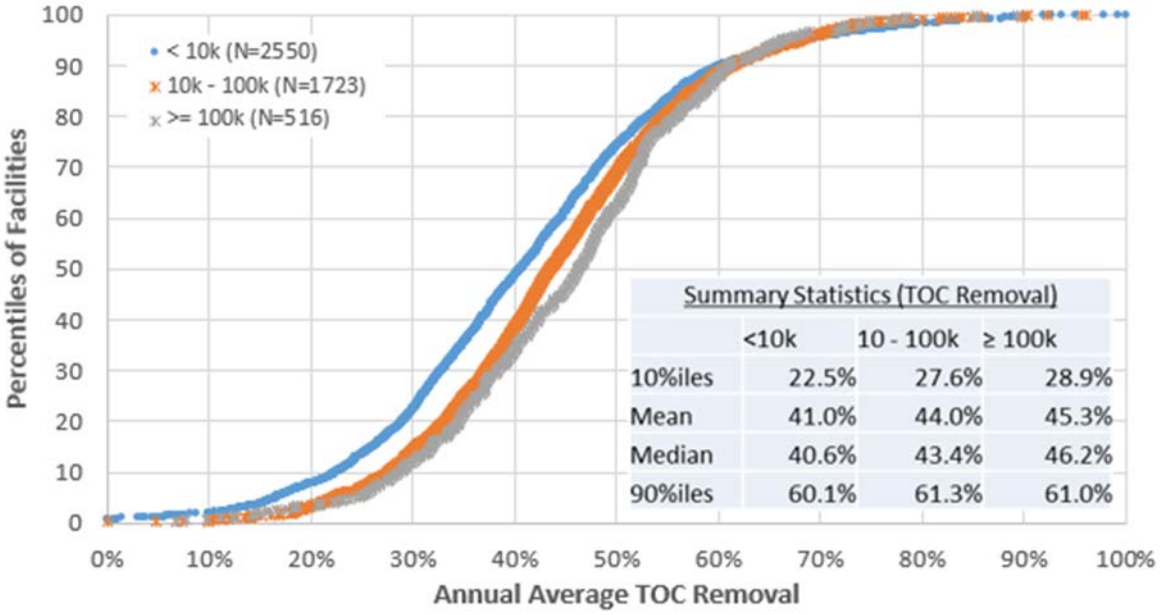
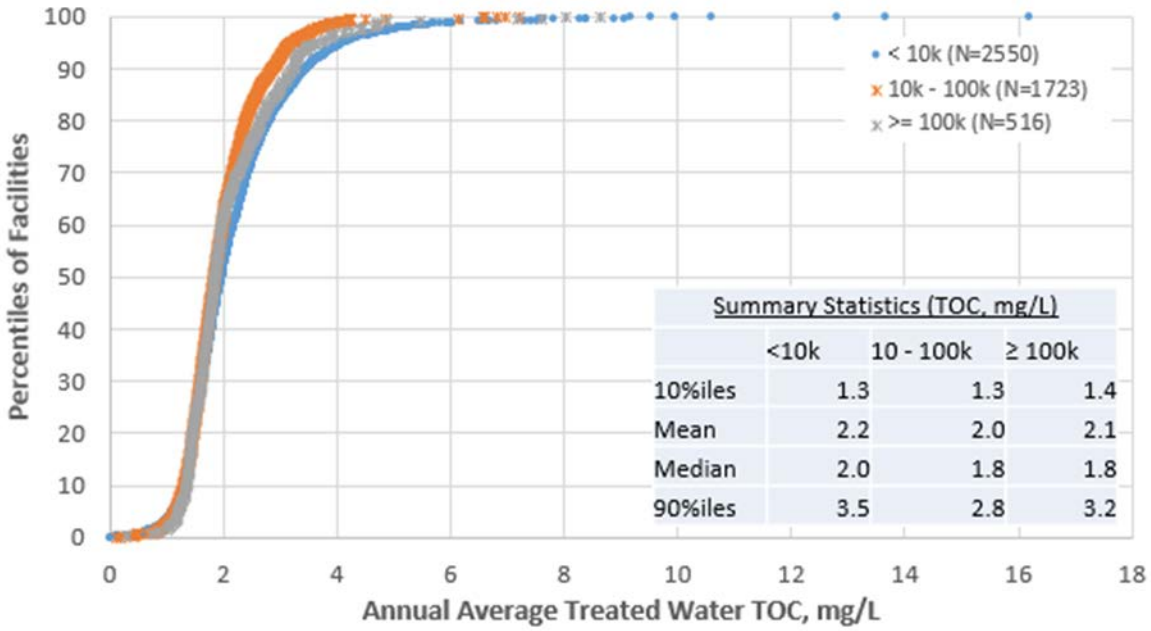


Exhibit 7.6: Treated Water TOC Levels by System Size from SYR3 ICR Dataset (Based on Paired TOC Data from 2006-2011)



7.3.1.4 Limitations of Paired TOC Data from SYR3 ICR

As indicated in Appendix C of this document, there are 21 states included in the paired TOC dataset. While this dataset is substantial, EPA is not able to assess the completeness of the paired TOC data records among these 21 states since it did not have: 1) the state inventory number of

facilities (or plants) with conventional treatment trains and 2) information about the application and use of alternative criteria for TOC removal and record management. With respect to the national representativeness of the TOC paired dataset, EPA also notes that some "big" states (i.e., ones with a relatively large number of systems serving relatively large populations, and in some cases, relatively high TOC levels in source water) are not included in the dataset, including California, Texas and Florida.

In addition, the DBP ICR dataset indicates that, in general, ground water (GW) systems have much lower source and finished water TOC levels (see Exhibit 6.14 and 6.15 versus Exhibits 6.12 and 6.13) than surface water systems (SW). However, some of these systems using conventional treatment with or without softening (mostly Florida systems) had TOC levels comparable to SWs with high TOC levels. The paired TOC dataset from the SYR3 ICR essentially only included SW systems and provided little additional TOC occurrence data for GW systems.

EPA's understanding is that the paired TOC data from the SYR3 ICR for SW systems is the largest and most comprehensive dataset (since the DBP ICR dataset in 1997-1998) to indicate, at a national level, treatment performance among plants for TOC removal and TOC levels in treated water.

7.3.2 Information on Conventional Treatment

EPA does not have recent information on the number of water systems using conventional treatment. However, at the time of the DBP ICR, the majority of surface water treatment plants serving 100,000 or more people were conventional treatment plants (including the ones with softening) (i.e., 272 out of 301 filtration plants, see Exhibit 7.3). The AWWA Disinfection Committee (AWWA, 2000a and 2000b) reported that the small and medium SW systems also commonly used a conventional treatment process. In addition, as indicated in Exhibit 6.14, the DBP ICR data also showed that those ground water systems with relatively high TOC in their source water also used conventional treatment (with or without softening).

As described in Section 7.2, the surface water conventional treatment plants that are required to implement the TOC removals specified in the 3x3 matrix must monitor TOC in the source water prior to any treatment, including oxidant addition. The treated water TOC also must be monitored no later than the combined filter effluent turbidity monitoring location. Thus, the TOC removal results from the SYR3 ICR data presented in Section 7.3.1 reflect the collective treatment performance of the three individual treatment units (i.e., coagulation/flocculation, sedimentation and filtration) in the conventional treatment plants. Thus, the removal of organic matter by a conventional treatment train depends on the operating conditions for each of these units, given source water quality.

Many plants were achieving higher percentages of TOC removal than required during the SYR3 ICR period. Such operation of enhanced coagulation may be due to what was referred to as "turbo" enhanced coagulation in the Economic Analysis for the Stage 2 D/DBPR (see Exhibit 7.2). Also, new studies indicate that additional TOC removal can be achieved by operating the filtration unit in a biological mode (Liao et al., 2014, 2015; Delatolla et al., 2015; Pharand et al., 2015). This approach for operating a conventional treatment plant may enable an additive or

synergic performance of "turbo" enhanced coagulation and biofiltration, collectively resulting in greater TOC removals.

7.3.2.1 Enhanced Coagulation

This section focuses on new information on coagulants and coagulation aids. Aside from source water quality conditions, removal of organic matter through enhanced coagulation depends on multiple operating factors, including pH, coagulant type and dose, coagulation aid type and dose and hydraulic conditions in both coagulation and sedimentation basins. Hydraulic conditions and pH are well understood from information collected during development of the Stage 1 and Stage 2 D/DBPRs, thus the focus on coagulants and coagulation aids here.

Most common coagulants are aluminum or ferric salts and TOC removal to some extent can be increased by increasing the coagulant dose. A new coagulant is polyaluminum chloride (PAC). Its use, in lieu of aluminum chloride or ferric chloride, could improve the efficiency of enhanced coagulation at certain pH ranges (Hassan et al., 2010). For instance, TOC/DOC/UV_{254} removal could be 10 percent more and resultant reduction of TTHM formation potential could be 20–30 percent more when PAC is used instead of ferric chloride (Hassan et al., 2010).

Tzoupanos and Zouboulis (2009) developed a composite coagulant by introducing a cationic polyelectrolyte (CPE) into PAC. They observed more efficient coagulation, compared to the independent applications of CPE and PAC, due to more effective particle aggregation and reduction of overall CPE dosage.

The effectiveness of PAC for enhancing coagulation was also evaluated in several studies. Some of these studies (Kristiana et al., 2011; Dunn and Knappe, 2013; Chu et al., 2015; Watson et al., 2015; Plourde-Lescelleur et al., 2015) collectively demonstrated that the addition of PAC could help with removal of both chlorination DBPs and their precursors as part of DOC. As Hanigan et al. (2015) found PAC to be effective for removing NDMA precursors, Chu et al. (2015) showed that the use of PAC also resulted in a significant reduction of nitrogenous DBPs (including NDMA). Lin et al. (2015) found that PAC worked best with small molecular weight DOC. It is worth noting that since PAC was ineffective at reducing bromide levels, enhanced coagulation with PAC could result in a shift to more brominated DBPs as the Br^-:DOC ratio increases (Watson et al., 2015).

Jiang and Wang (2004) demonstrated that potassium ferrate could perform better than ferric sulfate for treating waters containing humic and fulvic acids for reducing UV_{254} absorbance, removing dissolved organic carbon (DOC) and lowering the THM formation potential. A later literature review by Darko et al. (2014) confirmed that the efficiency of ferrate for removing dissolved organic matter was higher than that of traditional coagulants ferric and aluminum salts. Ferrate ion initially can act as a strong oxidant (potentially as a disinfectant as well) and then a coagulant after being converted to ferric ion. A study from Lim and Kim (2009) showed that the removal rate of humic acid using ferric sulfate was improved by pretreatment with a very small dose of ferrate. The reaction between ferrate and humic acid was completed within a minute. However, engineering aspects of ferrate generation and any unintended consequences associated with a field application of ferrate in water treatment may need to be further characterized.

Several new coagulants have been identified and tested. Jarvis et al. (2012) compared DOC removals using a novel zirconium oxychloride-based coagulant (Zr-Coag®) to removal using ferric sulfate and alum in batch (jar tests) and pilot scale experiments. Results showed greater DOC removal and lower THM4 formation potential for the Zr-Coag® treated water (100.7 +/- 15.0 µg/L) compared to THM formation potential after ferric sulfate treatment (163.1 +/- 36.7 µg/L). Jar test data revealed an optimum Zr-Coag® dose of between 5 and 15 mg/L at a pH of 5 to 6. A limitation of this work is that it was conducted using one source water with low turbidity (3.5 NTU) and low alkalinity (< 10 mg/L).

Organic polymers are commonly used coagulation aids. Since Wilczak et al. (2003) reported that some polymers (such as polyDADMAC) could contain organic nitrogen and could contribute to the NDMA precursor material, investigation of coagulation aid alternatives has been ongoing (Cornwell et al., 2015). *The Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d) presented more detailed discussion on NDMA formation related to use of polymers.

In addition to raw water TOC and alkalinity levels, bromide in the raw water could also be important to DBP formation potential in treated water, particularly for brominated DBPs (which appear more toxic than chlorinated DBPs; see Chapter 4). Studies from Kalscheur et al. (2006) and Watson et al. (2015) showed that TOC removal did not necessarily translate to a proportional reduction in brominated DBP formation potential in treated water. Kalscheur et al. (2006) reported that lime softening of source water with bromide concentrations of around 160 mg/L (three orders in magnitude higher than typical U.S. water, USEPA, 2005g) resulted in a significant shift to brominated DBPs and actually increased THM4 formation. Similarly, Watson et al. (2015) found that enhanced coagulation resulted in a shift to more brominated DBPs as the ratio of bromide to DOC increased after treatment.

Overall, the information reviewed as part of the SYR3 indicates that in some cases TOC may not be an adequate performance indicator for the enhanced coagulation process, for brominated DBP or NDMA formation potentials. Nevertheless, the new development and application of these innovative materials can help improve the performance of enhanced coagulation in terms of reduced DBP formation potentials.

7.3.2.2 Biological Filtration

Biofiltration (such as slow-sand filtration) has been used for water treatment for more than 100 years (Collins et al., 1992). Operating the filtration unit in a conventional treatment plant in a biological mode was not included in the technologies considered in the compliance decision tree for the Economic Analysis for the Stage 2 D/DBPR (see Exhibit 7.2), due to the lack of recognized full-scale experience and accepted design and operating parameters. Since the promulgation of the Stage 2 D/DBPR, there has been an increased interest in applying biological filtration to remove organic DBP precursors and trace contaminants in drinking water. The WRF has identified biological filtration as a focus area and set a goal to "determine biofiltration effectiveness at removing contaminants, define benefits and communicate to key stakeholders and to provide utility guidance on optimizing biofiltration" (WRF, 2015a). WRF has initiated numerous projects pertaining to biological filtration for removal of organic DBP precursors. The

WRF also has established the "North American Biofiltration Knowledge Base" (WRF, 2015b) to share fundamental knowledge on: 1) the use of biological filtration in water treatment and 2) the field operational and monitoring data from some utilities.

The 1998 DBP ICR data showed that the percent TOC removal through the filters following the coagulation/sedimentation basins in the SW conventional treatment plants was 8 percent on average (see the footnote of Exhibit 7.3). Lauderdale et al. (2014) found that biological filters commonly removed 10–20 percent of organic carbon, while removals had been reported to vary from 5 percent to 75 percent.

Some studies have found that GAC biofilters can remove more DBP precursors than anthracite/sand biofilters (Lauderdale et al., 2014; McKie et al., 2015; Azzeh et al., 2015; Chowdhury et al., 2010). With all of these medium types, biological filtration has been shown to reduce THM and HAA formation potentials by higher percentages compared to DOC removal percentages (McKie et al., 2015; Azzeh et al., 2015; Delotolla et al., 2015; Pharand et al., 2015). While ozonation prior to biofiltration has not been demonstrated to significantly increase DOC removal, biofiltration is known to better remove assimilable organic carbon produced by ozonation (Krasner et al., 2012; Pharand et al., 2015). Adding nutrients has not been found to significantly enhance biofiltration performance (McKie et al. 2015; Azzeh at al. 2015; Lauderdale et al. 2014).

Researchers have also investigated biological filtration for its removal of precursors of unregulated DBPs. Some studies have shown that biological filtration can reduce NDMA precursors in many, but not in all cases. During those studies, a reduction of NDMA precursors after biological filtration with pre-ozonation was observed (Sacher et al., 2008; Farré et al., 2011; Liao et al., 2014). Particularly, in studies of biological filtration with GAC media, Liao et al. (2014) found that NDMA precursor removal was greater than DOC removal. Another study found that while NDMA formation was reduced by biological filtration in some plants, in many plants biofiltration led to an increase in NDMA formation potentials, which probably was caused by sloughed bacteria or soluble microbial products (Krasner et al., 2015). Thus, if removing the precursors of DBPs in general becomes part of the treatment goals, it may be necessary to monitor the performance of parameters other than TOC (McGuire el al., 2014).

In addition to potential removal of DBP precursors or reduction in DBP formation potentials, biofiltration may also be capable of reducing levels of organic DBPs, particularly when GAC is used as a medium (Wu and Xie, 2005; Johnson et al., 2009; Lou et al., 2014). By studying the effects of empty bed contact time (EBCT) and water temperature on the removal of HAAs in a biological activated carbon (BAC) filter with 8 days of running time, Wu and Xie (2005) suggested a 10 minute EBCT for 4ºC water and a 5 minute EBCT for water at 10ºC or higher to achieve an HAA removal efficiency of 50 percent or higher. Lou et al. (2014) demonstrated that, at 10–60 minutes of EBCT and 24–26 ºC, 30–50 percent removal of THM and greater than 80 percent removal of HAAs could be achieved through a pilot-scale BAC filter over 9–11 days. The BAC filter was included by Johnson et al. (2009) as part of their study for localized treatment of DBPs in distribution systems. They concluded that development of biological activity in the GAC column could significantly prolong the unit operation. Similar to a GAC column, however, a BAC filter would remove the chlorine residual completely, resulting in the need to rechlorinate downstream in the distribution system.

Upstream treatment can also affect biofiltration performance. For instance, McKie et al. (2015) found that PAC coagulant reduced bioactivity on filters, possibly due to a reduction in available phosphorus (as a nutrient). Thus, effective integration of enhanced coagulation and biofiltration in a conventional treatment train will be vital for maximizing removal of organic matter and control of DBP mixtures in the treated water. Sohn et al. (2007), by examining DOC removal after individual treatment processes in a plant with coagulation, a sand filter, ozone and a biological filter, observed that: 1) both coagulation and ozonation units removed large-molecular-weight organic compounds better than small ones and 2) biological filtration removed small organics better than large ones. Chu et al. (2015) investigated the overall performance of a conventional water treatment process followed by ozonation and biological activated carbon filtration and showed significantly higher removals of both DOC and organic nitrogen, as compared to the conventional treatment alone.

A potential drawback of converting a traditional rapid rate filter to a biological filter is that extracellular polymeric substances from the biological community can contribute to an increased head loss and fouling of filter underdrains. Azzeh et al. (2015) and Lauderdale et al. (2012) found that application of hydrogen peroxide at low doses (< 1.0 mg/L) could reduce the head loss by up to 45 percent without compromising biological performance, although higher doses were found to negatively impact the DBP precursor removal performance. Lauderdale et al. (2012) concluded that the optimal hydrogen peroxide dose is site-specific and dependent on multiple factors, such as temperature, source water and upstream treatment. Another potential issue is that if systems convert an active filter to biofiltration by removing the chlorine residual entering the filter, oxidized manganese that has built up on the filter media may be reduced and released (Kohl and Dixon, 2012).

Biological filtration can have additional benefits beyond further removing organic DBP precursors. A study by Lauderdale et al. (2014) showed that biological filtration allowed for a 50 percent reduction in coagulant dose. In addition, the use of biological filtration may produce more biologically stable water, which can help control biofilm growth and stabilize disinfectant residuals in distribution systems (McGuire et al., 2014).

7.3.3 Information on Non-Conventional Treatment

Based on the DBP ICR data, non-conventional treatment plant types include direct filtration, in-line filtration, slow sand filtration, surface water unfiltered treatment and ground water disinfection only (see Exhibit 6.14 and Exhibit 6.15 of Chapter 6). In general, TOC levels in the source water of surface water unfiltered plants or ground water plants with disinfection only are much lower than conventional or non-conventional filtration treatment plants (see Exhibit 6.14 and Exhibit 6.15 of Chapter 6). The discussion presented in this section focuses on direction filtration, in-line filtration and slow sand filtration.

There is little new information on removal of DBP precursors or reduction of DBP formation potentials by non-conventional filtration treatment plants. This may be attributable to: 1) non-conventional treatment plants not needing to meet the TT requirements for TOC removal under the Stage 1 D/DBPR; and 2) the DBP precursor levels (as indicated by TOC) in source water as well as treated water in non-conventional plants are generally much lower (see Exhibit 7.3).

According to Nieminski and Perry (2015), filtration type can be categorized into high-rate versus low-rate filtration from the perspective of hydraulic loadings. The high-rate filters include the filters used in conventional/softening treatment, direct filtration and in-line filtration plants; the low-rate filters include slow sand filters and bank filtration (see Section 7.4 for discussion on bank filtration).

Exhibit 7.3 shows percent TOC removals from source water to filter effluent among different filtration treatment plants participating in the DBP ICR. The direct filtration or in-line filtration plants (without sedimentation basins) performed similarly, with mean TOC removals of 11–18 percent, about 50 percent less than the removals achieved by the conventional/softening treatment plants. Yet, some of the direct filtration or in-line filtration plants had relatively high TOC levels in the raw water (up to 4.2 mg/L) and in the filtered water (up to 2.7 mg/L), respectively.

As with filters in conventional/softening plants, the filters in direct or in-line filtration plants may be converted into biofilters for further removal of TOC. Exhibit 7.3 also indicates that the slow sand filtration plants generally treat source water with low turbidity and TOC levels (even lower than the levels seen in in-line filtration plants). Yet, relatively high percent TOC removals can be achieved (i.e., 28 percent as a mean). This may be because slow sand filters generally have a long running time and biological fixed-film growth can occur naturally within the filters, if the disinfectant residuals (including free chlorine or chloramines) in the influent are absent or sufficiently low (Collins et al., 1992; Eighmy et al., 1993). Since slow sand filtration plants normally require a larger land area and need less operational attention as compared to other filtration plants, they are used more frequently in small versus large or medium systems (Collins et al., 1992; Eighmy et al., 1993).

7.3.4 Information on Potential Add-on Physical Removal Unit Processes

One approach that has been used for additional removal of DBP precursors is to include physical removal unit processes in a treatment train (normally following filtration). These unit processes commonly include GAC (adsorption), membranes (including microfiltration or nanofiltration) and ion exchange. To ensure the reasonable effectiveness of these treatment units, specific pre-treatment is typically included, particularly for surface waters. As indicated in Exhibit 7.2, GAC and membranes were included as treatment technologies for compliance with the existing D/DBPRs. For the Stage 2 D/D/DBPR, for systems that disinfect their source water (i.e., non-consecutive systems), best available technologies (BATs) were defined as 1) enhanced coagulation or enhanced softening, plus GAC 10, 2) nanofiltration and 3) GAC 20 plus chlorine (USEPA, 2006a), based on the assessment that most water systems would be able to meet MCLs for TTHM/HAA5 with these treatment technologies.

This section discusses new information (since development of the Stage 2 D/DBPR) on applicability, effectiveness and unintended consequences of these unit processes.

7.3.4.1 Adsorption by GAC

The adsorbent materials used for water treatment are either carbon-based (e.g., GAC) or non-carbon-based. Since non-GAC adsorption is mostly used to remove contaminants such as arsenic and radionuclides, rather than DBP precursors (Schendel et al., 2009), it is not discussed here.

One longstanding concern about organic precursor removal is the extent to which it causes a shift in chlorination DBP mixtures to more brominated species when source water bromide levels are relatively high (Summers et al., 1993; Symons et al., 1993; Sohn et al., 2006). To further understand this issue, EPA reassessed the data from the ICR Treatment Study Database (ICRTSD), which contains extensive bench- and pilot-scale data on the effectiveness of GAC and nanofiltration in controlling natural organic matter (NOM) DBP precursors (USEPA, 2000f). This section summarizes the analytical results from this data source, along with pertinent new literature. Additional details about EPA's analysis of the data from ICRTSD are provided in Appendix C of this document. Overall, EPA's analysis generally shows increased percent reduction of the sum of the BrTHMs (sometimes referred to as THM3, which is the sum of the three BrTHM species) as TOC removal by GAC increases (e.g., from a target effluent level of 2 mg/L to 1 mg/L) for source waters with high bromide concentrations. It also shows that bromoform formation increases as bromide concentrations increase and that bromoform becomes the dominating species when source water bromide concentrations exceed 200 µg/L.

7.3.4.1.1 Analysis of Data from ICRTSD for GAC

Background. The DBP ICR required surface water systems serving more than 100,000 people with raw water TOC levels greater than 4.0 mg/L and ground water systems serving more than 50,000 people with finished water TOC levels greater than 2.0 mg/L to conduct bench or pilot studies of GAC or nanofiltration for the control of DBP precursors (USEPA, 1996b). A total of 99 treatment studies, including 63 with GAC and 36 with nanofiltration, were conducted and the results submitted to EPA (USEPA, 1996b; Hooper and Allgeier 2002; USEPA, 2006a). The ICR Treatment Study represents the most extensive evaluation of GAC for DBP control under field conditions, with a wide range of source water quality and distribution system characteristics (Hooper and Allgeier, 2002). EPA used the ICRTSD to guide the selection of BATs in developing the Stage 2 D/DBPR (Hooper and Allgeier, 2002; Bond and Digiano, 2004).

In the treatment studies, samples were analyzed for THM4 and HAA6 (a subset of samples were also analyzed for HAA9) using simulated distribution system (SDS) testing to assess DBP formation in distribution systems. The SDS test simulates the average distribution system conditions at an individual plant, such as residence time, water pH and temperature, with free chlorine as the primary and residual disinfectant.

Analytical Approach. The impacts of TOC removal by GAC on DBP formation were evaluated as a function of the bromide concentration in source water. Prior to analysis, the GAC influent and effluent water quality data were extracted from the ICRTSD based on the effluent TOC concentration of 1 and 2 mg/L, respectively. The 1- and 2-mg/L TOC datasets contain 259 and 191 records, respectively. Data were then placed into low- and high-bromide groups based on the median bromide concentration of 64 µg/L for the 1-mg/L TOC dataset and 75 µg/L for the 2-mg/L TOC dataset. Statistical analysis (including 10th percentile, median and 90th percentile) was performed on SDS-THM4 (the sum of four regulated THM species), SDS-THM3 (sum of three BrTHM species), SDS-HAA9 (nine species of haloacetic acids (HAAs)) and SDS-HAA-Br (six brominated HAAs). Bromine incorporation factor and percentage of bromide incorporation (PBI) were calculated using equations from literature to evaluate the extent of bromine incorporation into DBP groups (Sohn et al., 2006).

Summary of Analysis. The treatment data show that: 1) the percentage removal in BrTHMs increases as TOC removal by GAC increases from a target effluent level of 2 to 1 mg/L for source waters with high bromide concentrations; and 2) bromoform formation increases as the bromide concentration increases and bromoform becomes the dominating species when source water bromide concentrations exceed 200 µg/L for the high-bromide group. The removal of BrTHMs is less significant for the low-bromide waters because BrTHMs were formed at lower levels in those waters. GAC treatment resulted in a smaller PBI in treated water for both THMs and HAAs, similar to the effect of coagulation, where a smaller percent of bromide incorporation was observed for coagulated water (Sohn et al., 2006). Formation of brominated DBPs may have been limited by precursor availablity at low TOC levels. Results of the GAC influent and effluent water quality for the 1- or 2-mg/L TOC datasets are provided in Appendix C of this document.

Limitations of ICR Treatment Study Dataset. The ICRTSD studies were conducted from July 1997 to December 1998, prior to promulgation of the Stage 1 D/DBPR. Water systems may have optimized their treatment strategies after the promulgation of these rules, which may affect how well the results of the GAC treatability studies represent the post-Stage 1 conditions. Furthermore, the SDS tests used average residence time in the distribution system. Since compliance under the Stage 2 D/DBPR is based on samples taken at locations representing maximum residence time in the distribution system, the SDS DBP levels in the ICRTSD could underestimate DBP formation for compliance with the Stage 2 D/DBPR.

7.3.4.1.2 GAC Literature Review

This section summarizes new information from the literature on GAC for the removal of organic DBP precursors, inorganic DBP precursors, organic DBPs and inorganic DBPs, respectively.

Removal of Organic DBP Precursors. GAC has a long history of use in the United States for removing certain organic compounds. Numerous studies published after development of the Stage 2 D/DBPR provide an improved understanding of the applicability and effectiveness of GAC for removal of organic materials. According to McGuire et al. (2014), the water system in Cincinnati, Ohio is the first utility in the United States to install a modern GAC treatment system with regeneration on site and a capacity of 215 million gallons per day. There are at least a dozen additional GAC plants in the Ohio Valley, Texas, Arizona and elsewhere. Although some were originally installed to remove NOM for DBP control, many utilities are realizing other benefits in addition to the original purposes.

Researchers have identified and evaluated key factors to be incorporated into predictive models for GAC unit design (Bond and Digiano, 2004; Chiu et al., 2012). Particularly, they evaluated the relationships between GAC service life and source water type, feed water quality, GAC particle size and EBCT. Preliminary bench-scale testing showed that prechlorination shortly before GAC filtration resulted in lower THMs in the distribution system, compared with the use of GAC without prechlorination (Ghosh et al., 2011).

Other studies evaluated the efficiency of GAC for removal of precursors of nitrogenous DBPs, including NDMA (Chiu et al., 2012; Hanigan et al., 2012; Hanigan et al., 2015). These studies looked at removal of NDMA precursors in river waters containing wastewater effluent, the effect

of the use of pre-oxidants and removal of NDMA precursors originating from polyDADMAC coagulants.

Removal of Inorganic Precursors. Researchers have conducted bench scale testing of new adsorbents that can remove additional bromide and iodide compared to traditional GAC and PAC. These new adsorbents are superfine PAC, silver-impregnated activated carbon and silver-doped carbon aerogels (Zhang et al., 2015; Ikari et al., 2015; Sánchez-Polo et al., 2006; Sánchez-Polo et al., 2007). Superfine PAC, which has significantly smaller particle sizes than PAC, achieved 90 percent removal of iodine following prechlorination (Ikari et al., 2015). Silver-doped carbon aerogels likewise have been found to increase adsorption of bromide and iodide by a factor of 3 to 12 times that of conventional GAC (Sánchez-Polo et al., 2006). However, one potential unintended consequence of full-scale use of the silver-doped aerogel treatment method is the possible leaching of the carbon polymer precursors.

Removal of Organic DBPs. Johnson et al. (2009) conducted a literature review on THM4/HAA5 removal by GAC and indicated that a 70 percent or more reduction of both THM4 and HAA5 could generally be achieved. A pilot study from Babi et al. (2007) showed that the removal capacity of GAC exhibited the order of DOC > HAAs > THMs, which was consistent with observations from the study conducted by Kim and Kang (2008), but contrary to findings of Xie and Zhou (2002), who indicated that GAC breakthrough of HAA5 occurred more quickly than breakthrough of THM4. This inconsistency could be attributable to biodegradation of DOC and HAAs occurring within the adsorption unit (Babi et al., 2007; Kim and Kang, 2008; Johnson et al., 2009). Xie et al. (2004) concluded that GAC could be used for short-term removal of preformed THMs (through adsorption) and long-term removal of preformed HAAs (adsorption plus biodegradation). Booth et al. 2006 demonstrated the effectiveness GAC for removing NOM and controlling THM4 and HAA5 in high bromide waters using free chlorine during distribution although higher percentages of the brominated species were formed.

Xie et al. (2004) recommended retaining 5 percent of the old GAC in the column to expedite bioactivity development after replacement for better HAA removal. Johnson et al. (2009) noted that the design variables for the removal of THM4 and HAA5 by GAC include EBCT, use of a pressurized or gravity flow system, type of carbon used, backwash frequency, velocity and species being adsorbed. For THM4, the more brominated species had greater adsorption capacities than the more chlorinated species; for HAA5, the more halogenated species had higher adsorption capacities than mono-HAA. Removal of nitrosamines (including NDMA) by GAC is discussed in the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d).

Removal of Inorganic DBPs. In addition to removal of organic DBPs, GAC also exhibits some capacity for removal of inorganic DBPs. In a full-scale study conducted by Hoehn et al. (2003), GAC contactors were found to achieve 63 percent of average chlorite removal with influent concentrations up to 0.8 mg/L but with very long EBCTs ranging from 48 to 130 minutes. Several researchers observed that chlorite removal by GAC involved two steps: 1) chlorite adsorption on GAC sites and 2) subsequent reduction to chloride. Such an observation was also supported by some earlier studies (Gonce and Voudrias, 1994; Hoehn et al., 2003; Collivignarelli et al., 2006). Gonce and Voudrias (1994) showed that the most effective chlorite removal occurred at pH 5. They further indicated that chlorate was not reduced by GAC, but was only

physically and reversibly sorbed. Thus, much less removal of chlorate by GAC was observed, compared to chlorite. Collivignarelli et al. (2006) indicated that chlorite removal was reduced when GAC was preloaded with organic matter and specific ions (e.g., nitrate). Their study also showed that thermally regenerated GAC demonstrated good removal for both organic matter (70-80 percent) and chlorite (100 percent). With exhausted GAC, organic matter removal was reduced from 40-50 percent (without chlorite) to 5-7 percent (when water was spiked with chlorite); chlorite removal remained significant at ~ 50 percent. Huang and Cheng (2008) studied effects of activated carbon on removal of bromate and observed that carbons with more mesopores adsorbed more bromate. Wood-based carbons contained more mesopores than coconut or coal-based carbons, resulting in a high removal capacity for bromate. Chen et al. (2012) employed cationic surfactant loading to modify GAC to enhance bromate removal. With such modified GAC, bromate was removed mostly through an ion exchange process, and the removal increased with a decreased pH. Xu et al. (2015) prepared and tested nano-iron hydroxide-impregnated GAC (Fe-GAC) for adsorption and reduction of bromate. They found that while GAC alone could reduce some bromate, Fe-GAC could greatly enhance the bromate removal capacity and removal rate, with the optimal pH being 6-8. Both Chen et al. (2012) and Xu et al. (2015) observed that other anions (e.g., PO_4^{3-} and SO_4^{2-}) exhibited inhibiting effects on bromate removal.

7.3.4.2 Membranes

Membrane filtration is a separation technology that pushes or pulls water through a fixed barrier and includes microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO). The primary difference between each type of filtration is the pore size and the operating pressure range of the membranes. The results from the ICR Treatment Study mentioned in the previous section showed that all ground water plants, if they used NF, were able to meet the 80 µg/L TTHM and 60 µg/L HAA5 MCLs with a 20 percent safety factor (i.e., were able to keep TTHM and HAA5 below 64 µg/L and 48 µg/L, respectively) at the average residence time monitoring locations (USEPA, 2005g). NF is less expensive than GAC for high-TOC ground waters, which generally require minimal pretreatment prior to the membrane process. Also, NF is an accepted technology for treatment of high-TOC ground waters in Florida and parts of the Southwest (Thorsen and Flogstad, 2006).

Becker et al. (2013) indicated that MF and UF processes were essentially particle removal processes and were not any more effective than conventional filtration processes in DBP reduction. In contrast, high pressure membrane systems such as NF and RO could directly remove NOM and drastically reduced DBP precursors. Netcher and Duranceau (2015) demonstrated that settled water turbidities greater than 1 NTU could be expected to have detrimental impacts on the efficiency of the subsequent UF process. The results from the studies conducted by Patterson et al. (2012) and Plourde-Lescelleur et al. (2015) confirmed the effectiveness of nanofiltration. One unintended consequence of membrane technologies may be that they can result in removal of alkalinity from the finished water, which can lead to increased lead and copper corrosion and may affect compliance with the Lead and Copper Rule (Becker et al., 2013).

7.3.4.3 Ion Exchange

Ion exchange (using cation and anion resins) is a process that removes dissolved ions from water and replaces them with other similarly charged ions. Schendel et al. (2009) also pointed out that one of the key factors affecting the efficiency of anion exchange at removing the targeted contaminants is the extent to which competitive ions (such as chloride and sulfate) are present in the water. The results from the studies of Singer et al. (2009) and Watson et al. (2015) confirm this observation.

One of the most studied ion exchange processes is magnetic ion exchange (MIEX), where the anion exchange resin is supplemented with magnetic iron oxide to facilitate resin extraction and regeneration. Booth et al. 2006 demonstrated MIEX to be effective in controlling THM4 and HAA5 in high bromide waters using free chlorine during distribution although higher percentages of brominated species were formed. New research has found that MIEX may preferentially remove organic precursors with high SUVA (specific ultraviolet absorbance) and low molecular weights (Plourde-Lescelleur et al., 2015; Hanigan et al., 2013; Singer et al., 2009; Mergen et al., 2009; Drikas et al., 2011; Watson et al., 2015; Metcalfe et al., 2015). Drikas et al. (2011) found that very hydrophobic acids represented a significant portion of the NOM removed by MIEX. Other researchers found these types of acids could be correlated to DBP formation (McKie et al., 2015; Chang et al., 2013). The study conducted by Metcalfe et al. (2015), with ion exchange configurations other than MIEX, confirmed the effectiveness of anion exchange for removing UV-absorbing materials.

Unlike other organic DBP precursor removal techniques such as enhanced coagulation, anion exchange (including MIEX) can also remove bromide and iodide (by 21-91 percent) (Hsu and Singer, 2010; Phetrak et al., 2014; Walker and Boyer, 2011; Xu et al., 2013; Echigo et al., 2007). Depending on the Br^-:DOC in the water, however, a shift to a higher percentage of brominated DBPs in treated water may still occur (Watson et al., 2015).

Several studies have found that the use of chloramines following ion exchange treatment can lead to increased NDMA formation (Gan et al., 2013; Watson et al., 2015). NDMA formation likely occurs because most anion exchange resins are composed of amines, which have been demonstrated to be NDMA precursors (Krasner et al., 2013; Flowers and Singer, 2013). The observed contribution to NDMA formation from MIEX is between 5 and 10 ng/L (Watson et al., 2015; Gan et al., 2013), although researchers note that concentrations can be much higher if preformed chloramines are used with no free chlorine contact time (Gan et al., 2013). In addition to NDMA precursors, a recent study found that ion exchange resins could be a direct source of nitrosamines in finished water (Watson et al., 2015).

A challenge of ion exchange treatment is disposal of the waste brine from resin regeneration. Walker and Boyer (2011) demonstrated the use of bicarbonate as the mobile counter-ion and sodium bicarbonate for regeneration instead of chloride-form anion exchange to address disposal concerns.

7.3.4.4 Other Unit Processes

Many studies have been conducted to develop some innovative approaches for further removal of DBP precursors and/or control of DBP formation. Some of these approaches have not been applied to pilot- or full-scale plants and are not summarized here. This section only covers oxidation and electrolysis, which have been tested at the bench- or pilot-scale and may have applicability in full-scale treatment.

Disinfectants (typically including ozone, chlorine dioxide and free chlorine) have been applied as oxidants at the beginning of treatment trains to chemically transform DBP precursors to forms that result in lower DBP formation potentials. Other oxidants used include hydrogen peroxide and permanganate. Such an operation is often referred to as pre-oxidation. The national survey conducted by the AWWA Disinfection Committee in 2007 (AWWA, 2008) showed that 36 percent of SW systems used pre-oxidation. Matilainen and Sillanpää (2010) provided a detailed review of more than 50 oxidation research studies conducted between 2006 and 2009. They noted that, although oxidation processes showed promise, circumstances in the research studies were often impractical for full-scale plants and there were very few full-scale applications. In addition, their review found that oxidation processes could cause a shift to lower molecular weight compounds and that incomplete oxidation by several oxidants had been shown to increase DBP formation potentials. Appendix C of this document includes a synopsis of some new studies related to advanced oxidation.

Electrolysis involves the oxidation of bromide to bromine followed by volatilization of bromine through the use of an electrical current (Kimbrough and Suffet, 2006; Kimbrough et al., 2011; Kimbrough et al., 2012). Electrolysis has been found to remove 27–54 percent of source water bromide when tested at the pilot scale on California State Water Project water. Important factors for optimization include flow rate through the electrolysis reactor and contact time. For optimization, Kimbrough and Suffet (2006) reported that the current applied should increase as the flow becomes greater and the contact time shortens. Based on evaluation of five different reactor bodies and varying placement of anodes within the reactors, Kimbrough et al. (2011) concluded that full-scale reactors should maximize the surface area of the anodes and be as shallow as possible to maximize the volatilization of bromine. A possible unintended consequence is an increase in brominated haloacetonitriles; however, Kimbrough and Suffet (2006) noted that the observed overall levels were very low, which made it unclear if the increase was significant.

7.4 Information on Source Water Management

The information reviewed during the SYR3 process also reveals that some industrial activities (e.g., hydraulic fracking or coal power generation) can increase bromide levels in drinking water sources (see Chapter 6 of this document) and typical conventional treatment trains appear ineffective at removal of bromide (States et al., 2013). Also, several new studies indicate that municipal wastewater discharges and/or occurrence of algal blooms nearby water intakes can increase the levels of DBP precursors in source water (Callinan et al., 2013; Saunders et al., 2015). This information relates to the importance of watershed vulnerability characterization and effective source water management practices.

A watershed vulnerability characterization that includes information about wastewater contributions, land use (including point and non-point pollution sources) and streamflow variations over time (for example, sewage contributions during low flow conditions) could help to inform considerations about DBP formation potentials. For example, as noted by Krasner et al. (2015), source waters with relatively elevated sewage contributions have been associated with increased nitrosamine formation.

Approaches to characterizing vulnerabilities were identified in the literature. Several papers discuss the use of fluorescence excitation/emission spectroscopy to characterize source water DOC and track changes over time (Hua et al., 2007; Rosario-Ortiz et al., 2007; Bridgeman et al., 2011; Pifer and Fairey, 2012). For example, Rosario-Ortiz et al. (2007) used fluorescence analysis to distinguish between waters affected by microbial activity (e.g., by wastewater influence) and those that were only minimally affected. Fluorescence excitation/emission spectroscopy is non-destructive, and the potential exists for using it as an on-line, source water monitoring and management tool (Bridgeman et al., 2011).

Weiss et al. (2013) developed a model for making source water selection decisions based on real-time DBP precursor concentrations. Such a model could be used by utilities with multiple source waters, intakes or intake depths. Modeling results showed that DBP precursors could be reduced by modifying diversion decisions based on real-time DBP precursor concentrations in different reservoirs.

Pre-treatment processes for lowering DBP formation potentials in water sources include raw water storage/pre-sedimentation and bank filtration. Raw water storage/pre-sedimentation can help to reduce seasonal variation of source water quality and pre-settle some particulates (including some organic matter). The national survey conducted by the AWWA Disinfection Committee in 2007 (AWWA, 2008) showed that 31 percent of SW systems (including those of all sizes) used raw water storage/pre-sedimentation.

Depending on site conditions, bank filtration has been shown to be an effective method to improve source water quality and thus reduce the treatment burden on the existing treatment trains. Literature indicates that bank filtration can not only remove some pathogens but can reduce the formation potentials of DBPs associated with chlorination and chloramination (Brown et al., 2015).

Depending on site conditions (including geological conditions and land ownership), bank filtration, if appropriately constructed and used, can improve source water quality and thus reduce the treatment burden on a treatment train. Bank filtration appears to be more commonly used in Europe (Wang et al., 2002).

The removal of organic compounds by bank filtration can depend on the flow path the water takes to the collector well and the oxygen content of the water. In general, the longer the flow path to the collector well, the better the removal. Temperature can affect both the biological activity of the filtration and the flow dynamics (Brown et al., 2015).

Bank filtration has been found to be effective in removing low molecular weight assimilable organic carbon from source waters (Brown et al., 2015). A few studies have examined bank

filtration for the removal of NDMA precursors and found 64 percent reduction of NDMA formation potential, 49 to 72 percent removal of TOC and 58 to 68 percent reduction of UV absorbance (Krasner et al., 2015). However, about 20 percent of the removal of these indices could be attributed to dilution of the river water with ground water, rather than removal during bank filtration. A study of four full-scale bank filtration facilities found DOC removals of between 12 and 93 percent, with an average of 55 percent. About 10–25 percent of the removal was due to dilution by ground water (Partinoudi and Collins, 2007).

7.5 Information on Changing Disinfection Practices in Treatment Plants and Distribution Systems

Disinfection practices generally refer to the collective water quality and treatment conditions under which a disinfectant or disinfectants are applied and disinfectant residuals are maintained during treatment and distribution, including disinfectants used as pre-oxidants discussed earlier. The Agency regularly collects information on disinfection practices, since it is critical for understanding DBP formation and occurrence. Information about disinfection practices is available in the 1997-1998 DBP ICR (USEPA, 2000e), the 2008-2010 UCMR 2 (USEPA, 2012c) and the 2013-2015 UCMR 3 (USEPA, 2016h). Further, it is expected that additional information about disinfection practices will be collected as part of UCMR 4 (USEPA, 2015)). In addition, the AWWA Disinfection Systems Committee periodically (about every 10 years since 1978) conducts a national survey in this area (AWWA, 2008). The data from these sources are collectively presented in Chapter 6 of this document, in the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d) and in the *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e), with the detailed discussion of various factors, including disinfection practices, affecting formation/occurrence of different groups of DBPs. In particular, the current distribution of disinfectant usages and changes in this distribution are characterized and presented in Chapter 6 of this document and further discussed in the *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e).

The following summary is based on those discussions, while the section "Alternative Disinfectants" in Appendix C of this document includes a synopsis of new studies related to common individual or combined disinfectants, including chlorines, ozone, chlorine dioxide and UV. The section "Advanced Oxidation Processes" in Appendix C of this document also provides a synopsis of new studies related to these disinfectants that can be used as oxidants as part of strategies for controlling DBP formation.

Various combinations of disinfectants and precursor removal processes have been used to achieve the DBP MCLs while also meeting the microbial standards. As predicted in the Economic Analysis for the Stage 2 D/DBPR (USEPA, 2005g), the multiple national datasets (including from the DBP ICR, UCMR 2 and UCMR 3) have collectively shown an increasing trend in the number of systems using alternatives to chlorine during the past two decades. This observation is consistent with the observation from the AWWA periodical surveys (AWWA, 2008) mentioned earlier. Numerous systems have shifted their primary disinfectant from free chlorine to chloramines, ozone, chlorine dioxide and UV, including combinations of such disinfectants, and have shifted to using chloramines from free chlorine as a disinfectant residual in the distribution system.

Overall, this trend implies that different organic DBPs other than chlorinated DBPs may become more prevalent over time, especially NDMA. The same may be true for certain inorganic DBPs such as bromate and chlorite, which as associated more strongly with alternative disinfectants. More detailed discussion on controlling formation and occurrence of nitrosamines (including NDMA) is presented in the *Six-Year Review 3 Technical Support Document for Nitrosamines* (USEPA, 2016d). As discussed earlier, new information also informs the extent to which different types of DBPs may be controlled depending upon where they are applied in the treatment train and/or in combination with other disinfectants. For instance, pre-ozonation in conjunction with biofiltration can help removal of precursors of several classes of chlorination DBPs. EPA recognizes that the extent to which occurrence and associated health effects data may be lacking for one group of DBP contaminants versus another, as well as for DBP mixtures, may make treatment decisions challenging.

Regarding forms of chlorine used as free chlorine or for formation of chloramines, EPA has seen a clearly increasing national trend toward using hypochlorite stock solution or on-site generation of hypochlorite in lieu of chlorine gas. This shift is likely due to security concerns of transport and storage of chlorine gas. The implications of this shift in chlorine source have become apparent. In the UCMR 3 dataset, for example, chlorate levels are significantly higher among systems using hypochlorite stock solution or on-site generation of hypochlorite, compared to those using chlorine gas. The analytical results from the UCMR 3 dataset also show that the use of chlorine dioxide can lead to a high occurrence of chlorate. The *Six-Year Review 3 Technical Support Document for Chlorate* (USEPA, 2016e) presents more information on use of hypochlorite versus chlorine gas and associated implications. In addition, the DBP ICR data indicates that among systems serving at least 100,000 people that chlorate can co-occur with chlorite when hypochlorite or chlorine dioxide is used. Since both hypochlorite and chlorine dioxide are being used more frequently, they are probably being used more frequently in conjunction with each other, which can lead to higher levels and frequencies of chlorate/chlorite co-occurrence if no effective control measures are implemented. The water industry has provided tools that can help utilities to manage the concentrations of chlorate in water treated with hypochlorite stock solution. For instance, a web-based predictive tool for chlorate formation during storage of hypochlorite solution can be found on the AWWA website (http://www.awwa.org/resourcestools/waterandwastewaterutilitymanagement/hypochloriteassessmentmodel.aspx).

Many distribution systems provide a relatively long contact time, which may inadvertently lead to DBP formation after the treated water leaves the treatment plants. New information indicates that system-specific models can be developed to help operators optimize DBP control strategies in distribution systems. Behzadian et al. (2012) used an NSGA-II algorithm coupled with the EPANET hydraulic model to concurrently optimize chlorine residuals and THM formation resulting from booster disinfection operations. Cruickshank (2010) showed how hydraulic models can be used to assess the impact of control strategies, such as flushing, tank turnover and bleed water at zone boundaries, on water age. A Rhode Island utility developed an empirical model to limit THM4 levels in water leaving a finished water storage tank (Oneby et al., 2009). The calibrated model helped operators decide which sources of supply to use depending on current conditions (e.g., water temperature).

7.6 Information on Removing DBPs after Formation in Treatment Plants and/or Distribution Systems

Since the promulgation of the Stage 2 D/DBPR, EPA notes the availability of new information on DBP removal using aeration processes through volatilization (i.e., removing volatile DBP compounds from water by transporting them to a gas phase). As discussed by Johnson et al. (2009), all of these DBP removal or reduction technologies may be used as a localized treatment approach in the distribution system. Utilities treat only the flow necessary at specific locations in the distribution system (rather than treating the entire flow at the centralized treatment plant) to comply with the MCLs for TTHM/HAA5 under the Stage 2 D/DBPR. Since DBP removal through biofiltration or GAC adsorption was discussed earlier in this Chapter, this section focuses on the new information on aeration processes.

Overall, aeration can be an effective process to lower THM4 levels (more effectively for chloroform than the brominated species), but may have little effect on HAA5 levels. It is not clear, however, how this type of treatment will affect levels and formation potentials of "not-so-volatile brominated DBPs" downstream and water quality stability in distribution systems (Ghosh et al., 2015).

Three basic types of aeration systems have been identified from the mechanical perspective: surface aeration, spray aeration and diffused aeration/air stripping (Ghosh et al., 2015; Johnson et al., 2009; Brooke and Collins, 2011; Duranceau, 2015). Removals for individual DBPs depend on their Henry's Law constants. Chloroform is removed to a greater extent, while brominated species are removed to a lesser extent (Johnson et al., 2009). DBPs of low volatility Johnson et al. (2009), based on a pilot study, indicated that while aeration (through air stripping) was effective to lower THM4 levels, it had no effect on HAA5.

Ghosh et al. (2015) studied surface and spray aeration side by side in the clearwells in full-scale plants. Both systems were able to achieve between 19 and 34 percent THM4 removal and the THM4 removal efficiency of the spray aeration system was marginally better (about 5 percent). Ghosh et al. (2015) indicated that the overall THM4 reduction could be influenced by multiple factors, including variation of hydraulic residence times in the clearwell, formation of THM4 within the clearwell and dilution of the aeration-treated water with the incoming water. This research team also observed that such operations could reduce the baffling factor for quantifying disinfection credits from the clearwell.

Because water systems must meet the TTHM MCL at each sampling location as part of the Stage 2 D/DBPR, some water systems have opted to use aeration technologies to lower THM4 levels at certain locations in their distribution systems (Ghosh et al., 2015; Duranceau, 2015). Aeration systems may be installed inside storage facilities or located outside of storage facilities. Aeration systems inside storage facilities commonly use diffused aeration, where air is injected at the bottom and spray aeration, where water is sprayed through air from nozzles at the top (Brooke and Collins, 2011). Other in-tank aeration methods include surface aeration, where aerators float on the water's surface and low-profile aerators (Jensen et al., 2010; Johnson et al., 2009). Aeration systems located external to storage facilities include air stripping trays or packed towers, membrane contactors and spray/bubble vessels (Brooke and Collins, 2011; Johnson et al., 2009).

Several studies have documented the effectiveness of various forms of post-treatment aeration for THM4 control (e.g., surface aerators in Phoenix, Arizona, as reported by Jensen et al. (2010); spray aerators in Suisun City, California, as reported by Walfoort et al. (2008); and spray aerators in Ballinger, Texas, as reported by Fiske et al. (2011). Brooke and Collins (2011) found that the removal rates for individual THM species were similar for spray aeration, but removals of chloroform were higher when a diffused aeration system was used. THM4 removal in post-treatment aeration facilities has been found to range from 47 to 93 percent depending on several variables, including air to water ratio, droplet travel distance, water temperature and droplet mean diameter (Brooke and Collins, 2011).

Several studies have considered whether distribution system aeration to remove THM4 also reduces the water's chlorine residual, which may be an unintended consequence. Individual researchers have not found this to be a problem in full-scale installations (Johnson et al., 2009; Sinfield and Niday, 2015). The removal of chlorine residual may require the application of booster chlorination, which requires additional management. In contrast to the negative impacts of residual striping, one system found that aeration improved the mixing conditions in the storage tank, which in turn led to reduced chlorine decay in the tank, and overall a lower chlorine dose necessary for maintaining minimum disinfectant residual levels through the entirety of the distribution system (Sinfield and Niday, 2015). The degree of residual stripping versus reduction in residual decay will rely on many factors, pH, temperature and the aeration system to name a few.

One aspect of aeration processes as currently employed is that the removal of DBPs at any midpoint in the distribution may have little impact on controlling the continual formation of DBPs further downstream of the aeration system. While additional DBP formation does occur, one study found that after 170 hours DBP concentrations were half of what they had been before aeration (Johnson et al., 2009). Nevertheless, the changes in water quality after localized treatment could vary based on site-specific conditions in individual utilities.

8 Consideration of Other Regulatory Revisions for MDBP Rules

In addition to the review of maximum contaminant level goals (MCLGs), maximum contaminant levels (MCLs) and treatment technique (TT) established by the National Primary Drinking Water Regulations (NPDWRs), EPA considered whether other regulatory revisions, such as monitoring and reporting requirements, should be considered as part of the Six-Year Review (SYR) process.

The Implementation Branch of the SYR protocol decision tree requires information regarding whether a change in a contaminant's MCL or TT, or the availability of new health effects information, will affect the monitoring or reporting requirements for a particular contaminant. For the Third Six-Year Review (SYR3), EPA focused this review on implementation issues that were not already being addressed through alternative mechanisms, such as a part of a recent or ongoing rulemaking. In addition to this criteria, EPA considered potential implementation-related revisions if they:

(1) Represented a potential change to an NPDWR, as defined under section 1401 of SDWA;

(2) Were "ready" for rulemaking — that is, the problem to be resolved had been clearly identified, along with specific options to address the problem under the current regulatory framework; and

(3) Would clearly improve the level of public health protection and/or provide a meaningful opportunity for cost savings (either monetary or burden reduction) while not lessening public health protection.

The output of the Implementation Branch is a determination regarding whether EPA should consider revisions to the monitoring or reporting requirements of an NPDWR. It is the final branch of the decision tree.

EPA used the protocol to evaluate which of these issues to consider under SYR3. After EPA had a consolidated list of implementation-related issues, it shared that list with the Association of State Drinking Water Administrators to obtain input from state drinking water agencies concerning the significance and relevance of the issues. Implementation issues will be considered as part of the activities associated with potential future rulemaking efforts; some of these might be addressed through regulatory revision or clarification, while others might be handled through guidance.

Examples of implementation issues that are related to the MDBP rules include consecutive system monitoring and chlorine burn, both of which are described further below. Additional implementation issues related to the MDBP rules are described in Appendix D. Implementation-related issues for the chemical phase rules are discussed in a separate document (USEPA, 2016g).

8.1 Stage 2 D/DBPR Consecutive System Monitoring

Monitoring in some combined distribution systems may be insufficient to adequately characterize DBP exposure. Some large, hydraulically complex combined water distribution systems may be conducting monitoring that is not adequate to characterize exposure throughout

the distribution system. Under the Stage 2 D/DBPR, EPA provided an alternative for states to use to modify THM4 and HAA5 monitoring requirements for consecutive and wholesale systems, in lieu of the existing modification process under 40 CFR §141.29, which requires EPA concurrence. As a special primacy condition (40 CFR §142.16(m)), states may apply for approval to modify monitoring without case-by-case EPA concurrence. Such approval requires that every system in the combined distribution system have at least one compliance monitoring location, so that compliance determinations are based on samples taken within the individual distribution system. EPA anticipated that states would ensure that the number of compliance monitoring locations and frequency of sampling after modification would remain sufficient to adequately characterize DBP exposure and protect public health.

8.2 Stage 2 D/DBPR Compliance Monitoring - Chlorine Burn

Compliance monitoring for DBPs in some systems may not fully capture DBP levels to which customers are exposed throughout the year. Under 40 CFR §141.621(a)(2), including footnote 2, monitoring frequency and timing are specified for surface water and ground water systems based on a system's population size category. Systems that use chloramines as a residual disinfectant (generally as part of a compliance strategy to meet DBP MCLs) often temporarily switch to free chlorine as the residual disinfectant for a period (from 2-8 weeks) in order to control nitrification in the distribution system. This practice is commonly called a "chlorine burn." During the chlorine burn, higher levels of DBPs (i.e., THM4, HAA5 and other chlorination DBPs) are expected to form. Systems often conduct their compliance monitoring outside of the chlorine burn period, and therefore, potentially higher THM4 and HAA5 levels are not included in compliance calculations. Actual exposures may be significantly higher than reported exposures in such cases.

Additional Information Related to Chlorine Burn

The effects of chlorine burn periods on exposure to DBPs might become increasingly important in light of the adverse health effects (reproductive and developmental) related to short-term exposure to DBPs in chlorinated drinking water (refer to Chapter 4 for a discussion of health risk information about reproductive and developmental toxicity). Further, such elevated concentrations of DBPs, depending upon their levels and duration, could be important for more accurately assessing running annual average (RRA) exposures. For example, if the burn period were for a month, the theoretical contribution of that month's THM4 or HAA5 occurrence could represent one-third of the occurrence for that quarter and if considered, could substantially affect the actual average concentration for that quarter as well as that for the RAA.

Data gaps exist for several areas related to chlorine burn – e.g., the percent of the industry that uses this practice, the frequency and length of time for which the burns are performed and the levels of DBPs produced by short-term exposures during those periods.

To further assess these data gaps and other issues pertaining to chlorine burn practices, EPA conducted a literature review on the potential impacts of chlorine burn on DBP formation

(USEPA, 2014b). Specifically, EPA conducted the literature review to gather available information on the following:

- Typical chlorine burn practices adopted by PWSs, including timing, frequency, duration, free chlorine dose (especially relative to the dose before chlorine burn) and any other treatment operational changes;
- Water quality monitoring for DBP and chlorine residual levels during chlorine burn vs. state requirements (if any);
- Public notification practices adopted by PWSs vs. state requirements;
- Research projects to evaluate the effect of chlorine burn on DBP formation;
- Guidance documents or industry standards on chlorine burn practices adopted by primacy agencies and the water industry (such as from the American Water Works Association (AWWA) or the 10-state standards); and
- Alternative nitrification control strategies and how they compare with the chlorine burn practice.

The literature review shows that for utilities that use chloramine and either have had nitrification problems, or have nitrification controls, a reported 25 to 40 percent have used free chlorine burns to control nitrification (USEPA, 2014b). These proportions of utilities implementing chlorine burns are similar to the 22 percent of 63 utilities reported from a 2003 survey by Harms and Owen (2004).

In a free chlorine burn, chloramine in a distribution system or in part of a distribution system is replaced with sufficient free chlorine to oxidize excess ammonia and eliminate substrate used by ammonia-oxidizing bacteria. Although some utilities implement chlorine burns as a matter of routine operations (and may do so under state requirements in some cases), chlorine burns increase DBP formation. AWWA's manuals, M20 and M56 (AWWA 2006, 2013), provide guidance and recommendations for minimizing nitrification and practices that minimize DBP formation. In particular, AWWA (2013) recommends that chlorine burns be "a last resort" for controlling nitrification given the increased THM4 and HAA formation during chlorine burns. While free chlorine burns are primarily used to mitigate nitrification events, some utilities have reported using free chlorine burns for biofilm reduction. AWWA (2006) reports that switching periodically to free chlorine might also reduce growth of chloramine-resistant bacteria. The surveys reviewed in the literature study tended to focus on medium and larger utilities.

An example of the unintended consequences of a temporary switch to use of free chlorine was identified for a large U.S. city (Huerta et al., 2015). In that example, the city temporarily switched its disinfectant at a treatment plant in response to concerns about nitrification in distribution systems. Data were made available about these temporary switches, made in May 2009 and October 2014. During these events, THM4 values were often higher than 200 ppb and sometimes higher than 300 ppb, while HAA5 values were often higher than 100 ppb and sometimes higher than 200 ppb.

Estimation of the Effect of Chlorine Burn on DBP Levels

Data are available in the DBP ICR dataset (further discussed in Chapter 6) and the ICR Treatment Study Data (ICRTSD, further discussed in Chapter 7) that could be used to estimate

the impact of a switch in disinfectant use, specifically from chloramine to chlorine, on the levels of DBPs. In addition to field samples, utilities prepared simulated distribution system (SDS) samples for their treatment plants. The SDS is a test method developed to predict the amounts of DBPs that form based on simulated conditions in the treatment plant and distribution system. Some of the key parameters affecting the SDS conditions are incubation time, temperature, pH and chlorine residual. Previous studies have shown good correlation between SDS results and field test results (McGuire et al., 2002). Samples that were disinfected using chloramine in the ICR DBP dataset and using free chlorine in the ICRTSD could be linked using the same plant ID number and calendar quarter to compare the difference in DBP levels under the two disinfectant uses. In this manner, the impact on THM4 and HAA5 from a switch in disinfectant from chloramine to chlorine could be used to mimic the impact of a chlorine burn.

EPA conducted a preliminary review of these data, based on 44 quarters from 20 plants. The results from this review suggested that plants may observe substantial increases in THM4 levels, and a smaller increase in HAA5 levels, when chlorine is used as the residual disinfectant compared to chloramine. For a majority of plants, the projected increase would be approximately 30–40 μg/L or greater but in some cases more than 80 μg/L. Additional information about this effort are provided in Appendix E to this document.

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List of Appendices

Appendix A. Additional Information for Health Effects of Regulated Organic Disinfection Byproducts (DBPs), Regulated Inorganic DBPs and Regulated Disinfectants (Appendix to Chapter 4)

Appendix A provides additional information about the health effects of the regulated organic disinfection by-products (DBPs), regulated inorganic DBPs and the regulated disinfectants. The information included in Appendix A supplements information provided in Chapter 4 – Health Effects. To aid in cross-referencing, this appendix uses the same subheading numbering and titles that appear in Chapter 4.

A.1 Regulated Organic DBPs

A.1.1 Toxicity Studies

A.1.1.1 Trihalomethanes (THMs)

This section presents animal toxicity study information that was available during the development of Stage 1 and Stage 2 D/DBPRs for bromoform, bromodichloromethane (BDCM), dibromochloromethane (DBCM) and chloroform. The information includes studies of carcinogenicity, mutagenicity/genotoxicity and reproductive/developmental effects that were performed for each of those trihalomethanes. Details of the studies include: nominal dose, route of exposure, duration of exposure, gender of species and strain of the species.

A.1.1.1.1 Bromoform

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

The National Toxicology Program (NTP) conducted research on the carcinogenicity of bromoform in 1989. Bromoform was administered by gavage in corn oil to male and female F344/N rats and to male and female B6C3F1 mice either once (single dose of 2,000 mg/kg), for 14 days (doses ranged from 600-800 mg/kg), 13 weeks (doses ranged from 12-200 mg/kg), or 2 years (doses of 0, 100 or 200 for rats and 0, 50 or 100 for mice) (NTP, 1989a). NTP concluded that there was clear evidence of carcinogenicity based on tumors in the large intestine (colon or rectum) in female rats, some evidence in male rats and no evidence in mice.

Mutagenicity/Genotoxicity

Most *in vitro* studies with bromoform in Salmonella typhimurium were negative, with a few studies having equivocal results, both with and without metabolic activation. Positive results were reported for *in vitro* studies on DNA damage and mixed results for increased sister chromatid exchange, chromosomal aberrations and DNA strand breaks. Bromoform was tested in *in vivo* studies in rats and mice, showing positive results for sister chromatid exchange and sex-linked recessive lethal mutations, mixed results for chromosomal aberrations and negative

results for DNA strand breaks, micronuclei formation and unscheduled DNA synthesis (NTP 1989a; USEPA, 2005d).

Reproductive/Developmental

The following reproductive and developmental studies on bromoform were reviewed by EPA and documented in EPA's *Drinking Water Criteria Document for Brominated Trihalomethanes* (USEPA, 2005d):

Ruddick et al. (1983) investigated the reproductive and developmental toxicity of bromoform administered in doses of 50, 100 or 200 mg/kg/day by gavage in corn oil to pregnant Sprague-Dawley rats on gestational day (GD) 6 through 15. A statistical analysis of the published data demonstrated a significant increase in sternebral anomalies, resulting in a developmental No-Observed-Adverse-Effect-Level (NOAEL) and Lowest-Observed-Adverse-Effect-Level (LOAEL) of 50 and 100 mg/kg/day, respectively. No maternal effects were observed, resulting in a NOAEL of 200 mg/kg/day.

NTP administered bromoform at 50, 100 or 200 mg/kg/day by gavage in corn oil to Swiss CD-1 mice using a continuous breeding protocol for 7 days pre-cohabitation and 98 days cohabitation (NTP, 1989b). The NOAEL and LOAEL for developmental and general toxicity were 100 and 200 mg/kg/day, respectively, based on postnatal survival, liver histopathology and changes in liver and kidney weights. The maternal NOAEL and LOAEL were 100 and 200 mg/kg/day, respectively, based on decreased body weights.

A.1.1.1.2 Bromodichloromethane

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

Bromodichloromethane (BDCM) was found to be carcinogenic in rats and mice after administration by gavage in corn oil (NTP, 1987). Groups of F344N female and male rats were administered BDCM at 0, 40 or 80 mg/kg/day and groups of 50 male and female B6C3F1 mice were administered BDCM at 0, 50 or 100 mg/kg/day, both groups received varied doses 5 times a week for 104 weeks. Tumors were observed in the large intestine in male and female rats, in the liver in female mice, and in the kidney in male mice and in male and female rats. The slope factor for BDCM is based on renal tumors in male rats.

The carcinogenicity of BDCM has also been studied when administered in drinking water. In George et al. (2002), BDCM was administered in drinking water with mean daily doses of 3.9, 20.6 and 36.3 mg/kg/day for male F344/N rats and 8.1, 27.2 and 43.4 mg/kg/day for B6C3F1 male mice. BDCM was found not to be carcinogenic in the male mice; however, it produced an increased incidence of hepatocellular neoplasms in the male rats. Another study found an increase in the incidence of liver neoplasms when female Wistar rats were administered BDCM in drinking water (Tumasonis et al., 1987). Neoplasms were not observed in the kidney or large intestine in these studies. No neoplastic effects were observed in male mice administered BDCM in drinking water or in Wistar rats fed microencapsulated BDCM (George et al., 2002; Aida et al., 1992). The difference in these results may be explained in part by factors such as the stability

of BDCM in feed and water, the influence of a vehicle and different rates of absorption and metabolism following different vehicles of administration. For instance, when BDCM was administered by gavage in corn oil at 50 and 100 mg/kg to male F344/N rats, DNA hypomethylation in the colon was greater and more rapid than when it was administered in drinking water at concentrations of 350 and 700 mg/L (Pereira et al., 2004a).

Hooth et al. (2002) and McDorman et al. (2003a) administered BDCM in drinking water to male and female *Tsc2* mutant Long-Evans (Eker) rats for 4 or 10 months. This particular strain of rats is highly susceptible to the effects of renal carcinogens. No increased incidence of tumors was observed.

Putative pre-neoplastic lesions were observed in the intestine and kidney in rats exposed to BDCM in drinking water in studies with durations of less than one year: aberrant crypt foci were observed in the colon of F344 and Eker rats (DeAngelo et al., 2002; McDorman et al., 2003b) and atypical tubules and hyperplasia were observed in the kidney of Eker rats (McDorman et al., 2003b).

Mutagenicity/Genotoxicity

In vitro studies have reported mixed results. Mutagenicity studies in *Salmonella typhimurium* reported mixed results, both with and without metabolic activation, while tests in mouse lymphoma cells were positive with metabolic activation. Mixed results were reported on tests for sister chromatid exchange and chromosomal aberrations, both with and without metabolic activation. Studies on DNA strand breaks showed mixed results, and primarily positive results were reported in studies on DNA damage and micronuclei formation. In *in vivo* studies, results were positive for sister chromatid exchange and chromosomal aberrations, mixed for micronuclei formation and negative for DNA strand breaks and unscheduled DNA synthesis (USEPA, 2005d).

Reproductive/Developmental

The following reproductive and developmental studies on BDCM were reviewed in EPA's *Drinking Water Criteria Document for Brominated Trihalomethanes* (USEPA, 2005d):

Ruddick et al. (1983) administered BDCM to pregnant Sprague-Dawley rats by gavage in corn oil at doses of 50, 100 or 200 mg/kg/day on GDs 6 through 15. The maternal NOAEL and LOAEL were 100 and 200 mg/kg/day, respectively based on significantly decreased maternal body weight gain. There were no teratogenic effects observed. Sprague-Dawley rats maintained their litters following BDCM exposure of 100 mg/kg on GDs 6 through 10. The small number of litters in this study may have limited detection of significant effects at lower doses.

Klinefelter et al. (1995) observed treatment-related effects on sperm characteristics in F344 rats during a chronic cancer bioassay in which BDCM was administered in drinking water at approximately 0, 22 or 39 mg/kg/day. Sperm velocities were significantly decreased at 39 mg/kg/day at a 52-week interim sacrifice. No effect on sperm characteristics were observed in reproductive studies by NTP (1998a) or Christian et al. (2002a) in Sprague-Dawley rats administered BDCM in drinking water at concentrations similar to or higher than those used by Klinefelter et al. (1995).

Narotsky et al. (1997) administered BDCM to F334 rats by gavage in either corn oil or an aqueous vehicle containing 10 percent Emulphor® at dose levels of 0, 25, 50 or 75 mg/kg/day on GDs 6 through 15. Full litter resorptions were observed at doses of 50 and 75 mg/kg only if exposure occurred on GDs 6 through 10, which is the luteinizing hormone (LH)-dependent period of pregnancy. The developmental NOAEL and LOAEL were 25 and 50 mg/kg/day, respectively, based on full litter resorption (NTP, 2006). The BDCM administered in the aqueous vehicle resulted in significantly reduced maternal body weight gain at the lowest dose tested.

NTP conducted a short-term reproductive and developmental screening test with BDCM administered in drinking water to Sprague-Dawley rats (NTP, 1998a). The study was designed to evaluate developmental and female and male reproductive endpoints. NTP concluded that BDCM was not a reproductive or developmental toxicant in this study at any of the doses tested, resulting in NOAELs of 68 and 116 mg/kg/day for male and female rats, respectively, for these endpoints.

Bielmeier et al. (2001, 2004) investigated the mode of action for full litter resorption induced by BDCM in F344 rats in a number of studies.

- In a study to investigate strain comparison between F334 rats and Sprague-Dawley rats, females were dosed with BDCM by aqueous gavage in 10 percent Emulphor® on GDs 6 through 10. The incidence of full litter resorption was 62 percent in the F344 rats and 0 percent in the Sprague-Dawley rats. Surviving litters from both strains appeared normal with no observed effect on post-natal survival, litter size or pup weight. The authors identified a LOAEL of 75 mg/kg/day based on full litter resorption in F344 rats. A NOAEL was not identified.
- In a study to investigate the critical period for induction of full litter resorption in F344 rats, pregnant rats were dosed with BDCM in 10 percent Emulphor® on GDs 6 through 10 (the LH-dependent period) and GDs 11 through 15 (the LH-independent period, when pregnancy is maintained by placental lactogens). Full litter resorption occurred in rats dosed on GDs 6 through 10 but not in rats dosed on GDs 11 through 15.
- LH and progesterone serum profiles were characterized during a critical period of gestation during which BDCM was administered. A reduction in serum LH level with a corresponding reduction in progesterone concentration was observed and the authors suggest that BDCM alters LH secretion rather than altering luteal responsiveness alone. However, the significant decrease in serum LH concentration is likely not the sole determinant of pregnancy loss.
- The ability of progesterone to prevent BDCM-induced pregnancy loss supports the conclusion that the mode of action for pregnancy loss due to BDCM is maternally mediated rather than the result of direct effects on the embryo. The ability of human chorionic gonadotropin (CG), an LH agonist, to prevent BDCM-induced pregnancy loss suggests that full litter resorption is mediated, at least in part, by an effect of BDCM on maternal LH secretion. These results do not rule out a possible effect of BDCM on luteal responsiveness to progesterone, as previously suggested by Bielmeier et al. (2001).

The Chlorine Chemistry Council (CCC) sponsored a number of reproductive and developmental studies with BDCM in rats and rabbits (CCC, 2000a, 2000b, 2000c, 2000d).

- A range-finding study was conducted in male and female Sprague-Dawley rats. BDCM was administered in drinking water to parental rats from 14 days pre-mating and lasting until day of sacrifice (Christian et al., 2001a). The NOAEL and LOAEL for pups was based on decreased pup weight and decreased pup weight gain. Doses could not be determined due to the effects of reduced water consumption and reduced feed consumption in the parental generation females.
- A developmental toxicity study was conducted in which female Sprague-Dawley rats were exposed to BDCM in drinking water on GDs 6 through 21 (Christian et al., 2001a). The developmental NOAEL and LOAEL were 45 and 82 mg/kg/day, respectively, based on a significant number of ossification sites per fetus. The maternal NOAEL and LOAEL were 18.4 and 45 mg/kg/day, respectively, based on reduced maternal body weight and body weight gain.
- A range-finding study was conducted in New Zealand White pregnant rabbits administered BDCM in drinking water (Christian et al., 2001a). The developmental NOAEL was approximately 76.3 mg/kg/day, which was the highest dose tested. The maternal LOAEL was approximately 4.9 mg/kg/day, the lowest dose tested, for reduced body weight gain.
- A developmental toxicity study was conducted in New Zealand White pregnant rabbits administered BDCM in drinking water on GDs 6 through 29 (Christian et al., 2001a). The developmental NOAEL was 55.3 mg/kg/day, the highest dose tested. The maternal NOAEL and LOAEL were 13.4 and 35.6 mg/kg/day, respectively, based on decreased body weight gain.
- A reproductive study was conducted in Sprague-Dawley rats administered BDCM in drinking water on GDs 6 through 21 (Christian et al., 2002a). A marginal effect was observed on estrous cyclicity in F1 females and a small but significant delay in F1 generation sexual maturity. The parental NOAEL and LOAEL values were 4.1-12.6 and 11.6-40.2 mg/kg/day, respectively, based on reduced body weight and body weight gain in F0 females and F1 males and females. The reproductive NOAEL and LOAEL values were also 4.1-12.6 and 11.6-40.2 mg/kg/day, respectively, based on delayed sexual maturation. The study authors have questioned whether delayed sexual maturation in F1 males with reduced body weight should be considered reproductive toxicity or general toxicity.

An *in vitro* model in primary cultures of human term placental trophoblasts was used to study the effect of BDCM on chorionic gonadotropin (CG) secretion (Chen et al., 2003, 2004). BDCM reduced secretion of immunoreactive and bioactive CG, which suggests that BDCM affects the placenta and reduces CG production by preventing formation of syncytiotrophoblasts, the major CG-producing cell type. The authors also showed that BDCM reduced CG secretion by primary cultures of already-differentiated human syncytiotrophoblasts, suggesting possible effects on both syncytiotrophoblast formation and on CG production. The authors noted that placental trophoblasts are the sole source of CG during normal human pregnancy and play and major role in the maintenance of the fetus.

The potential mode of action related to pregnancy loss following exposure to BDCM has been discussed in EPA's *Drinking Water Criteria Document for Brominated Trihalomethanes* (USEPA, 2005d). Exposure of F344 rats to BDCM on GDs 8 through 9 were associated with reduced serum progesterone levels. There was no effect on LH levels. Bielmeier et al. (2001) suggested that BDCM exposure disrupts corpora lutea responsiveness to LH, which led to decreased serum progesterone levels and pregnancy loss. The experiments conducted by Bielmeier et al. (2004) were designed to re-examine maternal LH profiles during exposure to levels of BDCM known to cause pregnancy loss, using a more sensitive assay for LH than used by Bielmeier et al. (2001). Bielmeier et al. (2004) then demonstrated that concurrent treatment with progesterone or with human CG, which is an LH agonist, prevented BDCM-induced pregnancy loss. Pregnancy loss was attributed to disruption of LH secretion.

Studies suggest that reduced LH secretion (Bielmeier et al., 2002) and reduced luteal responsiveness to LH (Bielmeier et al., 2003) may both contribute to BDCM-induced full litter resorption in F344 rats (USEPA, 2006a). However, several investigators have failed to observe full litter resorption in Sprague-Dawley rats exposed to BDCM, suggesting that these effects may be strain specific (Ruddick et al., 1983; Bielmeier et al., 2001; Christian et al., 2001a). Christian and colleagues conducted developmental toxicity studies with BDCM in which pregnant Crl (a strain) Sprague-Dawley rats and rabbits were allowed to drink BDCM-containing water ad libitum instead of being exposed via gavage administration. Full litter resorption was not observed, and there were no adverse effects on embryo-fetal viability at levels up to 900 ppm (Christian et al., 2001a). The authors suggested that the difference in sensitivity might be due to the different reproductive performance and endocrine physiology of the species and strains or the difference in toxicokinetics resulting from the route of exposure.

A.1.1.1.3 Dibromochloromethane

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

DBCM was administered by gavage in corn oil to male and female F344/N rats and to male and female B6C3F1 mice (NTP, 1985). NTP determined that there was equivocal evidence of carcinogenicity in male mice and some evidence in female mice based on the incidence of hepatocellular adenomas (males and females) and the combined incidence of hepatocellular adenomas and carcinomas (females).

Mutagenicity/Genotoxicity

In vitro mutagenicity studies in *S. typhimurium* with DBCM showed mixed results, with positive results primarily reported in studies without metabolic activation. Studies were primarily positive for sister chromatid exchange and mixed for chromosomal aberrations, DNA strand breaks and DNA damage. *In vivo* studies reported positive results for chromosome aberrations, sister chromatid exchange and DNA damage and negative results for micronuclei formation, DNA strand breaks and unscheduled DNA synthesis (NTP 1985; USEPA, 2005d).

Reproductive/Developmental

Reproductive and developmental studies on DBCM were reviewed in EPA's *Drinking Water Criteria Document for Brominated Trihalomethanes* (USEPA, 2005d):

Borzelleca and Carchman (1982) evaluated the toxicity of DBCM administered in drinking water for seven weeks in a two-generation reproductive study in ICR Swiss mice. A LOAEL of 17 mg/kg/day was identified based on decreased postnatal body weight in the F2B generation but was assumed to be "marginal" because the effects were noted in only one of the F2 litters, there were no other adverse effects, and the number of litters and pups examined was unclear.

Ruddick et al. (1983) investigated the reproductive and developmental toxicity of DBCM administered by gavage in corn oil to pregnant Sprague-Dawley rats on GD 6-15. The NOAEL for developmental toxicity was 200 mg/kg/day, the highest dose tested. The study was limited by the small number of litters.

NTP conducted a short-term reproductive and developmental toxicity screen in Sprague-Dawley rats administered DBCM in drinking water for 35 days (NTP, 1996). No effects were observed and the NOAELs for males and females were 28.2 and 47.8 mg/kg/day, respectively.

A.1.1.1.4 Chloroform

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

Renal tumors (tubular cell adenoma and carcinoma) were observed in male Osborne-Mendel rats after a 78-week exposure to 90 mg/kg/day chloroform by gavage in corn oil and hepatocellular carcinoma was observed in all groups of male B6C3F1 mice exposed to gavage doses ≥138 mg/kg/day chloroform in oil for 78 weeks (NCI, 1976).

Kidney tumors were observed in ICI (a strain) mice chronically exposed to 60 mg/kg/day chloroform by gavage, but not in those exposed to 17 mg/kg/day (Roe et al., 1979). Under the same experimental conditions, chloroform exposure had no effect on the frequency of tumors in C57BL, CBA and CF-1 mice. Hepatic neoplastic nodules were increased in female Wistar rats chronically exposed to 200 mg/kg/day chloroform in drinking water (Tumasonis et al., 1987). Liver tumors in male and female mice and kidney tumors were observed in male and female rats and mice dosed by gavage in corn oil for 5 days a week for 78 weeks (Dunnick and Melnick, 1993).

In a two-year drinking water study by Jorgenson et al. (1985), chloroform was administered to male Osborne-Mendel rats and to female B6C3F1 mice at concentrations up to 160 and 263 mg/kg/day in rats and mice, respectively. A significant increase in renal tumors in rats was observed and was associated with cytotoxicity and regenerative hyperplasia. These histopathology results support chronic renal tubule injury as the mode of action underlying the renal tumor response. There were no liver tumors in female mice.

Mutagenicity/Genotoxicity

The majority of *in vitro* mutagenicity studies with chloroform in *S. typhimurium* and *Escherichia coli*, both with and without metabolic activation, were negative. Several studies showed positive results, but these positive results may be due to the use of cytotoxic concentrations of chloroform or use of ethanol as a diluent, resulting in formation of ethyl carbonate, an alkylating agent that can lead to mutations. Studies were negative for *in vitro* tests of chromosomal aberrations and unscheduled DNA synthesis and mixed for sister chromatid exchange. *In vivo* studies of chromosomal abnormalities, sister chromatid exchange and micronuclei formation showed mixed results, while studies on DNA damage or repair were negative. The positive results in some of the *in vivo* studies could be due to the use of cytotoxic concentrations (USEPA, 2001a; WHO, 2004a).

EPA concluded that "the weight of evidence indicates that even though a role for mutagenicity cannot be excluded with certainty, chloroform is not a strong mutagen and that neither chloroform nor its metabolites readily bind to DNA" (USEPA, 2001a). WHO (2004a) concluded that the weight of evidence indicates that chloroform does not have significant genotoxic potential, and the International Life Sciences Institute (ILSI) (1997) also concluded that the preponderance of evidence indicates that chloroform is not strongly mutagenic.

Reproductive/Developmental

The following reproductive/developmental effects of chloroform in animal studies were reviewed in the EPA's document *Toxicological Review of Chloroform in Support of Summary Information on the Integrated Risk Information Systems* (USEPA, 2001a), the World Health Organization's (WHO) document *Concise Chemical Assessment Document 58: Chloroform* (WHO, 2004a) and Health Canada's document *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document-Trihalomethanes* (Health Canada, 2006).

Thompson et al. (1974) conducted a study to evaluate the teratogenicity of chloroform in Sprague-Dawley rats and Dutch-belted rabbits. Pregnant rats were administered chloroform by gavage at doses up to 126 mg/kg/day on GDs 6 through 15. Decreased body weight gain and mild fatty changes in the liver were seen in the dams at 50 mg/kg/day and a significant increase in the frequency of bilateral extra lumbar ribs and a significant decrease in fetal weight were reported at 126 mg/kg/day. The maternal NOAEL and LOAEL were 20 mg/kg/day and 50 mg/kg/day, respectively, and the developmental NOAEL and LOAEL were 50 mg/kg/day and 126 mg/kg/day, respectively. Pregnant rabbits were administered doses up to 50 mg/kg/day via gavage on GDs 6 through18, with decreased weight gain reported in the high dose dams and no evidence of teratogenicity or fetotoxicity. The maternal NOAEL and LOAEL were 35 mg/kg/day and 50 mg/kg/day, respectively, and the developmental NOAEL was 50 mg/kg/day.

Ruddick et al. (1983) evaluated the reproductive and developmental effects of chloroform administered by gavage in corn oil to pregnant Sprague-Dawley rats on GDs 6 through 15 and fetuses were examined for viability and external malformations on GD 22. Decreased body weight gain and increased liver weights were observed in the dams at 100 mg/kg/day and lower body weight was observed at 400 mg/kg/day in the fetuses, but no teratogenicity. Maternal

NOAEL and LOAEL values of 200 and 100 mg/kg/day, respectively, and a developmental NOAEL of 400 mg/kg/day, the highest dose tested, were determined.

NTP conducted a reproductive and fertility study on CD-1 (ICR) BR outbred albino mice. Chloroform was administered via gavage at doses up to 41 mg/kg/day for 18 weeks during the breeding period and the offspring were administered 41 mg/kg/day through young adulthood (NTP, 1988). Hepatocellular degeneration in females was the only effect observed in offspring, with no significant effects on fertility or on reproductive parameters. A NOAEL of 41 mg/kg/day was identified for fertility (WHO, 2004a). A NOAEL or LOAEL for toxicity (hepatocellular degeneration) was not determined because histopathology was not performed on the low- and mid-dose mice (USEPA, 2001a).

A.1.1.2 Haloacetic acids (HAAs)

A.1.1.2.1 Monochloroacetic acid

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

EPA has not classified monochloroacetic acid (MCAA) for carcinogenicity. MCAA was administered in water by gavage to F344N rats and B6C3F1 mice in two-year bioassays (NTP, 1992b). There was no evidence of carcinogenic activity in rats or mice. Similarly, MCA was not carcinogenic in a drinking water study conducted by DeAngelo et al. (1997) in F344 rats.

Mutagenicity/Genotoxicity

Most *in vitro* mutagenicity studies with MCAA in *S. typhimurium*, *E. coli* and cultured mammalian cells were negative. MCAA showed positive results in the mouse lymphoma assay and for sister chromatid exchange without metabolic activation and negative results for chromosomal aberrations and for sex-linked recessive mutations. An *in vivo* bone marrow assay reported positive results by intraperitoneal injection and negative results by the oral or subcutaneous routes (NTP, 1992b).

Reproductive/Developmental

The following studies were reviewed in Health Canada (2008a):

Smith et al. (1990) published an abstract of a developmental study with MCAA administered to Long-Evans rats by gavage at doses up to 140 mg/kg/day on GD 6-15. Maternal toxicity and heart malformations in the fetuses were observed in the high dose group, but no statistical data were provided in the abstract.

Johnson et al. (1998) administered MCAA in drinking water to pregnant Sprague-Dawley rats at approximately 193 mg/kg/day. No adverse reproductive, developmental or teratogenic effects were observed; however, complete fetal examinations were not performed.

A.1.1.2.2 Dichloroacetic acid

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

In drinking water studies, dichloroacetic acid (DCAA) caused an increased incidence of hepatic adenomas and adenocarcinomas in male B6C3F1 mice (Daniel et al., 1992) and in male F344 rats (DeAngelo et al., 1996). A study conducted by DeAngelo et al. (1999) was used by EPA to quantify cancer risk from ingestion of DCAA in drinking water based on a significant increase in the incidence of hepatocellular carcinoma in male B6C3F1 mice (USEPA, 2003d). The mode of action is not clearly understood. Extrapolation to low dose was performed by assuming a no-threshold linear dose-response curve. EPA considers DCAA to be a likely human carcinogen based on positive carcinogenic response in the two species of rats and mice and in both sexes and clear evidence of a dose response (USEPA, 2003d).

Mutagenicity/Genotoxicity

Primarily negative results were reported for DCAA from *in vitro* mutagenicity studies in *Salmonella typhimurium,* while one study of prophage 8 induction in *E. coli* reported positive results. Mixed results were reported for *in vitro* studies on chromosomal aberrations, DNA strand breaks, DNA repair and the mouse lymphoma mutation assay. Mixed results were also reported for *in vivo* studies on micronuclei formation, DNA strand breaks and DNA adduct formation (USEPA, 2003d).

EPA concluded that DCAA is a weak mutagen and that it induced mutations and chromosome damage at high concentrations, but that there is uncertainty as to its genotoxicity at lower doses (USEPA, 2003d). The information on mode of action did not support a nonlinear quantification of risk; however, the data on mutagenicity suggest that DCAA is not a direct-acting mutagen (USEPA, 2003d).

WHO concluded that there is some evidence that DCAA is genotoxic at high concentrations but that these effects are not likely to be involved in the mechanism of DCAA tumorigenesis (WHO, 2000).

Reproductive/Developmental

The following reproductive and developmental studies on DCAA were reviewed by EPA, WHO, NTP and Health Canada. (WHO, 2000; U.S EPA, 2003d; NTP, 2007a; Health Canada, 2008a):

Katz et al. (1981) investigated the reproductive effects of DCAA in Sprague-Dawley rats (3-month gavage study) and beagle dogs (13-week capsule study). No adverse effects were noted in female rats, while in male rats, adverse effects on the testes, including testicular germinal epithelial degeneration and aspermatogenesis were noted at 500 and 2,000 mg/kg/day, the two highest doses. Similar testicular effects were noted in the dogs at doses ranging from 50 –100 mg/kg/day.

Bhat et al. (1991) administered male Sprague-Dawley rats DCAA in drinking water for 90 days. Decreased testes weight, tissue atrophy, and few spermatocytes and no mature spermatozoa in the seminiferous tubules were observed in the rats at 1,100 mg/kg/day, the only dose tested.

Cicmanec et al. (1991) investigated the reproductive effects of DCAA in beagle dogs, administering doses up to 72 mg/kg/day in gelatin capsules for 90 days. Testicular changes were reported in the males at all doses, including syncytial giant cell formation and degeneration of testicular germinal epithelium. Prostate glandular atrophy was also noted at 39.5 and 72 mg/kg/day. The reproductive LOAEL was 12.5 mg/kg/day, the lowest dose tested, based on testicular changes, and this LOAEL was used as the point-of-departure for determining the RfD of 0.004 mg/kg/day (USEPA, 2003d).

Toth et al. (1992) administered DCAA for 10 weeks by gavage to Long-Evans rats at doses up to 125 mg/kg/day. Significant reductions in the absolute weight of the preputial gland and epididymis were noted at all dose levels and there were effects on sperm morphology and decreased sperm counts at the higher doses. A LOAEL of 31.25 mg/kg/day, the lowest dose tested, was identified based on the organ weight changes in the preputial gland and epididymis.

Epstein et al. (1992) conducted a series of developmental studies in pregnant Long-Evans rats administered DCAA by gavage at doses up to 3,500 mg/kg/day for various time periods between GDs 6-15. Reduced mean fetal body weight and increased cardiac malformations were observed at 1,900 mg/kg/day and an increased incidence of cardiac defects were observed at 2,400 and 3,500 mg/kg/day. A developmental LOAEL of 1,900 mg/kg/day, the lowest dose tested, was determined.

Smith et al. (1992) administered DCAA to pregnant Long-Evans rats by gavage on GD 6 -15. A significant decrease in maternal weight gain and hypertrophy in the liver, spleen and kidneys were reported at 140 and 400 mg/kg/day. An increase in cardiac abnormalities, reduced fetal crown-rump length and reduced fetal body weight were observed at 400 mg/kg/day. A statistically significant increase in soft tissue anomalies was observed at 140 and 400 mg/kg/day. Maternal and developmental NOAELs of 14 mg/kg/day and LOAELs of 140 mg/kg/day were determined.

Linder et al. (1997) administered DCAA orally to male Sprague-Dawley rats for up to 14 days at doses up to 1,440 mg/kg/day to evaluate testicular toxicity. On day 14, a significant decrease in epididymal weight was observed at 480 and 1,440 mg/kg/day, and epididymal sperm count was decreased at $\geq$ 160 mg/kg/day.

Fisher et al. (2001) administered DCAA by gavage at 300 mg/kg/day to pregnant Sprague-Dawley rats on GD 6-15. No malformations of the heart were reported in the offspring.

A.1.1.2.3 Trichloroacetic acid

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

TCAA increased incidences of liver tumors in male B6C3F1 mice exposed via drinking water (Bull, 2002; Bull et al., 1990) and tumors were also observed in less-than-lifetime studies in female B6C3F1 mice (Pereira, 1996). However, no treatment-related tumors were observed in male F344/N rats (DeAngelo et al., 1997).

Mutagenicity/Genotoxicity

Most *in vitro* studies with TCAA in *S. typhimurium* and in mammalian systems resulted in negative results for mutagenicity, with positive results in one study investigating SOS DNA repair in *S. typhimurium* and equivocal results in a study on mouse lymphoma cells. *In vivo* studies have shown mixed results. Positive results were reported for chromosomal aberrations and mixed results for micronuclei formation and DNA strand breaks (Health Canada 2008a; IARC 2014).

Reproductive/Developmental

The following reproductive and developmental studies on TCAA were reviewed in Health Canada's document *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document-Haloacetic Acids* (Health Canada, 2008b) and in EPA's document *Toxicological Review of Trichloroacetic acid in Support of Summary Information on the Integrated Risk Information System* (USEPA, 2011a):

Smith et al. (1989b) conducted a developmental study in Long-Evans rats administered TCAA by gavage at doses up to 1,800 mg/kg/day on GD 6-15. Maternal toxicity was observed at all doses based on significant increases in spleen and kidney weights and developmental toxicity was also observed at all doses based on significant decreases in mean fetal weight, significant decreases in fetal crown-rump length and increases in the frequency of cardiac malformations. Maternal and developmental LOAELs of 330 mg/kg/day were determined, which was the lowest dose.

Johnson et al. (1998) administered TCAA in drinking water at 290 mg/kg/day to pregnant Sprague-Dawley rats. A significant decrease in body weight gain of the dams and a significant increase in the number of resorptions, number of implantation sites, and cardiac soft tissue malformations were observed at this dose. The maternal and developmental LOAELs were 290 mg/kg/day.

Fisher et al. (2001), administered 300 mg/kg/day of TCAA via gavage to pregnant Sprague-Dawley rats on GD 6-15. A significant reduction in maternal body weight and fetal body weight, but no increase in cardiac malformations were reported. Maternal and developmental LOAELs of 300 mg/kg/day were determined.

A.1.1.2.4 Monobromoacetic acid

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Reproductive/Developmental

Health Canada (2008a) and WHO (2004b) reviewed the following reproductive/developmental study on MBAA:

Linder et al. (1994a) administered MBAA as a single gavage dose or daily gavage doses for 14 days to male Sprague-Dawley rats and no reproductive effects were observed.

A.1.1.2.5 Dibromoacetic acid

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Mutagenicity/Genotoxicity

The results of mutagenicity and genotoxicity assays with dibromoacetic acid (DBAA) published prior to the Stage 1 and Stage 2 D/DBPR were reviewed by WHO (2004b) and Health Canada (2008a). Mixed results were reported from i*n vitro* studies with dibromoacetic acid in *S. typhimurium (*Saito et al., 1995; Giller et al., 1997; Morita et al., 1997; Kohan et al., 1998; Kargalioglu et al., 2002), while positive results were reported for DNA repair in the SOS chromotest and for DNA strand breaks, as measured in a comet assay (Giller et al., 1997; Plewa et al., 2002). Negative results were reported for micronuclei formation in a newt micronucleus test (Giller et al., 1997).

Reproductive/Developmental

The following reproductive and developmental studies on DBAA were reviewed in Health Canada's *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document-Haloacetic Acids* (Health Canada, 2008a) and WHO's *Brominated Acetic Acids in Drinking Water* (WHO, 2004b):

Linder et al. (1994a) administered single gavage doses of DBAA to male Sprague-Dawley rats and noted adverse effects on sperm count, morphology and motility.

Linder et al. (1994b) noted a number of adverse reproductive effects in a 14-day gavage study in male Sprague-Dawley rats administered DBAA at 0, 10, 30, 90 or 270 mg/kg/day. At the high dose, reduced testis and epididymis weights were observed. Decreased sperm counts and histopathological evidence of altered spermiation were observed at all doses. The LOAEL for the 14-day study was 10 mg/kg/day.

Linder et al. (1995), administered DBAA by gavage for 42 days to male Sprague-Dawley rats and paired them with unexposed females on various treatment days and during recovery. Treatment was stopped on day 42 due to adverse toxic effects, including labored breathing, tremor, difficulty moving hind limbs and severe weight loss. Fertility was significantly decreased in a time-dependent manner during treatment and until pairing on days 199-213 after treatment.

Sperm motility was significantly reduced after 16 or more days of treatment. No developmental toxicity was observed in the fetuses conceived during treatment. Artificial insemination of unexposed females with sperm from males treated for 16 or 31 days, but not for 9 days, resulted in an effect on the reproductive competence of the females.

Linder et al. (1995) conducted a second reproductive/developmental study with Sprague-Dawley rats using the same protocol as described above. The only significant reproductive effect at 10 mg/kg/day was a decrease in copulating pairs during study days 65-71. There was also a dose-dependent decrease in the number of males siring two litters during the final mating period, which was significant at 50 mg/kg/day. No significant reproductive effects were noted in unexposed females artificially inseminated with sperm from treated males. Histopathology results showed delayed or altered spermiation at 10 mg/kg/day and above. The NOAEL was 2 mg/kg/day.

Narotsky et al. (1996, 1997) administered DBAA by oral gavage in two developmental screening assays in CD-1 mice. Developmental effects were noted in the presence and absence of maternal toxicity but no statistical data were provided and the final studies were not published.

Vetter et al. (1998) administered single gavage doses of DBAA to male Crl:CD (Sprague-Dawley) BR rats. No effects on the sperm were observed, but there was mild histopathology in the testes.

Cummings and Hedge (1998) administered DBAA by gavage to female Holtzman rats on GD 1-8 and sacrificed on GD 9 or 20. The only effect was an increase of 170 percent in serum 17β-estradiol, resulting in a NOAEL of 125 mg/kg/day and a LOAEL of 250 mg/kg/day.

Balchak et al. (2000) administered DBAA in drinking water for 14 days to female Sprague-Dawley rats. Dose-related alterations of the estrous cycle were observed at doses of 90 and 270 mg/kg/day, but not at lower doses.

Christian et al. (2001b) administered DBAA in drinking water to male and female Crl:CD Sprague-Dawley rats starting 14 days prior to cohabitation and continuing through gestation and lactation (63-70 days of treatment). A slight but not significant reduction in mating performance at the highest dose was the only reproductive effect noted. The parental NOAEL was 66 mg/kg/day for males and 60 mg/kg/day for females, the highest dose tested. A NOAEL for developmental toxicity could not be determined.

Christian et al. (2002b) conducted a two-generation study in Sprague-Dawley rats administered DBAA in drinking water. Reproductive performance and development of female rats was not affected. Histopathology of the reproductive organs in the parental and F1 male pups revealed altered sperm production and some epididymal tubule changes in the mid- (22.4-55.6 mg/kg/day) and high-dose (52.4-132.0 mg/kg/day) rats and small or absent epidymides and small testes in the F1 high dose-males. The authors identified a parental NOAEL of 4.4-11.6 mg/kg/day based on increased liver and kidney weights.

Murr and Goodman (2005) did not observe changes in estrous cycle during a 20-week exposure at low doses of DBAA administered in drinking water to female Sprague-Dawley rats, although circulating serum estradiol levels were increased at weeks 3 and 11. The authors concluded that

these increases in estradiol were not linked to disruption of estrous cyclicity in Sprague-Dawley rats, which are a moderately estrogen-sensitive strain.

A.1.2 Epidemiology and Weight of Evidence

A.1.2.1 Cancer

A.1.2.1.1 Bladder Cancer

Case-Control Studies

Bove et al. (2007b) present results of a case-control study set in western New York State (182 male bladder cancer cases and 385 male controls enrolled between the years 1978–1986) in which estimates of total and specific THMs in tap water were combined with subjects' residential history and estimates of long-term tap water consumption. The highest quartile of estimated THM4 consumption (74.10-351.73 µg/day) was associated with an increased risk of bladder cancer, relative to the lowest quartile of THM4 consumption (0–38.04 µg/day; odds ratio (OR) = 2.34; 95 percent confidence interval (% CI): 1.01, 3.66). Estimates of the relative odds of bladder cancer comparing the highest to lowest quartiles of estimated exposure to THM4 and separately to each of the four specific THMs (bromodichloromethane, bromoform, dibromochloromethane and chloroform) were elevated and statistically significant for all but one of the specific THMs (dibromochloromethane). In these comparisons, the odds ratio for bromoform was the largest in magnitude (OR = 3.05; 95% CI: 1.51, 5.69). Bladder cancer risk was highest for those who consumed the greatest amount of water at points within the distribution system with the oldest post-disinfected tap water (the water that had been in the distribution system the longest following disinfection). Subjects consuming an average of 10 cups per day of water with mean water age of 188 hours post-disinfection had a greater than 5-fold increase in the odds of bladder cancer, relative to those consuming 5 cups per day of water with a mean water age of 13 hours post-disinfection (OR = 5.85; 95% CI: 1.93, 17.46). The study results also suggested an exposure-response relationship between higher risk of bladder cancer with increasing levels of THM4, bromodichloromethane and bromoform exposures.

This study adds to the weight of evidence showing a relationship between, long-term average THM4 exposure, long-term average specific THM exposure and bladder cancer risk. The estimated ORs may be subject to bias due to inappropriate control subject selection, exposure measurement error and residual confounding. Exposure measurement errors, assuming they are non-differential with respect to case status, would typically attenuate OR estimates. The study does not address associations among sensitive populations, other than gender, and does not assess genetic factors that may influence risk of bladder cancer associated with THM exposure. The study results are comparable with previous studies evaluating THM exposure in men and add to the evidence supporting the hypothesis that there is a positive association between THM exposure and bladder cancer risk among men. The study results may not be generalizable to populations consisting of both men and women. A strength of the study is the use of geocoding to increase specificity and interpolation approaches to better characterize DBP formation variability.

Villanueva et al. (2007) present results of a case-control study set in Spain (1,219 bladder cancer cases and 1,271 controls enrolled between the years 1998–2001) in which lifetime personal information on water consumption and other uses were collected. Long-term THM4 exposure from all exposure routes was associated with a two-fold increase in odds of bladder cancer incidence (OR = 2.1; 95% CI: 1.09, 4.02) comparing those in the highest quartile of average household THM4 level (>49 µg/L) to those in the lowest THM4 quartile (≤8 µg/L), with a statistically significant positive trend observed in the odds of bladder cancer for increasing quartiles of average residential THM4 level ($p_{trend}<0.01$). Study subjects with estimated exposure of >35 µg/day via ingestion had 1.35 times the odds of bladder cancer, relative to subjects that did not drink chlorinated water (95% CI: 0.92, 1.99); this association was higher in magnitude and statistically significant among men (OR = 1.61; 95% CI: 1.06, 2.44), but was in the opposite direction for women (OR = 0.47; 95% CI: 0.15, 1.51).

Those in the highest quartile for showering and bathing duration had an OR for bladder cancer of 1.83 (95% CI: 1.17, 2.87) relative to the lowest quartile, with a statistically significant positive trend observed ($p_{trend}<0.01$). Those who had "ever" swum in pools had 1.57 times the odds of bladder cancer, relative to those that had never swum in pools (95% CI: 1.18, 2.09), with a statistically significant trend observed with increasing the number of lifetime hours spent swimming ($p_{trend} = 0.02$). The results are suggestive of an increased bladder cancer risk not only with increasing exposure to THM4 via ingestion, but also due to exposure via other routes (dermal absorption and inhalation).

The authors also examined exfoliated cells in urine for micronuclei frequency in a subset of 92 female controls, for which there were 72 with adequate samples and 44 with complete THM4 exposure data. The authors reported that women exposed to THM4 levels above the median of 26 µg/L had a 70 percent increased probability of having a frequency of micronuclei above the median frequency of 9/1000 compared with those exposed to THM4 below the median concentration. The authors also noted that they observed higher associations for THM4 exposures through showering and bathing.

The study findings suggest that from the consideration of showering, bathing and swimming pool use that dermal (and perhaps also inhalation) routes of exposure, which were not explicitly considered by EPA in the attributable risk calculations supporting the Stage 2 rule, may contribute to the overall risk and that these routes may lead to a higher concentration directly in target organs than ingestion. The observation of positive associations between bladder cancers and municipal drinking water exposure/THM4 exposure only among men is consistent with similar gender-stratified results in other studies. The study does not address associations among sensitive populations, other than differences in gender, and does not assess genetic factors that may influence risk of bladder cancer associated with THM4 exposure.

The authors indicated that the positive association between micronuclei frequency and THM4 levels provides evidence of an intermediate marker of biological effect for THM4 exposure. They noted, however, that these results were limited by the small sample size. The study results are comparable with previous studies evaluating THM4 exposure in individuals and add to the evidence supporting the hypothesis that there is a positive association between THM4 exposure and bladder cancer risk.

Michaud et al. (2007) presented results of a case-control study set in Spain (397 bladder cancer cases and 1,271 controls enrolled between the years 1998-2001) in which total fluid intake (including coffee, beer, wine, liquor, champagne, soda, juices, tea, milk and water), water intake, lifetime THM4 exposure and interaction between the different exposure metrics were assessed with respect to risk of bladder cancer. Total fluid intake was associated with a decrease in the relative odds of bladder cancer comparing highest to lowest quintile of fluid intake (OR = 0.62; 95% CI: 0.40, 0.95). A statistically significant inverse association was observed for water intake, specifically, comparing highest to lowest quintile (OR = 0.47; 95% CI: 0.33, 0.66), with a negative trend observed ($p_{trend} < 0.0001$), but not for consumption of other individual beverages or total fluid intake not including water, but controlling for water intake in the model. The inverse association between water intake and bladder cancer risk persisted within each level of THM4 exposure; no statistical interaction was observed between water intake and THM4 exposure ($p_{interaction} = 0.13$). The results suggest that water intake is inversely associated with bladder cancer risk.

The study results provide some evidence that water intake is inversely associated with risk of bladder cancer. The study findings do not provide additional insights into the specific level of bladder cancer risks associated with DBPs, although the study assessed and did not observe a statistically significant interaction between THM4 and water intake. The finding of an inverse relationship between water intake and bladder cancer risk is consistent with findings in a prospective cohort study by the same lead author assessing bladder cancer in men (Michaud et al., 1999) and has implications for negative confounding of THM4-bladder cancer associations in studies that do not adjust for total water intake. The authors note a potential biological mechanism underlying the observed inverse association between water intake and bladder cancer: fluids flush out carcinogens or reduce their contact time with the urothelium. However, the absence of similar inverse associations between bladder cancer risk and total fluid intake not including water as observed in Michaud et al. (1999) prospective study noted above, and intake of total fluids including water in this study is perplexing. The authors speculate that, in this study population, water consumption provides a better estimate of long-term intake, as consumption is more consistent over time, relative to consumption of other beverages.

The study results are comparable with previous studies evaluating bladder cancer risk with respect to fluid intake and THM4 exposure in individuals and add to the evidence supporting the hypothesis that there is a positive association between THM4 exposure and bladder cancer risk and a negative association between water intake and bladder cancer risk.

Cantor et al. (2010) present results of a case-control study set in Spain (680 bladder cancer cases and 714 controls enrolled between the years 1998-2001) in which lifetime personal information on water consumption and water-related habits were collected. As noted earlier, this is a subset of a large case-control study population used in several other studies summarized here. The objective of this study was to investigate gene-environment interactions, including both individual and certain combined influences of DBP exposure and polymorphisms in glutathione S-transferase genes (specifically, GSTT1, GSTM1 and GSTZ1), cytochrome P450 genes (CYP2E1) and N-acetyltransferase 2 (NAT2) on bladder cancer risk. THM4 exposure was positively associated with bladder cancer, as previously reported in this study population. Estimated ORs and 95% CIs for bladder cancer were 1.2 (95% CI: 0.8, 1.8), 1.8 (95% CI: 1.1, 2.9) and 1.8 (95% CI: 0.9, 3.5) for THM4 quartiles 2, 3 and 4, respectively, relative to quartile 1.

Statistically significant associations were also observed between bladder cancer and NAT2 slow acetylator compared with rapid/intermediate genotypes (OR = 1.33; 95% CI: 1.06, 1.68) and GSTM1 null versus GSTM1 present genotypes (OR = 1.8; 95% CI: 1.4, 2.2), similar to associations reported previously in this study population, using different metrics (i.e., Villanueva et al., 2007; Michaud et al., 2007; Costet et al., 2011). Statistically non-significant elevated risks were observed for GSTT1 presence compared with null (OR = 1.21; 95% CI: 0.92, 1.59). Statistically non-significant elevations or decreases in relative odds for three functional single-nucleotide polymorphisms of GSTZ1 and three variants of CYP2E1 were also observed.

Associations between THM4 and bladder cancer were stronger among study subjects who were GSTT1 +/+ or +/– relative to those who were GSTT1 null ($p_{interaction}$ = 0.021), GSTZ1 rs1046428 CT/TT versus CC ($p_{interaction}$ = 0.018), or CYP2E1 rs2031920 CC versus CT/TT ($p_{interaction}$ = 0.035). Among a subset of subjects with forms of GSTT1 and GSTZ1 considered to increase the risk of bladder cancer, the ORs for quartiles 2, 3 and 4 of THM4 were 1.5 (95% CI: 0.7, 3.5), 3.4 (95% CI: 1.4, 8.2) and 5.9 (95% CI: 1.8, 19.0), respectively. The authors concluded that polymorphisms in key metabolizing enzymes modified DBP-associated bladder cancer risk, noting that the consistency of the findings with experimental observations of GSTT1, GSTZ1 and CYP2E1 activity strengthens the hypothesis that DBPs cause bladder cancer, and points to a potential mechanism of action, as well as classes of compounds likely to be implicated in increasing bladder cancer risk. The study findings provide additional insights into the level of bladder cancer risks associated with DBPs, particularly as they interact with specific genetic polymorphisms. The study also identifies potentially sensitive populations based on genetic polymorphisms of genes coding for key THM-metabolizing enzymes.

The study results are comparable with, and expand on, previous studies evaluating THM4 exposure in individuals and add to the evidence supporting the hypothesis that there is a positive association between THM4 exposure and bladder cancer risk, that the mechanism of action involves key metabolizing enzymes and that in the genes coding for these enzymes polymorphisms appear to modify DBP-associated bladder cancer risk. The study results are also consistent with experimental observations of GSTT1, GSTZ1 and CYP2E1 activity.[1]

Note that the two key polymorphisms, GSTT1(+) and GSTZ1 CT/TT, may be present in approximately 80 percent and 30 percent of the U.S. population, respectively (Regli et al., 2015). Moreover, about 24 percent of the population may have both polymorphisms present which Cantor et al. (2010) found to have a highly significant increase in the odds ratios for bladder cancer with increasing average THM4 levels in water. The Cantor et al. (2010) study results strengthen the evidence for the hypothesis that THMs cause bladder cancer, particularly in genetically susceptible individuals.

Chang et al. (2007) conducted a matched case-control study using data from the Taiwan Provincial Department of Health to investigate the association between bladder cancer and THM4 exposure in 65 municipalities in Taiwan. The case group consisted of 280 men and 123 women whose death certificate indicated bladder cancer as the cause of death. Controls were

[1] See, for example, Pegram et al. 1997, Glutathione *S*-transferase-mediated mutagenicity of trihalomethanes in *Salmonella typhimurium*: contrasting results with bromodichloromethane and chloroform, Toxicol. Appl. Pharmacol 144(1): 183-188.

matched to cases on gender, year of birth and year of death. Average THM4 tap water levels were estimated using monitoring data collected by the Taiwan EPA over a two-year period and categorized by quantile. The authors observed an elevated odds of bladder cancer for those in the 75^{th}-90^{th} percentile THM group (OR = 1.80; 95% CI: 1.18, 2.74) and for those in the >90^{th} percentile THM group (OR = 2.11; 95% CI: 1.43, 3.11), relative to those with estimated THM4 levels below the 75^{th} percentile. The trend of increasing relative odds with increasing average level of THM4 was statistically significant ($p_{trend}<0.001$).

Although misclassification of actual THM4 exposure is likely in this study, quantiles of exposure may be less subject to misclassification since they can help provide a general relative ranking of exposures. The results of this study are consistent with previous studies evaluating bladder cancer risk with respect to THM4 exposure from drinking water. Failure to adjust for smoking leaves open the possibility that most of the excess risk of bladder cancer-specific mortality associated with THM4 in this study may be due to smoking, under the assumption that THM4 exposure is positively associated with smoking. The magnitude of confounding by smoking is limited by the strength of this association (if any) between smoking and THM4 exposure. This study provides evidence in support of the hypothesis that there is a positive association between THM4 exposure through drinking water and risk of death from bladder cancer.

Pooled Data and Meta-Analysis Studies

Villanueva et al. (2006) pooled data from six case-control studies conducted in Europe (Italy, Finland and France) and North America (the United States and Canada) between the years 1978 and 2000, representing 2,729 cases and 5,150 controls, to evaluate whether total fluid intake of specific fluids is associated with bladder cancer risk. In this pooled analysis, total fluid intake was associated with a slight increased risk of bladder cancer in men (OR for a 1 liter/day increase in total fluid intake, OR = 1.08; 95% CI: 1.03, 1.14) with a statistically significant linear trend observed between increasing total fluid consumption and bladder cancer risk ($p_{trend}<0.001$), but not among women (OR = 1.04; 95% CI: 0.94, 1.15; $p_{trend} = 0.70$). Men in the highest category of total fluid intake (>3.5 liters/day) had 1.33 times the odds of bladder cancer (95% CI: 1.12, 1.58), compared to men in the lowest (≤ 2 liters/day). An increased risk was associated with intake of tap water (OR = 1.46; 95% CI: 1.20, 1.78), comparing those with tap water intake >2 liters/day to those with ≤ 0.5 liters/day ($p_{trend}<0.001$). Again, this association was statistically significant among men (OR = 1.50; 95% CI: 1.21, 1.88), but lower in magnitude and not statistically significant among women (OR = 1.19; 95% CI: 0.78, 1.81). No statistically significant associations were observed between a 1 liter/day increase in non-tap water intake and bladder cancer in men (OR = 1.03; 95% CI: 0.95, 1.12) or women (OR = 1.03; 95% CI: 0.85, 1.24). Statistically significant associations were not observed for the continuous measure of coffee consumption, but were observed for heavy coffee drinkers (>5 cups of coffee/day), relative to those who reported drinking fewer than 5 cups of coffee per day (OR = 1.26; 95% CI: 1.10, 1.44), an association which was again observed to be stronger among men than among women. As previously reported (Villanueva et al., 2004), THM4 exposure was also associated with bladder cancer risk in this pooled analysis. The authors reported that neither coffee exposure nor THM4 exposure confounded or modified the association between tap water intake and bladder cancer risk. The results are suggestive of an association between long-term THM4 exposure and bladder cancer risk among men, but not women. The authors concluded that the association of bladder cancer with tap water consumption, but not with non-tap water fluids,

suggests that carcinogenic chemicals in tap water may explain the increased risk of bladder cancer.

The results of this study provide evidence for the hypothesis that tap-water-based fluids may increase the risk of bladder cancer among men. Statistically significant associations were not observed between consumption of non-tap water and bladder cancer risk in this study. The strength of this evidence is limited by possible selection bias introduced by selection of unrepresentative control populations in the studies contributing to the pooled analysis and by non-random patterns of missing exposure data. Information bias and failure to condition on matching factors could have biased the observed ORs. It is unlikely that information bias, selection bias or confounding would result in a null result for women, but not in men.

The authors present but do not discuss in detail the observed association between long-term THM4 exposure and bladder cancer risk, as this information has been previously published. The new studies add to the evidence of increasing bladder cancer risk with increasing levels of tap water consumption, although the association was only observed among men but acknowledges that the results are inconsistent with the findings from other studies. The study also supports the hypothesis that there is a positive association between THM4 exposure and bladder cancer risk, although this was not the focus of the current study.

Costet et al. (2011) conducted pooled and meta-analytic analyses of data from three case-control studies set in three European countries (Finland, France and Spain), using data collected on a total of 2,381 cases and 3,086 controls to characterize the relationship between long-term exposure to drinking water DBPs and bladder cancer risk. The authors additionally report on a meta-regression incorporating data from European and North American studies examining the association between THM4 exposure and bladder cancer risk. Using meta-analytic techniques, long-term THM4 exposure to concentrations of >50 µg/L among men was found to be associated with a 47 percent increase in the odds of bladder cancer, compared to THM4 exposure to concentrations ≤ 5 µg/L (OR = 1.47; 95% CI: 1.05, 2.05). A linear positive trend of increasing bladder cancer risk with increasing THM4 levels was also observed among men (p_{trend} = 0.01). However, among women, long-term THM4 exposure of >50 µg/L was associated with a decrease in the odds of bladder cancer, compared to those with THM4 exposure ≤ 5 µg/L (OR = 0.70; 95%CI: 0.43, 1.14) and a linear trend was not evident (p_{trend} = 0.27). The authors did not further discuss the observed findings for women; note that women constituted only a small fraction (~19 percent) of the subjects in these European studies and an even smaller fraction of the cases (16 percent).

The results of studies on the association of bladder cancer with THM4 exposure measures were not among the one European study and the combined European and North American studies. The study provides evidence that estimates of the association between THM4 exposure and bladder cancer risk observed in one European country are generalizable to other European countries, and further, that associations observed in Europe are generalizable to the United States, and vice versa.

The Costet et al. (2011) study results provide evidence that long-term exposure to THM4 is associated with increased bladder cancer risk among men. Information bias and failure to condition on matching factors could have led to biased and imprecise results. It is not possible to

predict the magnitude and direction of selection bias and net bias due to confounding factors in this study. However, the consistency of the results across studies that used different control selection procedures and procedures to adjust for confounding factors is a strength of this work.

Ecological Study

Llopis-González et al. (2011) conducted an ecologic study leveraging aggregate district-level THM4 measurements and bladder cancer mortality data collected for 10 districts in Valencia, Spain to investigate the association between THM4 exposure and bladder cancer (along with digestive cancers). The authors reported a positive, non-monotonic relationship between ecologic measures of THM4 and age-standardized bladder cancer mortality among women, with the bladder cancer-specific mortality rate increasing with THM4 levels above 40 µg/L. No association between the district-level THM4 measurements and bladder cancer mortality was observed for men. The authors conclude that their results suggest a possible association between bladder cancer mortality in women and THM4 exposure at levels below the European Community legal limit of 150 µg/L during the eight-year study period of 2000 to 2007 (the limit was reduced to 100 µg/L in 2009).

This study provides weak evidence of an association between THM4 exposure and bladder cancer mortality among women, but not men. As an ecological study, this study has considerable limitations, including susceptibility to measurement error and potential bias due to confounding factors. The study does not provide additional insights into the specific level of bladder cancer risks associated with DBPs, nor to effect modification of DBP exposure by potential genetic and other susceptibility factors. The study does little to strengthen (or weaken) the evidence for the hypothesis that DBPs cause bladder cancer.

A.1.2.1.2 Colon/Rectal Cancer

Case-Control Studies

Bove et al. (2007a) present results of a case-control study set in a county in western New York State (128 white male rectal cancer cases and 253 white male controls enrolled between the years 1978-1986) in which estimates of THM4 and the four specific THMs in tap water were combined with subjects' residential history and estimates of long-term tap water consumption to estimate long-term average THM consumption. The primary objective of the study was to evaluate the association between THM consumption and rectal cancer risk. The authors observed a statistically significant positive association between rectal cancer and average bromoform consumption (µg/day) (OR = 1.85; 95% CI: 1.25, 2.74). Those in the highest quartile of estimated bromoform consumption (1.69–15.43 µg/day) had 2.32 times the odds of rectal cancer, relative to those in the lowest bromoform consumption quartile (0.09–0.64 µg/day) (95% CI: 1.22, 4.39; $p_{trend} = 0.002$). Positive associations between rectal cancer and average dibromochloromethane consumption (µg/day) (OR = 1.78; 95% CI: 1.00, 3.19) and bromodichloromethane consumption (µg/day) (OR = 1.15; 95% CI: 1.00, 1.32) were of borderline statistical significance. No associations were observed between rectal cancer and long-term average chloroform consumption (µg/day) (OR = 1.00; 95% CI: 0.98, 1.02) or THM4 consumption (µg/day) (OR = 1.01; 95% CI: 0.99, 1.03).

The study does not provide evidence that long-term consumption of THM4 is associated with rectal cancer risk. However, the study does provide some evidence supporting the hypothesis that consumption of specific THMs, particularly bromoform (or DBPs associated with bromoform occurrence), increases the risk of rectal cancer. The study does not address associations among sensitive populations, other than gender, and does not assess genetic factors that may influence risk of bladder cancer associated with THM exposure. The study results may not be generalizable to general populations consisting of men and women.

Kuo et al. (2009) present results of a matched case-control mortality study set in Taiwan (2,195 cases of colon cancer death and 2,195 matched controls were identified between the years 1997-2006 using death certificate data) in which THM4 were collected from 65 municipalities. The objective of the study was to evaluate the association between exposure to DBPs and colon cancer risk. No statistically significant associations between THM4 in drinking water and colon cancer mortality were observed in the study. The adjusted OR for colon cancer death comparing those in the highest category of total estimated THM4 concentration in drinking water (above the 75th percentile; >14.80 µg/L) was 1.04 (95% CI: 0.89, 1.21) compared to the lowest exposure group (the lowest 50th percentile; <6.03 µg/L). The OR for those in the "medium" THM4 category (50th–75th percentile; 6.03–14.80 µg/L) was 1.02 (95% CI: 0.87, 1.2) compared to the same reference group. (Note that the authors did not provide any further detail on the THM4 concentration ranges in the drinking water in the Taiwan municipalities in this study, but based on a 75th percentile of 14.80 µg/L these levels appear to be quite low relative to levels typically seen in chlorinated drinking water.

The results of the Kuo et al. (2009) study provide no evidence to support the hypothesis that DBP exposure, or specifically THM4 exposure, increases the risk of colon cancer mortality. The authors noted that their finding was consistent with most previous epidemiologic studies. Bias of the ORs due to non-differential errors in the estimation of THM4 exposure is a potential explanation of the negative finding. The negative finding could also reflect the relatively low THM4 concentrations and limited differentiation in exposure among the three exposure categories. The study does not address associations among sensitive populations. The study results showing no statistically significant association of THM4 with colon cancer are comparable with several, but not all previous studies evaluating THM4 exposure and colon cancer (mortality) risk.

Meta-analysis Study

Rahman et al. (2010) conducted a meta-analysis of 13 case-control (n = 10) and cohort (n = 3) studies published between 1978 and 2007 evaluating the risk of colorectal cancers in relation to DBPs in drinking water. The studies in the meta-analysis included the Hildesheim et al. (1998) and King et al. (2000) studies considered by EPA as part of the Stage 1 and Stage 2 D/DBPRs (USEPA, 2005g) and the more recent Bove et al. (2007a) study. Three of the included studies considered only colon cancer risk associated with DBP exposure (one cohort and two case-control), three considered rectal cancer only (all case-control) and seven considered both colon cancer and rectal cancer (two cohort, five case control). The authors pooled relative risks (RRs) comparing the highest exposure category to the lowest category from each study using separate random effects models for colon cancer and rectal cancer. The pooled RR estimates for colon cancer comparing highest to lowest exposure groups were 1.11 (95% CI: 0.73, 1.70) for cohort

studies, 1.33 (95% CI: 1.12, 1.57) for case-control studies and 1.27 (95% CI: 1.08, 1.50) combining both study types. Corresponding RR estimates for rectal cancer were 0.88 (95% CI: 0.57, 1.35), 1.40 (95% CI: 1.15, 1.70) and 1.30 (95% CI: 1.06, 1.59). The authors did not find evidence of a single particularly influential study. They concluded that publication bias was not evident in the colon cancer literature but may have been a minor issue for studies of rectal cancer. They also noted that estimated RRs for rectal cancer in association with DBP exposures may have been influenced by the poor quality of the contributing studies. However, the authors also noted that "although there was evidence that poor study quality affected results for rectal cancer, removal of the four studies with very low scores on measurement only reduced the pooled RR a little." The authors concluded that the study provides limited evidence of a positive association between colorectal cancer and exposure to DBPs in drinking water, citing the small number of qualifying studies and limitations in study quality as factors that hinder causal inference.

This meta-analysis provides limited but additional evidence in support of the hypothesis that long-term DBP exposure increases the risk of colorectal cancer. The authors noted their inability to make a strong causal statement regarding the association between DBP exposure and risk of colon and rectal cancers because of the small number of studies contributing to the analysis and quality issues.

A.1.2.1.3 Other Cancers

Chiu et al. (2010) collected data from the Taiwan Provincial Department of Health in order to study the association between pancreatic cancer and THM4 in 53 municipalities in Taiwan. Additionally, the authors further investigated modification of the relationship between THM4 exposure and risk of death from pancreatic cancer by calcium and magnesium levels in drinking water. The case group consisted of 594 males and 462 females whose death certificate indicated pancreatic cancer as the cause of death. THM4 levels were used as a marker for DBP exposure. THM4 exposure was assessed using average THM4 levels as reported by the Taiwan EPA over a two-year period. The authors reported an OR of 1.01 (95% CI: 0.85–1.21) for pancreatic cancer for those with estimated THM4 exposure above the median level (4.9 µg/L) compared to those with estimated drinking water THM4 below that level. No interaction between THM4 levels and calcium in drinking water was observed. However, the authors observed statistically significant effect modification by magnesium on the multiplicative scale ($p<0.05$), reporting increased odds of pancreatic cancer for those with THM4 levels above 4.9 µg/L, relative to those with THM4 less than 4.9 µg/L, among those with annual mean levels of magnesium in drinking water below the median (< 5.4 mg/L) (OR = 1.42; 95% CI: 1.00, 2.02).

This study does not provide evidence that risk of death from pancreatic cancer is associated with exposure to increased THM4 levels in drinking water. However, the results suggest a relationship between magnesium levels in drinking water and risk of death from pancreatic cancer associated with THM4 exposure. The findings show a statistically significant increase in the odds of pancreatic cancer death in those with individuals exposed to less than the median observed magnesium level of 5.4 µg/L but greater than the median observed THM4 level of 4.9 µg/L.

Kasim et al. (2006) conducted a population-based case-control study (686 cases, 3,420 controls) to investigate the relationship between DBP exposure and adult leukemia in Canada. The study utilized information from the Canadian National Enhanced Cancer Surveillance System. Additional information collected on subjects' residences and drinking water source history was linked with municipal water supply data to estimate individual chlorine DBP exposure. Overall, the odds of leukemia were not associated with duration of THM4 exposure. However, for those with estimated THM4 exposures greater than 40 µg/L, the researchers observed increasing odds of chronic myeloid leukemia with increasing duration of exposure. The OR was only statistically significant for those with duration of exposure >31 years, the highest category of exposure duration, and highest THM4 concentration category, > 40 µg/L (OR = 1.72; 95% CI: 1.01, 3.08). In contrast, they reported a protective association for chronic lymphoid leukemia for the longest duration and highest exposure category (OR = 0.60; 95% CI: 0.41, 0.87). Increasing duration of exposure to bromodichloromethane levels > 5 µg/L was not associated with risk of leukemia in this study.

The study provides limited evidence in support of the hypothesis that there is a positive association between developing adult leukemia and increased chlorination DBP exposure in drinking water. The results suggest that an increased risk for chronic myeloid leukemia is associated with increased duration and level of exposure to DBPs. However, for all other leukemia subtypes included in the study, the OR was found to decrease with increasing duration and level of exposure to chlorine DBPs; in the instances of lymphocytic leukemia and hairy cell leukemia, the study actually found a protective effect. While it is possible that the adult leukemia risk associated with exposure to chlorination DBPs in drinking water differs among the disease subtypes, the contrary findings of this study do not offer a clear indication of the overall chlorination DBP risk associated with adult leukemia. Interpreting the findings is particularly difficult due to the lack of other similar studies available for comparison. The authors also note that the primary concern in their study was that a low proportion of potentially eligible cases were included in the analysis. Of 1,997 adult leukemia cases identified, only 1,068 (53.5 percent) are represented. Case subjects were lost because of death (292 cases), refusal of physicians to give consent because of cases' ill health (160 cases) and refusal of the cases to participate (467 cases). The possibility of selection bias should be considered if nonrespondents differed from those analyzed in terms of the studied risk factors.

Karagas et al. (2008) reported what they described as a "preliminary analysis" assessing the relationship of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with THM4 exposure using case-control data (603 BCC cases, 293 SCC cases, 540 controls) originally gathered for an arsenic analysis. The authors reported an OR of 2.4 (95% confidence interval: 0.9, 6.7) for BCC and 2.1 (95% CI: 0.7, 7.0) for SCC, comparing those exposed from public water sources to more than 40 µg/L THM4 to those to a referent group with < 1 µg/L THM4, and those with 1 to 20 µg/L THM4 (OR = 0.9, 95%CI: 0.6-1.5 for BCC and OR = 0.9, 95% CI: 0.6-1.5 for SCC) and those with $\geq$20 to 40 µg/L THM4 (OR = 1.1, 95%CI: 0.7-1.8 for BCC and OR = 1.3, 95%CI: 0.7-2.3for SCC). The authors also reported for a group served by private wells OR = 1.1, 95%CI: 0.7-1.8 for BCC and OR = 1.1, 95%CI: 0.6-1.9 for SCC. No information was provided on the statistical significance of these results. The authors concluded that their results suggested that the relationship of DBPs with these forms of skin cancer warrants further exploration.

A.1.2.2 Reproductive and Developmental Effects

Birth Weight

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the Stage 1 and Stage 2 D/DBPRs, the epidemiological evidence base addressing the association between DBP exposure and birth weight outcomes consisted of 13 primary studies (including 4 cross-sectional studies, 7 cohort studies and 2 case-control studies) and 8 review papers, identified in Exhibit A.1 (USEPA, 2005g).

Exhibit A.1: Studies of Birth Weight Outcomes Evaluated for Stage 1 and/or Stage 2 D/DBPRs

Study	Developmental/Reproductive Health Outcome	Study Design
Savitz et al. (2005)	Term-Birth Weight	Prospective Cohort
Toledano et al. (2005)	LBW, very-LBW	Retrospective Cohort
Wright et al. (2004)	Term Birth Weight	Retrospective Cohort
Wright et al. (2003)	Term Birth Weight, Term-LBW	Retrospective Cohort
Yang (2004)	LBW	Cross-sectional
Jaakkola et al. (2001)	LBW	Cross-sectional
Källén and Robert (2000)	Birth Weight	Cross-sectional
Dodds et al. (1999)	LBW	Retrospective Cohort
Gallagher et al. (1998)	LBW; Term-LBW	Retrospective Cohort
Kanitz et al. (1996)	LBW	Cross-sectional
Bove et al. (1995)	LBW	Retrospective Cohort
Savitz et al. (1995)	LBW	Case-control
Kramer et al. (1992)	LBW	Case-control
Bove et al. (2002)	LBW	Review
Graves et al. (2001)	LBW	Review
Villanueva et al. (2001)	LBW	Review
Nieuwenhuijsen et al. (2000)	LBW	Review
Reif et al. (2000)	Birth Weight; LBW	Review
WHO (2000)	LBW	Review
Craun, ed. (1998)	LBW	Review
Reif et al. (1996)	LBW	Review

Abbreviations: LBW – Low Birth Weight

The results from this collection of studies were found by EPA to be inconsistent, although a number of these studies supported the possibility that DBP exposure is associated with adverse

birth weight outcomes (particularly for birth weight decrements), including (Kramer et al., 1992; Bove et al., 1995; Kanitz et al., 1996; Gallagher et al., 1998; Källén and Robert, 2000; Wright et al., 2003; Wright et al., 2004). EPA noted that the more recent studies at the time of Stage 2, which were also higher quality studies, provided some evidence of an association between birth weight outcomes and maternal DBP exposures during pregnancy; however, such evidence was limited largely to studies of average differences in a continuous measure of birth weight, rather than low birth weight outcomes.

Four studies evaluated risk of low birth weight and method of drinking water disinfection, one of which found some evidence of an association. Kanitz et al. (1996) assessed drinking water disinfection method (chlorine dioxide, sodium hypochlorite and chlorine dioxide/sodium hypochlorite) in a cross-sectional study conducted in Italy. The prevalence of low birth weight did not vary by disinfection method. Källén and Robert (2000) study assessed drinking water disinfection method (no chlorine, chlorine dioxide only, sodium hypochlorite only) in a cross-sectional study conducted in Sweden. They observed a statistically significant association between low birth weight among infants of mothers who lived in areas supplied by drinking water disinfected using sodium hypochlorite. Jaakkola et al. (2001) assessed maternal exposure to chlorinated drinking water during pregnancy in a cross-sectional study in Norway and found no evidence of an association with low birth weight. Similarly, Yang (2004) study compared the prevalence of low birth weight (LBW) in 113 municipalities supplied with chlorinated drinking water to that of 15 municipalities that were not supplied with chlorinated drinking water (but did not estimate DBP levels in drinking water) in a cross sectional study in Taiwan. No association was observed between residence in an area supplied by chlorinated water and low birth weight.

The studies evaluating the risk of low birth weight outcomes and estimated THM exposures during pregnancy generally did not observe associations between the two, although three studies do provide some evidence for the association. Kramer et al. (1992) estimated chloroform, bromodichloromethane (BDCM), DBCM and bromoform levels in drinking water in a case-control study set in Iowa. No associations were observed between odds of low birth weight and the THM exposures, with the exception of an elevated odds ratio for the association between low birth weight and chloroform exposure that was not statistically significant. Savitz et al. (1995) estimated maternal THM4 exposure in drinking water in a case-control study set in North Carolina. The odds of a low birth weight outcome were not associated with estimated maternal THM4 exposure. Dodds et al. (1999) estimated THM4 exposure during pregnancy among a cohort of women in Nova Scotia. Dodds et al. (1999) found no evidence of an association between THM exposure and low birth weight. Savitz et al. (2005) estimated THM4, HAA9 and TOX exposures as well as individual brominated THM (BrTHM) and HAA species during pregnancy in a prospective cohort study of three communities in the United States. Similarly, Savitz et al. (2005) observed no associations with term-low birth weight. Wright et al. (2003) estimated THM4 maternal exposures during pregnancy and for each trimester in a cross-sectional study in Massachusetts. They did not observe statistically significant associations between second trimester and entire-pregnancy average THM4 levels and low birth weight. In contrast, Bove et al. (1995) estimated maternal THM4 exposure in drinking water in a cross-sectional study in New Jersey and found a small association between THM4 levels and very low birth weight. Gallagher et al. (1998) estimated third-trimester THM levels in drinking water in a cohort of pregnant women in Colorado. Gallagher et al. (1998) observed strong, statistically significant association between term-low birth weight and high third-trimester THM4 exposure

and small, non-statistically significant associations between estimates of third-trimester THM4 exposure and low birth weight. Toledano et al. (2005) modelled THM4 in water zones in a large cross sectional study of three regions in England. Statistically significant associations were observed between THM4 and risk of LBW in one of the three regions. When assessing the association in all three regions combined, a small increase in the risk of LBW associated with THM4 was observed that was not statistically significant. A similarly small, non-statistically significant increase in risk of LBW was also observed for chloroform. They did not observe associations between LBW and BDCM or total BrTHMs.

The studies that assessed associations between DBP levels and differences in average birth, rather than a dichotomous low birth weight outcome, provided some evidence of an association. Wright et al. (2003) assessed associations between THM4 and both low birth weight (summarized above) and average birth weight. They observed statistically significant associations between second trimester and entire-pregnancy average THM4 levels and mean birth weight (but did not observe an association between THM4 levels and their low birth weight outcome). Wright et al. (2004) estimated THM4, chloroform, BDCM, total HAA, DCA and TCAA levels in a large retrospective cohort study of maternal third-trimester drinking water exposure and birth weight in Massachusetts. They observed an exposure-response relationship between estimated THM levels and reductions in mean birth weight as well as statistically significant reductions in average birth weight associated with BDCM and chloroform levels.

None of the review papers concluded that the weight of evidence was suggestive of a causal relationship between DBP exposure or exposure to chlorinated drinking water during pregnancy and risk of a low birth weight outcome. Only two reviews found some support, albeit inconclusive, for an association between DBP exposure (Nieuwenhuijsen et al., 2000) and exposure to chlorinated drinking water (Villanueva et al., 2001) during pregnancy and low birth weight outcomes.

New Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP associations with birth weight outcomes that became available subsequent to the promulgation of the Stage 2 D/DBPR. Twelve studies were identified and evaluated: four prospective birth cohort studies, five retrospective cohort studies, one case-control study, one cross-sectional study and one meta-analysis.

- Prospective cohort studies:
    - Hoffman et al. (2008a)
    - Patelarou et al. (2011)
    - Grazuleviciene et al. (2011)
    - Villanueva et al. (2011)
- Retrospective cohort studies:
    - Hinckley et al. (2005)
    - Lewis et al. (2006)
    - Yang et al. (2007)
    - Rivera-Núñez and Wright (2013)
    - Kumar et al. (2013)

- Case-control studies:
    - Danileviciute et al. (2012)
- Cross-sectional studies:
    - Zhou et al. (2012)
- Meta-analysis studies:
    - Grellier et al. (2010)

Five of the 11 observational studies were conducted in the United States (Arizona (Hinckley et al., 2005), New York (Kumar et al., 2013), Massachusetts (Lewis et al., 2006; Rivera-Nunez and Wright, 2013)) and 3 unspecified U.S. communities (Hoffman et al., 2008a), four cities in Europe (Spain (Villanueva et al., 2011), Lithuania (Danileviciute et al., 2012; Grazuleviciene et al., 2011) and Crete (Patelarou et al., 2011)), and 2 in Asia (Taiwan (Yang et al., 2007) and China (Zhou et al., 2012)). A primary birth weight outcome assessed in 6 of the 11 observational studies that considered birth weight outcomes was low birth weight LBW defined as birth weight <2,500 grams (Hinckley et al., 2005; Patelarou et al., 2011; Villanueva et al., 2011; Danileviciute et al., 2012; Grazuleviciene et al., 2011; Kumar et al., 2013). Term-LBW, defined as LBW among births ≥37 weeks of gestation, was assessed in 3 studies (Hinckley et al., 2005; Lewis et al., 2006; Yang et al., 2007), and differences in mean birth weights were assessed in 5 studies (Hoffman et al., 2008a; Villanueva et al., 2011; Zhou et al., 2012; Grazuleviciene et al., 2011; Rivera-Núñez and Wright, 2013). [Note: Studies addressing small for gestational age (SGA) outcomes were evaluated separately, see summary for SGA, below].

All but 2 (Patelerou et al., 2011; Zhou et al., 2012) of the 11 observational studies of birth weight endpoints assessed associations between birth weight outcomes and total trihalomethanes (THM4). Six of these nine studies additionally assessed specific THM concentrations (Danileviciute et al., 2012; Grazuleviciene et al., 2011; Hinckley et al., 2005; Hoffman et al., 2008a; Villanueva et al., 2011; Rivera-Nunez and Wright, 2013). Three of these studies additionally assessed total BrTHM (Patelarou et al., 2011; Villanueva et al., 2011; Rivera-Núñez and Wright, 2013), and three studies (Hinckley et al., 2005; Hoffman et al., 2008a; Rivera-Núñez and Wright, 2013) assessed specific haloacetic acid (HAA) species as well as HAA5 and/or HAA9. Rivera-Núñez and Wright (2013) additionally examined a DBP9 metric summing HAA5 and THM4 exposures. Five of the birth weight investigations assessed for this analysis quantified DBP levels in water sampled quarterly (Danileviciute et al., 2012; Grazuleviciene et al., 2011; Hinckley et al., 2005; Yang et al., 2007; Rivera-Nunez and Wright 2013), two used weekly water samples (Hoffman et al., 2008a and Lewis et al., 2006), and the sampling frequency varied for three other studies (Kumar et al., 2013; Patelarou et al., 2011; Villanueva et al., 2011). Zhou et al. (2012) assessed urinary creatinine-adjusted trichloroacetic acid (TCAA) as a DBP exposure biomarker. Nine of the 11 studies estimated tap water DBP concentrations (Danileviciute et al., 2012; Grazuleviciene et al., 2011; Hoffman et al., 2008a; Kumar et al., 2013; Lewis et al., 2006; Patelarou et al., 2011; Yang et al., 2007; Villanueva et al., 2011; Rivera-Nunez and Wright, 2013); four studies estimated internal THM dose (Hoffman et al., 2008; Danileviciute et al., 2012; Grazuleviciene et al., 2011; Villanueva et al., 2011). Exposures were typically quantified into categories (e.g., quantiles), but several studies also assessed associations between birth weight outcomes and continuously distributed DBP exposure metrics.

In a prospective cohort study, Hoffman et al. (2008a) found limited evidence of associations and no consistent patterns for term birth weight associations across the different study sites for the

various HAAs and other DBP exposure metrics. Although not statistically significant, they did detect some birth weight reductions consistent in magnitude with other studies for THM4 exposure (56 grams; 95% CI: -144, 32) ≥80 μg/L (vs <80 μg/L) and TOX exposures (40 grams; 95% CI: -109, 29) ≥192.7 μg/L (vs. ≤ 22.4 μg/L). Rivera-Núñez and Wright (2013) reported consistent birth weight reductions across all 3rd trimester HAA5 (range: 28-36 grams) and THMBr quintiles (range: 11-23 grams), but the largest associations were detected for DBP9 (the sum concentration of THM4 and HAA5) quintiles (range: 39-45 grams). Reductions in mean birth weight for THM4 quintiles (range: 9-23 grams) did not persist following additional adjustment for HAA5 levels in the multi-pollutant models. Compared to those in the lowest quartile, Zhou et al. (2012) found lower average birth weight (range: 40 to 62 grams) of infants whose mothers were in the highest two quartiles of creatinine-adjusted urinary TCAA concentrations for the overall population and even larger reductions (range: 82 to 160 grams) among a subset who had completed questionnaires with additional information on other potential confounding variables. Although no birth weight associations were reported in a Spanish study (Villanueva et al., 2011) across different THM metrics, Grazuleviciene et al. (2013) reported consistent, statistically significant, mean birth weight reductions for internal dose third trimester THM4, chloroform, bromodichloromethane and dibromochloromethane exposures in a prospective cohort study from Lithuania.

Several of these studies observed associations between birth weight outcomes and specific DBP species. Grazuleviciene et al. (2011) observed exposure-response relationships between internal dose of chloroform estimated for the entire pregnancy and for each trimester and decreasing mean birth weight (range: 53-59 grams for every 1 μg/day increase in chloroform). Rivera-Núñez and Wright (2013) observed statistically significant associations between specific DBP species (chloroform and bromodichloromethane) and mean birth weight deficits (range: 9-20 grams). These associations did not persist in multi-pollutant models (i.e., following further adjustment for other DBP exposures), which hasn't been examined in previous studies.

Danileviciute et al. (2012) assessed entire pregnancy and trimester-specific levels of specific DBP species (chloroform, dibromochloromethane and bromodichloromethane) and LBW risk. They observed elevated LBW risk associated with all three species, although the associations were statistically significant only among women with the GSTM1–0 genotype who had 3rd trimester or entire pregnancy chloroform exposure above the median level. In a separate investigation of the same study population, Grazuleviciene et al. (2011) observed exposure-response relationships between internal dose of chloroform estimated for the entire pregnancy and for each trimester and risk of LBW (OR range: 1.09-2.41) and internal dose and LBW risk. Hinckley et al. (2005) did not observe an association between chloroform and term-LBW in their retrospective cohort study, but they detected associations between exposure to specific HAAs (dibromoacetic acid (DBAA), in particular) and risk of term-LBW.

The studies of birth weight endpoints evaluated for this analysis focused primarily on third trimester DBP exposure, although most also presented association estimates for the first and second trimesters and the entire pregnancy. Rivera-Núñez and Wright (2013) reported consistent birth weight reductions regardless of whether second or third trimester exposure were evaluated. Lewis et al. (2006), however, reported that fetal growth was affected by high levels (≥70 μg/liter) of THM4 exposure experienced during the second trimester, having observed elevated, statistically significant elevations in the odds of term-LBW, relative to those with THM4 levels

<40 μg/liter only during that time period. Grazuleviciene et al. (2011) observed consistent associations between risk of LBW and of estimated categories of THM4, chloroform and bromodichloromethane levels across all trimesters; Danileviciute et al. (2012) observed the largest associations between THM4 and chloroform levels and LBW during the third trimester Hinckley et al. (2005) assessed smaller exposure time windows and found evidence suggesting a critical window for specific HAAs exposure effects on fetal growth between 33–40 weeks of gestation.

The results from the studies of DBP exposure during pregnancy and risk of adverse birth weight outcomes (term birth weight, LBW and term-LBW) were mixed; seven of the nine observational studies reported at least some evidence supporting the hypothesis that DBP exposure increases the risk of those adverse birth weight-related outcomes. There was no clear indication of greater consistency of reported associations, nor of exposure-response trends, among studies that used more sophisticated exposure assessment methodologies. The weight of evidence among the post-Stage 2 D/DBPR studies is suggestive of either no associations, or at most, small positive associations, between DBP levels in drinking water and adverse birth weight outcomes. The evidence provided by the articles reviewed for this analysis is not conclusive regarding the existence of an increased risk of LBW due to DBP exposure. There was little evidence of consistency regarding the magnitude of non-null associations or exposure-response relationships. With the exception of the Hoffman et al. (2008a) analyses and the Rivera-Núñez and Wright (2013) multi-pollutant-adjusted models, associations between DBP exposure estimates and birth weight outcomes were consistently observed during the third trimester and inconsistently in other trimesters and for the entire pregnancy period.

The one meta-analysis (Grellier et al., 2010), which included four reports of THM4 associations with LBW and four reports of THM4 and term-LBW outcomes (both sets included two studies reviewed for the DBP Stage 2 Rule (Gallagher et al., 1998; Wright et al., 2003) and two studies that were not (Hinckley et al. (2005); Lewis et al. (2006)), concluded that there is little or no evidence for associations between THM4 concentrations and risk of LBW or term-LBW; summary odds ratios corresponding to a small increase (10 μg/L) in THM4 were 1.00 and 1.034 for LBW and term-LBW, respectively, and were not statistically significant.

Susceptible Populations. Three of the studies (Danileviciute et al., 2012; Lewis et al., 2006; Rivera-Nunez and Wright 2013) reviewed in this analysis reported evidence of effect modification of associations between DBP exposure and adverse birth outcome; one by genotype and the others by race. Danileviciute et al. (2012) jointly considered the effects of DBP exposure and maternal genotypes and observed the strongest associations for third trimester THM4 and chloroform-exposed women with the GSTM1–0 genotype (OR: 4.37; 95% CI: 1.36–14.08, and OR: 5.06; 95% CI: 1.50–17.05, respectively). A corresponding increase in LBW risk associated with third trimester THM4 and chloroform exposure among women with the GSTM1-1 genotype were not observed (OR: 0.34; 95% CI: 0.09–1.24 and OR: 0.35; 95% CI: 0.10–1.28, respectively). LBW odds ratio estimates associated with third trimester THM4 and chloroform exposure were also notably higher among women with the GSTT1-0 genotype, relative to women with the GSTT1-1 genotype, although the interaction was not statistically significant.

In their case-control study, Lewis et al. (2006) observed an increased risk of term-LBW among women with an average THM4 exposure ≥70 μg/liter during the second trimester, relative to

those with estimated average THM4 exposure < 40 μg/liter (OR = 1.50, 95% CI: 1.07, 2.10). After stratifying the study population on race, however, they observed an estimated risk increase associated with high average THM4 exposure during the second trimester of 37 percent (OR = 1.37, 95% CI: 0.80, 2.36) among Caucasians and 60 percent (OR = 1.60, 95% CI: 1.03, 2.47) among all minority women combined (i.e., African Americans, Hispanics and Asians). However, the combination of multiple non-Caucasian racial and ethnic groups with different susceptibility to adverse reproductive outcomes into one group is a key limitation of this study which precludes drawing further conclusions from these data. A much larger study in Massachusetts by Rivera-Núñez and Wright (2013) found little evidence of effect measure modification by income, race/ethnicity or other covariates in the multivariate linear regression models of mean birth weight. Findings of differences in estimates of the risk of adverse birth outcomes within strata of genotype and race are noteworthy, but should be interpreted cautiously and should be examined in other studies.

Other notable contributions to the literature base. As noted earlier, accurate and precise assessment of DBP exposures was a major challenge for the DBP health effects evaluations included in this analysis, and indeed for many similar studies. Theoretically, evaluation of biomarkers of DBP exposure can be used as an alternative strategy, one that has the potential to overcome many of the difficulties in quantifying DBP levels in drinking water and resulting exposure. One of the nine studies reviewed for this analysis assessed associations between birth weight and a biomarker of DBP exposure; Zhou et al. (2012) evaluated the association between maternal urinary TCAA and birth weight. Using a single measurement of maternal TCAA quantified in urine sampled just prior to delivery, Zhou et al. (2012) detected an association between urinary TCAA and birth weight; the average birth weight of infants whose mothers were in the highest two quartiles of creatinine-adjusted urinary TCAA concentrations were much lower (62-160 grams) than those of infants whose mothers were in the lowest quartile of TCAA concentrations. Urinary TCAA has been demonstrated to be a reliable marker of HAA exposure from ingestion of drinking water (Bader et al., 2004; Froese et al., 2002; Zhang et al., 2009b), but it is unclear whether urinary TCAA would be accurate DBP surrogates for the volatile DBPs and other non-volatile DBPs. TCAA is also not specific to DBP exposure and could result from other environmental contaminants including trichloroethene, 1,1,1-trichloroethane and perchloroethene, complicating the source apportionment issue. Finally, the degree to which maternal TCAA sampled just prior to delivery, as was done in this study, adequately represents maternal DBP exposure during a hypothesized biologically relevant DBP exposure time window for birth weight-related indices was not evaluated by the investigators.

Post stage 2 D/DBPR, there are no new animal toxicity studies researching birth weight.

Small for Gestational Age

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the Stage 1 and Stage 2 DBPRs, the epidemiology evidence base regarding the association between DBP exposure and the fetal growth endpoint Small for Gestational Age (SGA, alternatively referred to as Intrauterine Growth Retardation (IUGR)) consisted of 10 primary studies (including 6 cross-sectional studies, 2 cohort studies and 2 case-control studies) and 6 review papers, identified in Exhibit A.2 (USEPA, 2005g).

Exhibit A.2: Studies of Small for Gestational Age Outcomes Evaluated for Stage 1 and 2 D/DBPRs

Study	Developmental/Reproductive Health Outcome	Study Design
Porter et al. (2005)	IUGR	Cross-sectional
Savitz et al. (2005)	SGA	Prospective Cohort
Infante-Rivard (2004)	IUGR	Case-control
Wright et al. (2004)	SGA	Cross-sectional
Wright et al. (2003)	SGA	Cross-sectional
Jaakkola et al. (2001)	SGA	Cross-sectional
Källén and Robert (2000)	IUGR	Cross-sectional
Dodds et al. (1999)	SGA	Retrospective Cohort
Bove et al. (1995)	SGA	Cross-sectional
Kramer et al. (1992)	IUGR	Case-control
Bove et al. (2002)	SGA	Review
Graves et al. (2001)	SGA	Review
Villanueva et al. (2001)	SGA	Review
Reif et al. (2000)	SGA	Review
Craun, ed. (1998)	SGA	Review
Reif et al. (1996)	SGA	Review

Abbreviations: SGA – Small for Gestational Age; IUGR – Intrauterine Growth Retardation.

The results from this collection of studies were found to be inconsistent, although a number of these studies supported the possibility that DBP exposure is associated with the SGA outcome, including (Wright et al., 2004; Wright et al., 2003, Bove et al., 1995; Kramer et al., 1992; Savitz et al., 2005):

Källén and Robert, (2000) assessed drinking water disinfection method (no chlorine, chlorine dioxide only, sodium hypochlorite only) in a cross-sectional study conducted in Sweden and Jaakkola et al. (2001) assessed maternal exposure to chlorinated drinking water during pregnancy in a cross-sectional study in Norway. Neither of these studies found evidence of an association between disinfection of drinking water and IUGR/SGA outcomes.

The studies evaluating the risk of SGA and estimated THM exposures during pregnancy reported inconsistent results, with one study finding no evidence of an association, six studies finding at least some evidence of associations of varying magnitudes and another finding an association only in a subset of infants with a specific genetic polymorphism. Dodds et al. (1999) estimated THM4 exposure during pregnancy among a cohort of women in Nova Scotia. They found no evidence of an association between THM exposure and SGA. Kramer et al. (1992) estimated chloroform, BDCM, DBCM and bromoform levels in drinking water in a case-control study set in Iowa and observed a statistically significant increased risk of IUGR associated with chloroform levels.

Bove et al. (1995) estimated maternal THM4 exposure in drinking water in a cross-sectional study in New Jersey and found a small but statistically significant association between THM4 levels and SGA. Wright et al. (2003) estimated THM4 maternal exposures during pregnancy and for each trimester in a cross-sectional study in Massachusetts. Wright et al. (2004) estimated maternal third-trimester drinking water THM4, chloroform, BDCM, total HAA, DCAA and TCAA levels in a cross-sectional study of and SGA in Massachusetts, observing an exposure-response relationship between estimated THM levels and SGA. Savitz et al. (2005) estimated THM4, HAA9 and TOX exposures as well as individual BrTHM and HAA species during pregnancy in a prospective cohort study of three communities in the United States and found that third-trimester THM4 levels above 80 µg/L were associated with a statistically significant doubling of the risk for SGA, compared to THM4 levels less than 80 µg/L. Porter et al. (2005) estimated trimester-specific and pregnancy-average exposures to specific THMs and HAAs, as well as THM4 and HAA5 in a cross-sectional study of pregnant mothers and their infants in Maryland. They did not observe any exposure-response trends in the odds of IUGR associated with increasing THM4 or HAA5 levels, nor did they observe increased IUGR risk associated with levels of specific THMs or HAAs. However, they did observe non-statistically significant elevated risk of IUGR associated with the two highest quintiles of THM4 and statistically significant elevated risk of IUGR associated with the two highest quintiles of HAA5.

Infante-Rivard (2004) estimated THM levels in drinking water for a case-control study in Montreal. Although she found no association between THM levels and intrauterine growth retardation overall, a statistically significant association was observed between THM exposure and intrauterine growth retardation among infants with the CYP2E1 gene variant, suggesting genetic susceptibility may modify risk of DBP effects on developmental outcomes.

None of the review papers concluded that the weight of evidence was suggestive of a causal relationship between DBP exposure or exposure to chlorinated drinking water during pregnancy and risk of SGA. Only one review reported some support, albeit inconclusive, for an association between exposure to chlorinated drinking water during pregnancy and SGA (Villanueva et al., 2001).

New Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP and SGA outcomes that became available subsequent to the promulgation of the Stage 2 D/DBPR. Fourteen studies were identified and evaluated: four prospective birth cohort studies, six retrospective cohort studies, three case-control studies and one meta-analysis.

- Prospective cohort studies:
    - Hoffman et al. (2008a)
    - Patelarou et al. (2011)
    - Grazuleviciene et al. (2011)
    - Costet et al. (2012) (also implemented a case-control sampling design)
- Retrospective cohort studies:
    - Hinckley et al. (2005)
    - Yang et al. (2007)
    - Horton et al. (2011)

    - Summerhayes et al. (2012)
    - Rivera-Núñez and Wright (2013)
    - Kumar et al. (2013)
- Case-control studies:
    - Aggazzotti et al. (2004)
    - Danileviciute et al. (2012)
    - Levallois et al. (2012)
- Meta-analysis studies:
    - Grellier et al. (2010)

Five of these new SGA studies were conducted in the United States: Arizona (Hinckley et al., 2005), Massachusetts (Rivera-Núñez and Wright, 2013), New York (Kumar et al., 2013), "two Southern U.S. communities" (Horton et al., 2011) and "three U.S. communities" (Hoffman et al., 2008a). Five studies were conducted in Europe: Italy (Aggazzotti et al., 2004), France (Costet et al., 2012), Lithuania (Danileviciute et al., 2012; Grazuleviciene et al., 2013) and Crete (Patelarou et al., 2011). One each was conducted in Australia (Summerhayes et al., 2012), Canada (Levallois et al., 2012) and Taiwan (Yang et al., 2007). Eight of these reports also assessed other fetal growth endpoints.

The SGA endpoint is a gestational age-adjusted measure of birth weight and a marker of fetal growth restriction. The definitions of SGA used in this literature are heterogeneous, but qualitatively similar. SGA is often defined as being less than or equal to the lowest 10^{th} percentile of weight from a reference population, commonly within categories of gender and race/ethnicity (e.g., Rivera-Núñez and Wright, 2013). However, this SGA definition is merely conventional, and several of the studies used alternative definitions. Aggazzotti et al. (2004), Hoffman et al. (2008a), Horton et al. (2011), Levallois et al. (2012), and Rivera-Núñez and Wright (2013) further restricted their case definitions to infants born after ≥37 weeks of pregnancy (i.e., term-SGA). Summerhayes et al. (2012) excluded infants with gestational age < 22 weeks and >43 weeks, as well as those with birth weight >5 standard deviations from the average for gestational age. Levallois et al. (2012) defined SGA as a neonate weighing less than the 10^{th} percentile weight for gestational age and gender. Hoffman et al. (2008a) defined SGA as present among infants with birth weight below the 10^{th} percentile specific to parity, in addition to gender and maternal race/ethnicity. Kumar et al. (2013) defined SGA as infant birth weight below the 10^{th} percentile of birth weight distribution among singleton live births in New York State for gestational age in weeks, year of birth and gender. Costet et al. (2012) defined their SGA outcome, which they referred to as fetal growth restriction as birth weight below the fifth percentile of the cohort's expected birth-weight distribution. Patelarou et al. (2011) defined SGA based on weight (SGA_{weight}) defined as a live born infant below the 10^{th} percentile of birth weight for gestational age in a referent population from Spain and also defined two additional endpoints based on body length (SGA_{length}) and head circumference ($SGA_{head\ circumference}$).

Estimation of gestational age is subject to error; gestational age can be derived from maternal report of last menstrual period (Kumar et al., 2013; Patelarou et al., 2011), estimated using ultrasound evaluation (Grazuleviciene et al., 2011), or from clinical estimates based on either ultrasound or the clinical examination (Rivera-Núñez and Wright, 2013; Costet et al., 2012; Summerhayes et al., 2012; Hoffman et al., 2008a). For example, Hoffman et al. (2008a) derived gestational age at birth using first trimester maternal report of date of last menstrual period,

which was corrected by ultrasound if the two estimates of gestational age differed greater than one week. The methodology used to estimate gestational age is not specified in six of the reports (Aggazzotti et al., 2004; Danileviciute et al., 2012; Hinckley et al., 2005; Horton et al., 2011; Levallois et al., 2012; Yang et al., 2007). The robustness of the study results to alternate SGA definitions (e.g., percentile cut-points, referent population, methods used to estimate gestational age) was examined in only one of the articles reviewed for this analysis (Summerhayes et al., 2012) where less than the 3rd percentile weight for gestational age was also considered and for which the authors noted there was some suggestion of a threshold, though noting that the investigation of threshold effects was limited in their study by the lack of an unexposed population.

Water sampled from municipal water distribution systems was used to estimate DBP exposure in 12 of the studies. Patelarou et al. (2011) obtained water samples from mothers' homes in addition to sampling from the public water supply network. The Aggazzotti et al. (2004) study assessed DBP levels in tap water sampled from mothers' homes. The frequency of water sampling was typically conducted quarterly, though the sampling frequency ranged from weekly to annually. The number of sampling sites used to assess DBP levels also varied by study. The representativeness of the samples taken was only formally evaluated in one study (Horton et al., 2011). Seven of 13 observational studies queried study participants' beverage consumption and water use behaviors (Aggazzotti et al., 2004; Costet et al., 2012; Danileviciute et al., 2012; Grazuleviciene et al., 2011; Hoffman et al., 2008a; Levallois et al., 2012; Patelarou et al., 2011).

All of the studies assessed associations between SGA and THM4; nine studies additionally assessed specific THM concentrations, other studies additionally assessed total BrTHMs (Patelarou et al., 2011; Rivera-Núñez and Wright, 2013). Five of the post-Stage 2 studies also assessed HAA5 and/or HAA9 (Hinckley et al., 2005; Hoffman et al., 2008a; Horton et al., 2011; Levallois et al., 2012; Rivera-Nunez and Wright, 2013) and three studies assessed individual HAAs (Hinckley et al., 2005; Levallois et al., 2012; Rivera-Núñez and Wright, 2013). Aggazzotti et al. (2004) assessed chlorite and chlorate in addition to THM4 and individual THMs. Two studies additionally examined total organic halides (TOX) (Hoffman et al., 2008a; Horton et al., 2011), one study examined a DBP9 metric (Rivera-Núñez and Wright, 2013), and another study summed up all chlorinated THMs and HAAs and all BrTHMs and HAAs (Horton et al., 2011).

Eleven of the 13 DBP studies examined tap water DBP concentrations in relation to SGA (Aggazzotti et al., 2004; Hinckley et al., 2005; Yang et al., 2007; Hoffman et al., 2008a; Horton et al., 2011; Summerhayes et al., 2012; Patelarou et al., 2011; Levallois et al., 2012; Costet et al., 2012; Rivera-Núñez and Wright, 2013; Kumar et al., 2013), seven studies specifically estimated DBP uptake based on individual-level data (Aggazzotti et al., 2004; Costet et al., 2012; Hoffman et al., 2008a; Patelarou et al., 2011; Grazuleviciene et al., 2011; Danileviciute et al., 2012; Levallois et al., 2012), and one study additionally examined TCAA concentrations in maternal urine sampled early in pregnancy (Costet et al., 2012). Exposures were typically quantified into categories (e.g., quantiles), but several studies also assessed associations between birth weight outcomes and continuously distributed DBP exposure metrics.

In the case-control study by Aggazzotti et al. (2004), THM levels were very low, with 23 percent of samples below the lower limit of detection. The reported frequency of use of tap water for

drinking was also low (14 percent), although almost 70 percent of the participants reported using tap water to make beverages such as coffee and tea. Chlorite and chlorate were also detected in 45 percent and 34 percent of water samples, respectively, with levels often observed to be very high. Small elevations in odds of term-SGA for reported personal water use for home cooking and showering/bathing were not statistically significant. THM4 exposure was not significantly associated with term-SGA (OR: 0.63; 95%CI: 0.31–1.28), comparing subjects exposed to tap water THM4 concentrations > 10 µg/L and who reported bathing/showering at least daily to those with lower THM4 concentrations or did not report bathing/showering at least daily. Compared to those with chlorite levels <20 µg/L or between 20 and 199 µg/L and at lower inhalation exposure level, those with chlorite levels ≥200 µg/L and considered to have low inhalation exposure had an odds ratio for SGA of 1.52 (95% CI: 0.91–2.54) while subjects with chlorite levels ≥200 µg/L and considered to have high inhalation exposure had an odds ratio for SGA of 1.70 (95%CI: 0.97–3.0).

Four studies estimated associations between DBP exposures for the entire pregnancy and specific to each trimester (Grazuleviciene et al., 2011; Danileviciute et al., 2012; Summerhayes et al., 2012; Patelarou et al., 2011), one study examined exposure during each of the three trimesters (Costet et al., 2012), another study examined second and third trimester exposures (Rivera-Núñez and Wright, 2013), another five specifically assessed associations with only third trimester exposure estimates (Aggazzotti et al., 2004; Hinckley et al., 2005; Hoffman et al., 2008a; Horton et al., 2011; Levallois et al., 2012), and two studies examined pregnancy average exposure estimates (Yang et al., 2007; Kumar et al., 2013).

The results from these epidemiologic studies of DBP exposure during pregnancy and risk of adverse SGA outcomes were mixed. Three studies did not report statistically significant evidence of increased risk of SGA associated with DBP exposure or evidence of exposure-response relationships (Horton et al. 2011; Patelarou et al. 2011; Yang et al., 2007). Two of these studies had very low THM levels which likely precluded evaluation of exposure-response trends. Associations in Rivera-Núñez and Wright study (2013) for SGA noted for THM4 and BDCM disappeared after further adjustment for HAA5 exposures, with no evidence of an exposure-response relationship. A fifth study (Kumar et al., 2013) observed no exposure-response trend, nor any statistically significant associations, other than a 7 percent and 10 percent increase in the odds of SGA among infants of mothers in the second lowest and lowest (of five) THM4 exposure categories, respectively. Summerhayes et al. (2012) detected statistically significant associations for SGA and 3rd trimester for the highest BDCM decile and the two highest THM4 and chloroform deciles. However, they did not observe any clear linear exposure-response trends for any DBP indicator or species in any trimester. The nested case-control study by Danileviciute et al. (2012) did not find statistically significant associations between greater than the median levels of exposure to THM4 or specific THM species in any trimester, with the exception of a 2.2-fold increase in the odds of SGA among those who had first trimester DBCM above the median, relative to those with DBCM less than the median level. However, all of the remaining 15 exposure metrics were consistently elevated within a range of 1.2 to 1.7 regardless of exposure window and type of THM metric that were examined. Results similar in magnitude (range 1.2 to 1.4) for internal dose tertiles for THM4, BDCM and CHCl3 were also detected in the overall cohort from this study base. Increased risks were noted in all BDCM categories as well. (Grazuleviciene et al., 2011).

In the study by Costet et al. (2012), THM4 ranged from 0.6 μg/L to 157 μg/L (mean (SD): 41.7 (16.1) μg/L). Average (SD) specific DBP levels were 9.3 (7.0) for chloroform, 8.2 (5.7) for bromoform, 13.8 (5.5) for DBCM and 10.4 (5.4) for BDCM. Based solely on water concentration exposure data, Costet et al. (2012) detected consistently elevated ORs (Range 1.3-1.4) for SGA and the three upper bromoform quartiles. The authors detected consistently elevated ORs (Range 1.5-2.4) for all three upper THM uptake quartiles for THM4, DBCM and BDCM and also in the upper quartile of bromoform. They also reported the largest associations with showering/bathing THM uptake exposures (OR range = 2.2-2.5).

Hinckley et al. (2005) observed small associations in ORs between SGA and continuous measures (relative increase in odds for every 1 μg/L increase in DBP) of third trimester THM4, chloroform, BDCM, DBCM and HAA5 exposures that were near the null of 1.00 and of borderline statistical significance; ORs observed for SGA and continuous third-trimester DBAA, DCAA and TCAA were higher (OR range: 1.01-1.6) and statistically significant for DCAA and TCAA based on categorical and continuous exposures. Levallois et al. (2012) did not observe a clear exposure-response relationship between SGA and third trimester THM4, and specific THM and HAA exposures, but they did observe an elevated SGA risk among infants of mothers with HAA5 concentrations in the highest quartile (relative to the lowest quartile) and among those with third trimester THM4 >80 μg/L. They also reported consistently elevated ORs for the highest ingestion quartile exposures for chloroform, THM4, DCAA, TCAA, HAA5 and HAA9; but increased risks were not evident when the total THM exposure pathway estimates based on pharmacokinetic modeling were evaluated. Hoffman et al. (2008b) observed an elevated SGA risk associated with third trimester THM4 ≥80 μg/L (compared to <80 μg/L), but did not detect statistically significant SGA risk associated with the highest quintile of residential THM4 concentrations (RR = 1.3; 95% CI: 0.7–2.3) or THM4 showering and bathing estimates (RR = 1.6; 95%CI: 1.0–2.7). The authors did not observe an association with highest quintiles of residential HAA5 concentrations (RR = 0.9; 95% CI: 0.5–1.6) or HAA5 tap water consumption estimates (RR = 0.8; 95%CI: 0.5–1.4) but saw some suggestion of an increased risk for the highest quintile of residential TOX concentrations (RR = 1.5; 95% CI: 0.9–2.5).

The weight of evidence based on the post-Stage 2 studies reviewed for this analysis is suggestive of a small positive association between SGA and some between DBP exposure metrics. In general, there was not strong support of exposure-response relationships between increased risk of SGA and DBP exposures although there was often elevated risk noted in the highest DBP exposure category which one would expect if there is a causal relationship. There was also some evidence of consistency regarding the magnitude of associations for different DCAA exposure metrics but no other strong signals were noted for individual DBP measures.

The one meta-analysis (Grellier et al., 2010) included in this report summarized the findings of six studies of THM4 associations with SGA, two of which (Hinckley et al., 2005; Hoffman et al., 2008a) were also reviewed for this analysis. The summary odds ratio based on the pooled analysis for a 10 μg/L increase in third trimester THM4 level estimated in the meta-analysis was statistically significant (OR = 1.01; 95% CI: 1.001−1.019). Although not statistically significant, the summary odds ratio was the same (OR = 1.01; 95% CI: 0.971−1.051) for a 10 μg/L increase in THM4 levels during the entire pregnancy based on four of the six studies reporting this measure.

Evidence of interaction. Two of the studies reviewed in this analysis reported evidence of effect modification of associations between DBP exposure and SGA; one by genotype and the other by smoking.

Building on earlier work assessing modification of associations between THM exposure and SGA by genetic polymorphisms conducted by Infante-Rivard (2004), Danileviciute et al. (2012) jointly considered the effects of DBP exposure and polymorphisms in maternal genotypes for glutathione S-transferases, critical enzymes in metabolic (detoxification) pathways. They found that odds ratios for SGA associated with having DBP exposure (THM4, chloroform and bromodichloromethane) above median levels were higher among women with *GSTM1–0*, relative to those with the *GSTM1–1* genotype. Similar differences in RRs for SGA associated with dibromochloromethane exposure were not observed between those with *GSTM1–0* and *GSTM1–1* genotypes. No differences in risk were observed comparing women with *GSTT1-1* genotype to women with *GSTT1-0* genotype. The earlier investigation of gene-by-environment interactions conducted by Infante-Rivard (2004) assessed polymorphisms in genes coding for *CYP2E1* and 5,10-methylenetetrahydrofolate reductase and observed elevated risk for SGA associated with the high THM4 exposure category (above the 90th percentile, corresponding to > 29.4 μg/L) only among those with the *CYP2E1* variant, reflecting a potential genetic susceptibility.

In their retrospective cohort study, Summerhayes et al. (2012) assessed interactions between THM exposure and socioeconomic indicators and smoking status. They did not observe evidence of interaction between socioeconomic status and THM exposure, but did find statistical evidence of an interaction between smoking and THM exposure. They observed generally larger associations between THM and SGA among infants of non-smoking mothers and weaker (i.e., RR estimates < 1) in infants born to smoking mothers. Interestingly, smokers also had higher levels of THM exposure, on average, relative to non-smokers.

The differences observed in estimates of SGA risk within strata of genotype and smoking status are noteworthy, but should be interpreted conservatively. These are novel findings but more research is needed to elucidate whether increased risks may occur in susceptible populations.

Pre-Term Delivery

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the Stage 1 and Stage 2 D/DBPRs, the epidemiology evidence base regarding the association between DBP exposure and the pre-term delivery (PTD) consisted of 10 primary studies (including 5 cross-sectional studies, 4 cohort studies and 1 case-control study) and 6 review papers, identified in Exhibit A.3.

Exhibit A.3: Studies of Pre-Term Delivery Outcomes Evaluated for Stage 1 and/or Stage 2 D/DBPRs

Study	Developmental/Reproductive Health Outcome	Study Design
Savitz et al. (2005)	PTD	Prospective Cohort

Wright et al. *(*2004)	PTD	Cross-sectional
Wright et al. *(*2003)	PTD	Cross-sectional
Yang (2004)	PTD	Cross-sectional
Jaakkola et al. *(*2001)	PTD	Cross-sectional
Dodds et al. *(*1999)	PTD	Retrospective Cohort
Gallagher et al. (1998)	PTD	Retrospective Cohort
Kanitz et al. (1996)	PTD	Cross-sectional
Savitz et al. (1995)	PTD	Prospective Cohort
Kramer et al. (1992)	PTD	Case-control
Bove et al. *(*2002)	PTD	Review
Graves et al. (2001)	PTD	Review
Villanueva et al. *(*2001)	PTD	Review
Reif et al. *(*2000)	PTD	Review
Craun, ed. (1998)	PTD	Review
Reif et al. *(*1996)	PTD	Review

Abbreviations: PTD – Pre-Term Delivery.

The results from this collection of studies did not provide much evidence of a deleterious effect of DBP on PTD risk. Three studies (Wright et al., 2004; Savitz et al., 1995; Jaakkola et al., 2001) actually observed an *inverse* relationship between DBP (exposure to chlorinated water in the study by Jaakkola et al., 2001) and risk of PTD - higher THM4 levels were associated with *lower* risk of PTD.

Three studies evaluated PTD and method of drinking water disinfection, one of which found some evidence of a positive association. Jaakkola et al. (2001) assessed maternal exposure to chlorinated drinking water (and water color) during pregnancy in a cross-sectional study in Norway and found a reduced risk of PTD among a subgroup of individuals exposed to chlorinated water who also have water with high color content. Kanitz et al. (1996) assessed drinking water disinfection method (chlorine dioxide, sodium hypochlorite and chlorine dioxide/sodium hypochlorite) in a cross-sectional study conducted in Italy and found no association between risk of PTD and disinfection method.

In contrast, Yang (2004) compared the prevalence of PTD in 113 municipalities supplied with chlorinated drinking water to that of 15 areas that were not supplied with chlorinated drinking water (but did not estimate DBP levels in drinking water) in a cross sectional study in Taiwan. The author reported OR for PTD of 1.37 (95% CI: 1.20-1.56) for chlorinating versus non-chlorinating drinking water areas and stated the results suggest there is an association between the consumption of chlorinated drinking water and PTD risk.

The studies evaluating the risk of PTD and estimated THM exposures during pregnancy generally did not observe any positive associations. These include Dodds et al. (1999), who estimated THM4 exposure during pregnancy among a cohort of women in Nova Scotia, and did not observe evidence of an association between THM exposure and risk of PTD; Wright et al.

(2003) who estimated THM4 maternal exposures during pregnancy and for each trimester in a retrospective cohort study in Massachusetts and observe no statistically significant associations between second trimester and entire-pregnancy average THM4 levels and PTD; Gallagher et al. (1998) in their cohort of pregnant women in Colorado did not observe any associations between estimated third-trimester THM4 levels in drinking water and PTD; and Savitz et al. (1995) who estimated maternal THM4 exposure in drinking water in a case-control study set in North Carolina and, again, found no association with PTD. Similarly, Kramer et al. (1992) observed no associations between estimated chloroform, BDCM, DBCM and bromoform levels in drinking water and "prematurity" in their case-control study set in Iowa.

Three studies provide evidence for an *inverse* association between DBP and PTD. Savitz et al. (2005) estimated THM4, HAA9 and TOX exposures as well as individual BrTHM and HAA species during pregnancy in a prospective cohort study of three communities in the United States and observed a weak, non-statistically significant inverse relationship between PTD and THM4. Wright et al. (2004) estimated THM4, chloroform, BDCM, total HAA, DCA and TCAA levels in a large cross-sectional study of maternal third-trimester drinking water exposure and birth weight in Massachusetts. They, too, observed a reduced risk of PTD associated with increasing THM exposures; they observed no relationship between PTD and HAAs.

None of the review papers concluded that the weight of evidence was suggestive of a causal relationship between DBP exposure or exposure to chlorinated drinking water during pregnancy and risk of PTD.

New Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP and PTD that became available subsequent to the promulgation of the Stage 2 D/DBPR. Eleven studies of DBP associations with PTD were identified and evaluated: three prospective birth cohort studies, five retrospective cohort studies, two case-control studies and one meta-analysis.

- Prospective cohort studies:
  - Hoffman et al. (2008b)
  - Patelarou et al. (2011)
  - Costet et al. (2012) (also implemented a case-control sampling design)
- Retrospective cohort studies:
  - Hinckley et al. (2005)
  - Yang et al. (2007)
  - Horton et al. (2011)
  - Kumar et al. (2013)
  - Rivera-Núñez and Wright (2013)
- Case-control studies:
  - Aggazzotti et al. (2004)
  - Lewis et al. (2007)
- Meta-analysis studies:
  - Grellier et al. (2010)

Five of these studies were conducted in the United States: Arizona (Hinckley et al., 2005), Massachusetts (Lewis et al., 2007; Rivera-Nunez and Wright, 2013), New York (Kumar et al., 2013), "two Southern U.S. communities" (Horton et al., 2011) and "three U.S. communities" (Hoffman et al., 2008b); three were conducted in Europe: Italy (Aggazzotti et al., 2004), France (Costet et al. 2012) and Crete (Patelarou et al., 2011); and one was conducted in Taiwan (Yang et al., 2007). All of these reports also assessed other fetal growth endpoints.

The PTD endpoint was defined as a live birth occurring prior to 37 weeks gestation in all but one of the studies; Kumar et al. (2013) defined pre-term births as live births with a gestational age of 37 weeks or less. Horton et al. (2011) and Hinckley et al. (2005) defined an additional endpoint, very PTD, as birth at less than 32 weeks of gestation. Gestational age was derived from maternal report of last menstrual period (Hinckley et al., 2005; Lewis et al., 2007; Kumar et al., 2013; Patelarou et al., 2011) or estimated using ultrasound evaluation. Costet et al. (2012) and Hoffman et al. (2008b) used a combination of these methods. For example, Hoffman et al. (2008b) derived gestational age at birth using first trimester maternal report of date of last menstrual period, which was corrected by ultrasound if the two estimates of gestational age differed greater than one week. Gestational age from one study (Rivera-Núñez and Wright, 2013) was based on clinician estimates, and the methodology used to estimate gestational age was not specified in three of the reports (Horton et al., 2011; Yang et al., 2007; Aggazzotti et al., 2004).

One study sampled tap water from women's homes in order to estimate DBP exposure (Aggazzotti et al., 2004), and one study assessed DBP in both representative locations of municipal water systems and in women's homes (Patelarou et al., 2011). In the remaining eight studies, DBP exposure was estimated in water sampled from various locations in municipal water networks; water sampling was conducted weekly or biweekly in three studies (Horton et al., 2011; Hoffman et al., 2008b; Lewis et al., 2007), quarterly in three studies (Rivera-Núñez and Wright, 2013; Yang et al., 2007; Hinckley et al., 2005) and at varying intervals in two studies (Kumar et al., 2013; Costet et al., 2012).

The number of sampling sites used to assess DBP levels varied by study, but most studies aggregate exposure averages across all sampling sites. Four of 11 studies queried study participants' beverage consumption and water use behaviors (Costet et al., 2012; Patelarou et al., 2011; Hoffman et al., 2008b; Aggazzotti et al., 2004). Other than one by Patelarou et al. (2011) which assessed only BrTHMs, all of the studies assessed associations between PTD and THM4; five studies additionally assessed specific THM concentrations (Rivera-Nunez and Wright 2013; Costet et al., 2012; Hoffman et al. 2008b; Hinckley et al. 2005; Aggazzotti et al., 2004), and Rivera-Núñez and Wright (2013) additionally assessed total BrTHMs. Four studies also assessed HAA5 or HAA9 (Rivera-Núñez and Wright, 2013; Horton et al., 2011; Hoffman et al., 2008b; Hinckley et al. 2005), and three studies assessed specific HAA exposures (Rivera-Núñez and Wright, 2013; Hoffman et al., 2008b; Hinckley et al. 2005). Rivera-Núñez and Wright (2013) additionally examined a DBP9 metric summing HAA5 and THM4 exposures. Aggazzotti et al. (2004) additionally assessed chlorite and chlorate levels. All of the studies estimated tap water DBP concentrations in relation to PTD. Four of the 10 studies (Costet et al., 2012; Patelarou et al., 2011; Hoffman et al., 2008b; Aggazzotti et al., 2004) combined DBP measures with assessments of individual water use behaviors to estimate personal exposures, while the remainder used only the aggregate DBP measures to estimate exposure. Exposures were

typically quantified into categories (e.g., quantiles), but several studies also assessed associations between birth weight outcomes and continuously distributed DBP exposure metrics.

An exposure-response trend between THM4 and PTD risk was detected in the study by Yang et al. (2007), albeit in municipalities with very low THM levels. Horton et al. (2011) found no statistically significant associations between pulmonary tuberculosis (PTB) and THM4 or HAA5, but did observe a linear exposure-response trend and statistically significant elevations in the odds of PTB associated with increasing total organic halide exposures, although the association was only observed among women served by the water system with higher concentrations of bromine-containing DBPs. Two studies (Kumar et al., 2013 and Rivera-Núñez; Wright, 2013) reported some statistically significant associations between DBP and PTD, although neither reported evidence of linear exposure-response trends. Relative to the lowest quintile of the respective DBP, Rivera-Núñez and Wright (2013) found there was some suggestion of associations between PTD and some DBP metrics. For example, among the highest HAA quartile (OR = 1.13; 95% CI: 0.95 to 1.33) which seemed to be largely attributable to DCAA quartile exposures (OR = 1.14; 95% CI: 1.03 to 1.26). Similar ORs observed in the odds of PTD with increased levels of other summary DBP indicators and specific THM and HAA were not statistically significant. Evidence of increasing PTD risk with increasing level of estimated exposure (i.e., no linear exposure response) was not observed for any of the DBP measures. Kumar et al. (2013) categorized THM4 into five groups and observed increased odds of PTD associated with the second, third and fifth categories of estimated THM4 exposure, relative to the lowest category, but did not observe a consistent exposure-response trend; the greatest increase in odds (14 percent) was observed for the second lowest category of THM4 and a statistically significant protective association (i.e., OR<1) was observed for the second highest THM4 category. Aside from the above findings, the results from these epidemiologic studies of DBP exposure during pregnancy and risk of PTD were largely negative.

The meta-analysis (Grellier et al., 2010) assessed six studies of PTD risk associated with THM4, including one study assessed in this analysis (Lewis et al., 2007), and found no evidence of elevated PTD risk associated with THM4 (summary OR = 0.99; 95% CI: 0.978-1.001) per 10 μg/L increase in THM4 exposures.

Congenital Anomalies

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the Stage 1 and Stage 2 D/DBPRs, the epidemiology evidence base regarding the association between DBP exposure and congenital anomalies consisted of 11 primary studies (including 3 cross-sectional studies, 3 cohort studies and 5 case-control studies) and 9 review or meta-analysis papers, identified in Exhibit A.4 (USEPA, 2005g).

Exhibit A.4: Studies of Congenital Anomaly Outcomes Evaluated for Stage 1 and/or 2 D/DBPRs

Study	Developmental/Reproductive Health Outcome	Study Design
Shaw et al. (2003)	Neural Tube Defects, Oral Clefts, Heart Defects	Case-control
Cedergren et al. (2002)	Heart Defects	Case-control
Hwang et al. (2002)	Neural Tube Defects, Oral Clefts, Heart Defects, Respiratory System Defects, Urinary Tract Defects	Cross-sectional
Dodds and King (2001)	Neural Tube Defects, Oral Clefts, Heart Defects, Chromosomal Abnormalities	Retrospective Cohort
Källén and Robert (2000)	Congenital Malformations	Cross-sectional
Dodds et al. (1999)	Neural Tube Defects, Oral Clefts, Heart Defects, Chromosomal Abnormalities	Retrospective Cohort
Klotz and Pyrch (1999)	Neural Tube Defects	Case-control
Magnus et al. (1999)	Neural Tube Defects, Oral Clefts, Heart Defects, Respiratory System Defects, Urinary Tract Defects	Retrospective Cohort
Bove et al. (1995)	Neural Tube Defects, Oral Clefts, Heart Defects, CNS Defects	Cross-sectional
Aschengrau et al. (1993)	Congenital Anomalies	Case-control
Shaw et al. (1991)	Heart Defects	Case-control
Hwang and Jakkola (2003)	Congenital Anomalies	Meta-analysis
Bove et al. (2002)	Congenital Anomalies	Review
Graves et al. (2001)	Congenital Anomalies	Review
Villanueva et al. (2001)	Congenital Anomalies	Review
Nieuwenhuijsen et al. (2000)	Congenital Anomalies	Review
Reif et al. (2000)	Congenital Anomalies	Review

Study	Developmental/Reproductive Health Outcome	Study Design
WHO (2000)	Congenital Anomalies	Review
Craun, ed. (1998)	Congenital Anomalies	Review
Reif et al. (1996)	Congenital Anomalies	Review

Abbreviations: CNS – Central Nervous System

The results from this collection of studies did not provide strong or consistent evidence of an association between exposure to chlorinated water or DBP and birth defects. Although by no means consistent, the evidence was stronger for an association between DBP and neural tube defects, as evidenced in several of the original scientific papers summarized below as well as in several of the review papers.

Four studies evaluated risk of congenital defects and method of drinking water disinfection, three of which found at least some evidence of positive associations. An increased risk of urinary tract and respiratory tract defects was found to be associated with chlorinated water, though other major congenital malformations showed no association with water source or type of water treatment (chlorination and chloramination) in a case-control study by Aschengrau et al. (1993) from Massachusetts.

Hwang et al. (2002) conducted a large cross-sectional study in Norway, comparing exposures to chlorinated water (and also water color levels) for mother's residence during pregnancy and risk of neural tube defects and defects of the heart, respiratory system, oral cleft and urinary tract. They observed associations between risk of "any birth defect", as well as cardiac, respiratory system and urinary tract defects and exposure to chlorinated water. In contrast, Källén and Robert (2000) assessed drinking water disinfection method (no chlorine, chlorine dioxide, sodium hypochlorite) in a cross-sectional study conducted in Sweden and found no associations with prevalence of congenital defects. Magnus et al. (1999) compared presence of chlorinated water in mothers' residences at the time of birth and neural tube defects, as well as defects of the heard, respiratory system, urinary tract and oral cleft. They observed statistically significant associations only between urinary tract defects and chlorination; associations were not observed for other outcomes or all birth defects combined.

The studies evaluating the risk of birth defects and estimated THM exposures during pregnancy remain inconsistent. Bove et al. (1995) assessed prevalence of neural tube defects, oral cleft, central nervous system and major heart defects and observed small but statistically significant increased risks associated with higher THM4 levels for neural tube defects, central nervous system defects, oral cleft defects and heart defects. Klotz and Pyrch (1999) also observed an association between highest and lowest tertile THM4 exposure levels of pregnant mothers and subsequent risk of neural tube defects (OR = 1.6; 95 % CI: 0.9-2.7). They also reported highest to lowest tertile results for HAA (OR = 1.2; 95 % CI: 0.5-2.6) and for HAN (OR = 1.3; 95 % CI: 0.6-2.5) which they described as "showing little relation to these defects." In a retrospective cohort study of THM4 levels among pregnant women living in Nova Scotia and subsequent risk of neural tube defects, oral clefts, heart defects, Dodds et al. (1999) did not observe any evidence of associations. They did note a non-statistically significant association between THM4 and chromosomal abnormalities. In another retrospective cohort study set in Nova Scotia, Dodds and

King, (2001) evaluated associations between estimated THM, chloroform and BDCM exposure and neural tube defects, oral clefts, heart defects and chromosomal abnormalities. Only estimated exposure to BDCM was found to be associated with increased risk of neural tube defects and cardiovascular anomalies. Chloroform was found to be associated with chromosomal abnormalities.

Three studies focused on associations between DBP and overall heart defects. Cedergren et al. (2002) examined DBP levels in the period from before inception through early pregnancy in a Swedish case-control study. Although they identified ten specific types of cardiac defects, their analysis focused on "any cardiac defect". They observed a statistically significant association between chlorine dioxide in drinking water and heart defects. They also found that THM concentrations equal to or greater than 10 μg/L were significantly associated with heart defects. They did not observe any association between cardiac defects and nitrate. In two case-control studies, however, Shaw et al. (2003) estimated THM in mothers' residences during a similar peri-conceptional period and did not find associations or exposure-response relationships between THM4s and conotruncal heart defects in either study. The studies were similarly negative for neural tube defects and oral clefts. Similarly, Shaw et al., (1990, 1991) observed no associations between cardiac anomalies and THM4 level in an earlier case-control study.

Five of the reviews/meta-analyses concluded that the evidence base evaluated provides at least some support for an effect of DBP exposure on risk of neural tube defects **(**Hwang and Jakkola, 2003; Bove et al. 2002; Villanueva et al., 2001; WHO, 2000; Reif et al., 1999; Graves et al., 2001) concluded that the findings regarding neural tube defects were inconsistent. Two reviews (Hwang and Jakkola, 2003; Graves et al., 2001) also concluded that the evidence base supported an association between DBP exposure and urinary system defects. Evidence of relationships between DBP exposure and birth defects, especially for those not mentioned above, was largely considered inconsistent, weak, insufficient and not convincing in the reviews.

New Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP and risk of congenital anomalies that became available subsequent to the promulgation of the Stage 2 D/DBPR. Eight studies of DBP associations with congenital anomalies were identified and evaluated: one prospective birth cohort study, three case-control studies, one cross-sectional study, two ecological studies and two meta-analysis studies.

- Prospective cohort studies:
    - Grazuleviciene et al. (2013)
- Case-control studies:
    - Righi et al. (2012)
    - Iszatt et al. (2011)
    - Luben et al. (2008)
- Cross-sectional studies:
    - Hwang et al. (2008)
- Ecologic studies:
    - Chisholm et al. (2008)
    - Nieuwenhuijsen et al. (2008)

- Meta-analyses:
    - Nieuwenhuijsen et al. (2009)
    - Hwang et al. (2008)

The Luben et al. (2008) study was conducted in Arkansas; four of the studies were conducted in Europe (Iszatt et al., 2011 and Nieuwenhuijsen et al., 2008 in the U.K., Righi et al., 2012 in Italy, and Grazuleviciene et al., 2013 in Lithuania) and one each in Taiwan (Hwang et al., 2008) and Australia (Chisholm et al., 2008).

The assessments of congenital anomalies in this literature were universally restricted to live births and implemented using medical records or registry databases. The endpoints assessed in these studies were defined variously as the occurrence of a specific anomaly (e.g., hypospadias, cleft lip, spina bifida), the occurrence of any one of a group of anomalies (e.g., heart, musculoskeletal, urogenital, neural tube defects), or as occurrence of "any" congenital anomaly. Several of the studies that assessed more specific outcomes also assessed more broad categories.

All of the studies assessed THM4, and three studies (Grazuleviciene et al., 2013; Iszatt et al., 2011; Chisholm et al., 2008) also assessed specific THM levels. Two of the studies additionally assessed total BrTHM (Iszatt et al., 2011; Nieuwenhuijsen et al., 2008), and Luben et al. (2008) assessed specific HAA and HAA5. Righi et al. (2012) evaluated chlorite and chlorate in addition to THM4.

Water sampled from locations in municipal water distribution systems were used to estimated DBP exposure in all seven observational studies reviewed. Two of the studies (Grazuleviciene et al., 2013; Iszatt et al., 2011) combined DBP data with water use behaviors to estimate individual DBP intake. Luben et al. (2008) assessed individual exposure in a subgroup of the study population. Water sampling was conducted quarterly in five studies and two studies assessed DBP measurements for the entire pregnancy using sampling frequency that was not specified. The number of sampling sites used to assess DBP levels also varied by study.

Four studies assessed exposure during the entire pregnancy (Grazuleviciene et al., 2013; Iszatt et al., 2011; Chisholm et al., 2008; Hwang et al., 2008); Grazuleviciene et al. (2013) also assessed trimester-specific exposures and month-specific exposures. The Luben et al. (2008) study of hypospadias specifically assessed exposure between weeks 6 and 16 of gestation. Four studies assessed only first trimester DBP exposure (Nieuwenhuijsen et al., 2008; Iszatt et al., 2011; Righi et al., 2012).

Both Chisholm et al. (2008) and Hwang et al. (2008) assessed an 'any congenital anomaly'. Chisholm et al. (2008) observed a statistically significant OR (1.22; 95% CI: 1.01–1.48) relating the presence of 'any' congenital anomaly to THM4 exposures; the association was observed for those in the 'high' level of THM4 (≥ 130 μg/L), relative to those in the lowest of three categories of THM4 exposure (< 60 μg/L). However, women in the middle category had a slightly lower risk of having a child with any congenital anomaly, relative to women in the lowest category of THM4 (i.e., no exposure-response trend). Hwang et al. (2008) observed an elevated OR (1.21; 95% CI: 1.07-1.36) among women with low THM4 (5-9 μg/L) relative to the reference group of women THM4 (0-4 μg/L), but not among women with higher THM4 levels (>10 μg/L).

Associations between THMs and cardiovascular anomalies were noted in four of the five studies which assessed them (Grazuleviciene et al., 2013; Nieuwenhuijsen et al., 2008; Chisholm et al., 2008; Hwang et al., 2008), with associations with ventricular septal defects consistently observed across the three studies which included this specific endpoint. Grazuleviciene et al. (2013) assessed cardiac anomalies as a group, but did not specifically assess ventricular septal defects. Hwang et al. (2008) observed an elevated OR (1.81; 95% CI: 0.98-3.35) for ventricular septal defects only among those in the highest category of THM4 exposure (≥20 μg/L), with no evidence of an exposure-response relationship. In an included meta-analysis, Hwang et al. (2008) noted ventricular septal defects as the only individual birth defect group to have a statistically significant OR in relation to THM4 exposure (OR: 1.59; 95% CI: 1.21–2.07). In the Hwang et al. (2008) study, the highest ORs for atrial septal defects (2.15; 95% CI: 0.70-6.60) and Tetralogy of Fallot (1.60; 95% CI: 0.61–4.23) were observed in the low THM4 category (5-9 μg/L). Chisholm et al. (2008) also observed a statistically significant increase in the odds of elevated cardiovascular anomalies in the highest THM4 exposure category. Grazuleviciene et al. (2013) also found evidence for an association between cardiovascular defects and high THM4 water concentration exposures (OR: 1.54; 95% CI: 0.89–2.68). They detected ORs for congenital heart anomalies in excess of 1.35 for all of the highest first trimester internal dose tertiles for THM4, chloroform, BDCM and DBCM and some evidence of an exposure-response relationship with increasing ORs across BDCM tertiles. Although their study results were largely null, with no statistically significant trends across THM exposure categories for either their broadly defined or more restricted sets of anomalies. Nieuwenhuijsen et al. (2008) did observe an association between high level of THM4 exposure (> 60 μg/L) and ventricular septal defects (OR: 1.43; 95% CI: 1.00–2.04) as well as between high bromoform exposure (> 4 μg/L) and major cardiovascular defects (OR: 1.18; 95% CI: 1.00–1.39) and also for gastroschisis (OR: 1.38; 95% CI: 1.00 – 1.92), an abdominal wall defect.

Chisholm et al. (2008) observed elevated odds of musculoskeletal and urogenital defects among those in the highest category of THM4, although these odds ratios were not statistically significant. They did not observe similarly elevated odds for integument congenital anomalies, respiratory system defects, or nervous system defects. THM4 in this study were not assessed in a way that was specific to a critical or biologically relevant time window of exposure. Other than the findings mentioned above, Nieuwenhuijsen et al. (2008) observed no associations between DBP exposure in the first 93 days of pregnancy (THM4, total BrTHM, or bromoform) and any of the other broadly defined or more restricted sets of anomalies they assessed. Grazuleviciene et al. (2013) reported statistically significant exposure-response relationships between congenital musculoskeletal anomalies and DBCM tertiles based on the first and second month exposure window (OR range 1.41 to 2.90) and for congenital urogenital anomalies based on internal dose BDCM first trimester tertiles. Women in the highest category of THM4 exposure in the Hwang et al. (2008) study had elevated odds of having a child with cleft palate (OR: 1.56; 95% CI:1.00–2.41). ORs for urinary tract defects were elevated across all THM4 categories (range: 1.24-1.65) in the Hwang et al. (2008) study, with the biggest increase seen for those in the low exposure category (5–9 μg/L), relative to the reference group (0–4 μg/L). None of the odds ratios for the urinary tract defect endpoint achieved statistical significance.

Although Righi et al. (2012) found little evidence of associations between first trimester THM exposures, which were generally low (3.8±3.6 μg/L), and birth defects, they did observe associations between high chlorite exposure and relative odds of renal defects, abdominal wall

defects and cleft palate, relative to those with the lowest category of chlorite exposure. They also detected associations between high chlorate exposure and relative odds of obstructive urinary defects, cleft palate and spina bifida, relative to those with the lowest category of chlorate exposure. An exposure-response relationship was also observed for musculoskeletal anomalies and DBCM exposure during the first and second months of pregnancy. The studies examining the risk of hypospadias associated with THM4 (Iszatt et al., 2011; Luben et al., 2008; Hwang et al., 2008) were all negative.

Nieuwenhuijsen et al. (2009) conducted a meta-analysis of 15 studies of DBP exposure and risk of congenital anomalies, including four studies reviewed for this report (Nieuwenhuijsen et al., 2008; Chisholm et al., 2008; Luben et al., 2008; Hwang et al., 2008). They found 17 percent excess risk of all congenital anomalies combined (95% CI: 3-34 percent), comparing low exposure to water chlorination or THM4 and a statistically significant excess risk of 58 percent (95% CI: 21-107 percent) for ventricular septal defects. The authors did not observe evidence of an exposure response relationship, and the finding was based on only three studies. Nieuwenhuijsen et al. (2009) conducted separate meta-analyses for categories of birth defects and specific anomaly endpoints if greater than two studies evaluated the same exposure index-congenital anomaly relationship, including the following: nervous system defects including neural tube defects, anencephalus, hydrocephalus, spina bifida, major cardiac defects, respiratory defects, oral cleft or cleft palate defects, cleft palate only, urinary tract defects, obstructive urinary defects and hypospadias. They observed no statistically significant relationships in these other meta-analyses. Although not statistically significant, they observed increases in the summary RRs for major cardiac defects (RR: 1.16; 95% CI: 0.98–1.37) and urinary tract defects (RR: 1.33; 95% CI: 0.92–1.92) comparing high to low chlorination by-product exposure.

Fetal Loss

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the Stage 1 and Stage 2 D/DBPRs, the epidemiology evidence base regarding the association between DBP exposure and fetal loss consisted of 10 primary studies (including 2 cross-sectional studies, 4 cohort studies and 4 case-control studies) and 9 review papers, identified in Exhibit A.5 (USEPA, 2005g).

Exhibit A.5: Studies of Fetal Loss Outcomes Evaluated for Stage 1 and/or 2 D/DBPRs

Study	Developmental/Reproductive Health Outcome	Study Design
Savitz et al. (2005)	Early and Late Pregnancy Loss	Prospective Cohort
Toledano et al. (2005)	Stillbirth	Cross-sectional
Dodds et al. (2004)	Stillbirth	Case-control
Dodds et al. (1999)	Stillbirth	Retrospective Cohort
Swan et al. (1998)	Spontaneous Abortion	Prospective Cohort

Study	Developmental/Reproductive Health Outcome	Study Design
Waller et al. (1998)	Spontaneous Abortion	Prospective Cohort
Bove et al. (1995)	Fetal Deaths	Cross-sectional
Savitz et al. (1995)	Spontaneous Abortion	Case-control
Aschengrau et al. (1993)	Neonatal Death, Stillbirth	Case-control
Aschengrau et al. (1989)	Spontaneous Abortion	Case-control
Bove et al. (2002)	Spontaneous Abortion, Fetal Death	Review
Graves et al. (2001)	Neonatal Death, Fetal Resorption	Review
Villanueva et al. (2001)	Spontaneous Abortion	Review
Nieuwenhuijsen et al. (2000)	Spontaneous Abortion, Stillbirth	Review
Reif et al. (2000)	Spontaneous Abortion, Stillbirth	Review
WHO (2000)	Miscarriage	Review
Craun, ed. (1998)	Stillbirth, Neonatal Death, Spontaneous Abortion	Review
Mills et al. (1998)	Spontaneous Abortion	Review
Reif et al. (1996)	Stillbirth, Neonatal Death, Spontaneous Abortion	Review

The results from this collection of studies provided relatively consistent evidence of an association between exposure to chlorinated water or DBP and pregnancy loss.

Three studies evaluated exposure to disinfected water or water source (as opposed to evaluating DBP levels in the water), all of which found some evidence of positive associations between exposure to disinfected water and risk of pregnancy loss. A case-control study by Aschengrau et al. (1989) set in Massachusetts evaluated water source (surface water versus other) among pregnant women and observed a statistically significantly association between having a surface water source and frequency of spontaneous abortion. A subsequent case-control study by Aschengrau et al. (1993), also set in Massachusetts, evaluated neonatal death and stillbirth by water source and two types of disinfection methods (chlorination or chloramination) found a non-statistically significant increase in the prevalence of stillbirths among participants with exposure to chlorinated (versus chloraminated) surface water. However, neonatal death was not found to be associated with water source or disinfection method. Swan et al. (1998) compared consumption of tap water and bottled water during early pregnancy in a cohort of women living in three different locations in California and observed a statistically significant increase in the frequency of spontaneous abortion at one of the three sites.

Bove et al. (1995) estimated maternal THM4 exposure in drinking water in a cross-sectional study in New Jersey and did not find association with fetal deaths. However, many of the studies reviewed did find associations between estimated THM exposure and pregnancy loss. Waller et

al. (1998) conducted a prospective cohort study of pregnant women in California and found that high estimated THM4 exposure (via ingestion and showering) during the first trimester of pregnancy was associated with a statistically significant increase in the risk of spontaneous abortion, compared to low levels of estimated THM4 intake. They also observed an exposure-response relationship between estimated THM4 ingested and spontaneous abortion. In a retrospective cohort study conducted by Dodds et al. (1999) in Nova Scotia, stillbirth was again found to be statistically significantly associated with THM4, and also with specific THMs, with higher risks observed among asphyxia-related stillbirths. In a subsequent case-control study conducted by Dodds et al. (2004), a statistically significant association between stillbirth and exposure to THM4, BDCM and chloroform was observed among women living in Nova Scotia and Eastern Ontario. Toledano et al. (2005) conducted what they characterized as a "large cross-sectional study" in England, modelling THM4 levels in three water zones and compared those estimates to rates of stillbirth. They found a statistically significant association between THM4 and risk of stillbirth in one of the three regions (OR = 1.21, 95% CI: 1.03-1.42), although when all three regions were combined, the elevation in risk of stillbirth was small and borderline statistically significant (OR = 1.11; 95% CI: 1.00-1.23). Risks were also elevated for chloroform, but no associations were observed between risk of still birth and BDCM or total BrTHMs. Savitz et al. (2005) estimated THM4, HAA9 and TOX exposures as well as individual BrTHM and HAA species during pregnancy in a prospective cohort study of three communities in the United States, comparing them to risk of pregnancy loss. They did not observe an association when high THM4 exposures were compared to low exposures. However, they did observe a statistically significant association between BDCM and pregnancy loss (OR = 1.58; 95% CI: 1.03-2.41). Although non-statistically significant, an increased risk of similar magnitude was seen between DBCM and pregnancy loss (OR = 1.30; 95% CI: 0.82-2.05). They also noted increased risks associated with pregnancy losses at greater than 12 weeks gestation for THM4, BDCM and TOX, but concluded that most results generally did not provide support for an association. In an earlier case-control study of THM4 concentration at the homes of pregnant women and estimated THM4 intake set in North Carolina, Savitz et al. (1995) found a statistically significant increase in the risk of miscarriage comparing high to low THM4 concentration, but not when comparing THM4 intake (THM4 concentration x amount of water consumption).

Four of the reviews concluded that the evidence base evaluated provides at least some support for an association between DBP exposure on risk of spontaneous abortion and fetal death/spontaneous abortion (Bove et al., 2002; Villanueva et al., 2001; WHO, 2000; Mills et al., 1998). Graves et al. (2001) concluded that there was no support for a relationship between DBP exposure and neonatal death. Nieuwenhuijsen et al. (2000) found the evidence supporting an association between THM exposure and spontaneous abortions/stillbirths to be weak. Craun, ed. (1998) concluded that although some associations have been observed in epidemiologic studies, the results do not constitute convincing evidence of a causal relationship between DBP and stillbirth, spontaneous abortion and neonatal death. Similarly, Reif et al. (1996, 2000) concluded that the evidence is inadequate for establishing a relationship between spontaneous abortion and DBP exposure.

New Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP and risk of fetal loss that became available subsequent to the promulgation of the Stage 2 D/DBPR; and found one study by Hwang and Jaakkola (2012).

Hwang and Jaakkola (2012) evaluated THM4 exposure among Taiwanese mothers of 3,289 stillbirths and 32,890 newborn control subjects in a case-control study. Water sampling was conducted quarterly in five studies and two studies assessed DBP measurements for the entire pregnancy using sampling frequency that was not specified. The number of sampling sites used to assess DBP levels also varied by study. Water sampling frequency for THM4s was conducted, at a minimum, four times per year for each water treatment plant. THM4 exposure was calculated by calculating an average of the modeled quarterly THM4 estimates for the water treatment plants serving each mother between the date of conception and the date of birth, weighted by the proportion of the trimester falling into each quarterly period. Estimated THM4 exposures were categorized into four groups (0–4 μg/L (the reference category), 5–9 μg/L, 10–19 μg/L, 20+ μg/L). Covariate adjusted odds ratios were slightly elevated in the low (OR: 1.02; 95% CI: 0.92–1.14), medium (OR: 1.10; 95% CI: 1.00–1.21) and high (OR: 1.06; 95%: 0.96–1.17) categories. The authors also presented a meta-analytic summary odds ratio incorporating the results of previous studies with their study and noted that it provided consistent evidence of increased risk, but showed some heterogeneity. The summary odds ratio estimated from a random-effects model was 1.21 (95% CI: 1.02-1.43) and interpreted by the authors as providing consistent evidence of an increased risk of stillbirth associated with THM4 exposure, although there was statistically significant heterogeneity observed between studies.

Male Reproductive Effects

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

For the Stage 1 and Stage 2 D/DBPRs, the epidemiology evidence base regarding the association between DBP exposure and male reproductive effects consisted of a single study conducted in California by Fenster et al. (2003) in which THM4 levels were estimated in drinking water sampled within three months prior to semen collection. The investigators evaluated sperm motility and sperm morphology, but found no associations with THM4 exposures.

Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP and male reproductive endpoints that became available subsequent to the promulgation of the Stage 2 D/DBPR. Five studies of DBP associations with male reproductive outcomes published after the Stage 2 D/DBPR Economic Analysis (EA) (2004-2013) were identified and evaluated: one prospective birth cohort study, one case-control study and three cross-sectional studies (USEPA, 2005g).

- Prospective cohort studies:
    - Luben et al. (2007)

- Case-control studies:
    - Iszatt et al. (2013)
- Cross-sectional studies:
    - Zeng et al. (2013)
    - Nickmilder and Bernard (2011)
    - Xie et al. (2011)

The Luben et al. (2007) study was conducted in the US; the Zeng et al. (2013) and Xie et al. (2011) studies were conducted in China, the Iszatt et al. (2013) study was conducted in the UK, and the Nickmilder and Bernard (2011) study was conducted in Belgium.

Four of the five studies (Iszatt et al., 2013; Zeng et al., 2013; Xie et al., 2011; Luben et al., 2007) included assessments of semen quality (e.g., (low) sperm count, sperm morphology (percent normal sperm), low motile sperm concentration, percent of sperm with DNA fragmentation and percent of immature sperm). Two studies assessed serum total testosterone levels (Zeng et al., 2013; Nickmilder and Bernard, 2011). Nickmilder and Bernard (2011) additionally assessed serum inhibin B levels. In all of the studies, a single semen sample was provided by each subject. Urine (and blood samples, when collected) was also sampled once for each subject. Studies that use a single-sample to represent average, typical or usual levels of a measurement (semen quality in this context) rely on an (often only implicit) assumption that there is little intra-individual variability in the measurement over time.

Only two of the five studies (Iszatt et al., 2013; Luben et al., 2007) assessed DBPs in municipal water systems. Iszatt et al. (2013) used quarterly water samples and Luben et al. (2007) used weekly or biweekly samples. Both studies attempted to estimate exposure in the 90 days prior to collection of the semen sample. The study by Nickmilder and Bernard (2011) assessed time spent in pools as a proxy for DBP exposure. The remaining two studies assessed biomarkers of DBP exposure. Xie et al. (2011) assessed urinary creatinine-adjusted TCAA concentrations and Zeng et al. (2013) assessed whole blood levels of THM. In these two biomarker studies, semen collection and urine/blood collection occurred on the same day.

The results from these epidemiologic studies of the association between DBP exposure and male reproductive outcomes were largely negative. Xie et al. (2011) assessed associations between urinary creatinine-adjusted TCAA concentration as a biomarker of DBP exposure and sperm quality and observed no statistically significant associations, nor clear evidence of exposure-response trends. Zeng et al. (2013) assessed concentrations of THMs in blood and found no associations with decrements in sperm motility, or sperm velocity. They did find that moderate levels (above the level of detection, but below the median of observable values) of BDCM and DBCM were associated with decreased sperm linearity, compared with levels below the level of detection. Exposure–response relationships were observed between elevated blood chloroform and THM4 concentration and decreased sperm concentration and between elevated blood DBCM concentration and decreased serum total testosterone. Zeng et al. (2014) detected reductions in sperm concentration with increasing BrTHM exposure levels (-0.26 (95% CI: -0.52, -0.01). Iszatt et al. (2013) and Luben et al. (2007) found little evidence of an association between DBP exposure and sperm quality parameters; however, sperm concentration reductions in Luben et al. (–0.23; 95% CI: –0.54, 0.07) for the BrTHM exposure metric were nearly identical to those observed by Zeng et al. (2014).

Nickmilder and Bernard (2011) assessed associations between sperm quality parameters and cumulative swimming pool attendance time as a proxy for exposure to chlorination byproducts in pool water among adolescent boys. It should be noted that swimming pools are a potential source of *both* DBP exposure and exposure to the disinfectants themselves. As such, the interpretation of observed associations is limited because the effects of DBP exposure and the effects of exposure to the disinfectants themselves cannot be distinguished. They found that, among the adolescents assessed in the study, inhibin B concentrations were inversely associated with time spent in indoor chlorinated pools before the age of 10, while total and free testosterone concentrations decreased with increasing amount of time spent in indoor chlorinated pools. Among those that swam in indoor chlorinated pools for more than 250 hours before the age of 10, or for more than 125 hours before age 7, had an almost 3-fold increase in the risk of having low (<10th percentile) serum inhibin B and/or total testosterone, relative to those who never swam in indoor pools during childhood. The authors did not observe associations between cumulative time spent in indoor pools and free testosterone, LH, follicle-stimulating hormone and dehydroepiandrosterone-sulfate, nor was low serum testosterone or inhibin B associated with attendance of outdoor chlorinated pools or those pools disinfected with copper–silver ionization.

Female Reproductive Effects

Information Available During Development of Stage 1 and Stage 2 D/DBPR

For the Stage 1 and Stage 2 D/DBPR, the epidemiology evidence base regarding the association between DBP exposure and female reproductive effects consisted of a single prospective cohort study in California. Windham et al. (2003) estimated THM exposure through two routes of exposure: showering (dermal / inhalation) and ingestion of drinking water and found that THM exposure may affect ovarian function. BrTHMs were statistically significantly associated with shorter menstrual cycles, especially for dibromochloromethane (DBCM). They did not observe strong or statistically significant association between THM4 exposure and luteal phase length, menses length, or cycle variability.

New Information Available Since Development of Stage 2 D/DBPR

EPA conducted a literature search to identify new epidemiology studies of DBP and female reproductive endpoints and identified one study by MacLehose et al. (2008). MacLehose et al. (2008) evaluated the association between exposure to specific DBP trihalomethanes, HAAs, brominated-trihalomethanes, brominated-HAAs, total organic halides and bromodichloromethane) and time to pregnancy. DBP ingestion, inhalation and absorption while bathing or showering were estimated among newly pregnant women enrolled in the Right From the Start prospective cohort study of reproductive outcomes conducted in three metropolitan areas of the US. Water samples were drawn from the distribution system at each site either weekly (for two sites) or every other week (for the site with consistently low DBP levels. Spatial variability of DBP levels was evaluated, and levels were found to be uniform. DBP concentrations were assigned to each menstrual cycle during which each woman attempted to conceive. The investigators calculated four metrics each for THM4, bromodichloromethane, brominated-trihalomethanes, brominated-HAAs and total organic halides (TOX): tap water concentration, amount ingested through drinking, absorbed DBP through inhalation and dermal absorption while showering or bathing (for THM4, bromodichloromethane, brominated-

trihalomethanes only), and "integrated measure" of THM4, bromodichloromethane, brominated-trihalomethanes in the bloodstream through ingestion and showering or bathing. The authors observed no evidence of an increased time to pregnancy among women with exposure to increasing levels of DBP.

Additional Observations on the Reproductive and Developmental Effects Based on the Epidemiology Evidence

Because of the extensive epidemiological information base addressing reproductive and developmental effects related to exposure to chlorination by-products, we summarize in this section the recurrent limitations that are evident in this epidemiologic literature, which include statistical considerations and potential sources of information bias, selection bias and confounding arising from study design choices, exposure assessment, health endpoint assessment and covariate assessment. It should be noted that disinfected drinking water can contain hundreds of disinfection byproducts. The measured exposures associated with reproductive health endpoints in these studies may directly affect the risk of reproductive outcomes; they may also be useful though imperfect indicators for the most relevant and potentially measured or unmeasured causative DBP exposures. In these epidemiologic studies, DBP exposure was most often assessed by quantifying THM4. Often, specific trihalomethanes, total HAAs, specific HAAs were also assessed. Less commonly quantified were other DBPs or DBP mixture surrogates such as total organic halides, chlorite and chlorate levels.

Recurrent patterns across the post-Stage 2 DBP studies include the following: 1) findings of positive associations (e.g., RRs greater than 1) between DBP indicators and adverse reproductive outcomes that were small in magnitude and sometimes null and 2) frequent absence of observed linear exposure-response relationships. The lack of consistent results across many of the aforementioned outcomes could have several possible explanations. Most of the studies reviewed included statistical adjustment for important confounders, including gestational age, maternal age, race, body mass index, marital status, smoking and parity, and comorbidities. Several studies attempted to additionally adjust for socioeconomic risk factors including education, income, health insurance and adequacy of prenatal care. However, the potential for residual confounding to bias study results and explain some of these is also a possibility as not all of the studies reviewed included adjustment for all of these risk factors for reproductive endpoints, and some of these potential risk factors (e.g., socioeconomic status) are difficult to measure.

Exposure misclassification (especially if non-differential) is a plausible explanation for the patterns noted above for the lack of inconsistent results or lack of exposure-response relationships. The limited exposure data focused on only a few surrogates to represent very complicated DBP mixture exposure scenarios might also explain some of the mixed study results and lead to exposure misclassification of the ideal exposure metric or truly relevant (set of) DBP exposure(s). In addition, the available data and exposure metrics often only represent a particular exposure route or groups of DBPs and may not be able to fully evaluate the potential for interactions to occur between DBPs and the adverse reproductive outcomes of interest.

The quality of the DBP exposure assessment in the epidemiologic literature reviewed for this analysis ranged from adequate to very detailed. Many of the studies evaluated objective measures of DBP levels in drinking water, assessed water consumption behaviors prior to birth

and constructed detailed metrics of DBP exposure and dose. Often, indirect estimates of DBP exposure were derived by linking (maternal) residence to water quality monitoring data. In studies using this exposure assessment methodology, DBP levels were often spatially aggregated. Such area-level assessments remain the most feasible procedure for categorizing exposure to multiple DBPs in large epidemiologic studies. Some of the studies reviewed implemented more refined exposure assessment that combined water quality monitoring data, or other similar assessments of DBP in centralized locations within a water system, with personal water usage information obtained from study participants. Such methodology has the potential to decrease exposure misclassification. However, there was no clear evidence that these studies were more likely to observe positive associations between DBP exposure and reproductive endpoints, relative to studies that did not assess water use behaviors. Notably, several of the studies reviewed assessed DBP exposure using a biomarker of exposure, albeit on a smaller scale than many of the larger studies. Development of inexpensive yet sensitive and specific biomarkers for DBP exposure has the potential to further minimize exposure misclassification. In their assessment of maternal urinary creatinine-adjusted TCAA as a DBP exposure biomarker in their study of effects on birth weight, Zhou et al. (2012), observed lower average birth weight among infants whose mothers were in the highest two quartiles of creatinine-adjusted urinary TCAA concentrations for the overall population. They saw even larger reductions among a subset of women who had completed questionnaires which allowed for additional adjustment of additional covariates that may have been confounders. The study of male reproductive endpoints and urinary TCAA conducted by Xie et al. (2011) was negative. Because TCAA and the other HAAs are non-volatile DBPs, it is unclear to what degree maternal urinary TCAA concentrations are valid and accurate DBP surrogates in this population, especially for the volatile DBPs. TCAA is not specific to DBP exposure and urinary TCAA levels could reflect exposure to other environmental contaminants. In the study of male reproductive endpoints and THM levels in blood conducted by Zeng et al. (2013), associations were observed between moderate levels of blood BDCM and DBCM and decreased sperm count and declined sperm linearity compared with low levels.

Suggestive exposure-response relationships of borderline statistical significance were observed between elevated blood TCM concentrations and decreased sperm concentration and between elevated blood DBCM concentration and decreased serum total testosterone. Blood THM levels are likely a more specific biomarker of exposure to volatile DBPs (e.g., THMs) across different exposure routes compared to urinary DBP measures. However, THMs are rapidly metabolized and may best represent baseline THM levels. Therefore, most of these measures would not reflect the impact of recent activities that may drive average or peak exposures during critical exposure windows. Although analysis of urinary TCAA and whole blood THM levels is more invasive, expensive and labor intensive, they are expected to be better exposure measures compared to assessments of DBP health effects that rely on routinely-monitored DBP measurements.

A biologically relevant time-window for exposure has been hypothesized for many of the reproductive health endpoints investigated in these studies. This is the period of fetal development during which it is thought that an exposure to a toxicant may exert its influence in development of the outcome. Many of the studies assessed DBP exposure specific to specific trimesters of pregnancy. Several studies of congenital anomaly endpoints and of sperm quality carried out exposure assessments targeted to well-characterized time-windows for exposure

effects. However, all of the cross-sectional studies as well as several of the cohort and case-control studies reviewed in this analysis assessed exposure at either a single point in time (including after the birth of the infant in a few studies), or alternatively characterized exposure for the entire pregnancy. If a true association indeed exists between DBPs and adverse reproductive outcomes, it is possible that no association would be observed even with a precisely measured exposure if the exposure assessment occurs outside of the biologically relevant time window for exposure effects. In a more plausible scenario, the observed measure of association would be attenuated if exposures assessed outside of the critical time-window for exposure are imperfectly correlated with exposures occurring during the most biologically relevant time periods.

Despite efforts to minimize errors in DBP exposure assessment, a certain degree of exposure misclassification remains inevitable in DBP health effects epidemiology. The impact of this is to decrease the sensitivity of the study to detect associations that may exist. The DBP exposure measurement error in these epidemiologic studies is likely to be predominantly non-differential with respect to reproductive outcomes; the use of infrequent (e.g., quarterly) water sampling, community level (as opposed to individual-level) exposure metrics and missing exposure data all have the potential to induce bias towards an observed null association between estimated DBP exposure and the adverse reproductive outcomes. Although they likely can provide a sense of the relative exposure rankings for the predominant DBPs, community level exposure metrics based on quarterly water sampling are not likely to fully capture the full extent of spatial and temporal variability in DBP levels over the course of a pregnancy or even smaller critical windows (e.g., a single trimester). However, observed associations between THM4 and reproductive outcomes were null or small and often not statistically significant, even among the studies that conducted more frequent sampling and those that implemented exposure assessment advancements (e.g., Hoffman et al., 2008a, Lewis et al., 2006; Patelarou et al., 2011).

Among the studies that assessed maternal water use activities, misclassification of exposures (both total water intake and to DBPs) is also likely due, for example, to errors in recall of water use and water consumption outside of the home. These errors are likely to be non-differential in the studies evaluated, and therefore would, on average, attenuate observed estimates of association toward the null. That being said, studies that query maternal water use and consumption have the potential to generate more accurate DBP exposure estimates, relative to studies that rely only on DBP levels measured in municipal water samples. For example, in the assessment of the SGA endpoint, Levallois et al. (2012), Danileviciute et al. (2012), Costet et al. (2012), Patelarou et al. (2011), Grazuleviciene et al. (2011), Hoffman et al. (2008a) and Aggazzotti et al. (2004) all obtained information on beverage consumption and/or water use from study participants. It is not clear that markedly different conclusions can be drawn from this subset of SGA studies, compared to the six studies that did not additionally survey participants' water use. In general, there was no clear indication of greater consistency of reported associations, nor of exposure-response trends, among studies that used more sophisticated exposure assessment methodologies.

With respect to observational studies addressing birth weight endpoints, there is the possibility of confounding of the observed associations by unknown and unmeasured risk factors for adverse birth weight outcomes that are also determinants of DBP exposure, independent of birth weight. However, all of the studies assessed for this report evaluated and adjusted for confounding by

multiple known risk factors for adverse birth weight outcomes, e.g., infant sex, gestational age, maternal age, socioeconomic indicators, prenatal care, marital status, parity, ethnicity, maternal body mass index, maternal smoking status, passive smoking during pregnancy, maternal disease history and alcohol consumption during pregnancy. There are two alternate scenarios of negative confounding which would result in the observation of no association, or a small positive association (due to observed RR being biased toward the null for a negative confounder), between DBP exposure and adverse birth weight outcomes assuming that there truly *is* a causal association between the two; the first is due to confounding by one or more factors that *increase* the risk of adverse birth outcomes and *decrease* in magnitude or prevalence with increasing DBP exposure, and the second is due to confounding by one or more factors that *decrease* the risk of adverse birth outcomes and *increase* in magnitude or prevalence with increasing DBP exposure (Walker, 1991). Correspondingly, moderate maternal physical activity has been associated with decreased risk of fetal growth restriction (Pivarnik, 1998) and may lead to increased water intake. If this water intake was largely due to bottled water use (which often has lower DBP levels) among a more health conscientious population as reported in some pregnancy cohorts (Forssén et al., 2007), then this may result in negative confounding.

Similarly, a strong risk factor like maternal smoking during pregnancy, which was unmeasured in some studies (Yang et al., 2007; Chisholm et al., 2008; Nieuwenhuijsen et al., 2009), may also lead to attenuation of study results due to negative confounding as it also has been shown to be linked to increased bottled water use activities and presumably lower DBP levels (Forssén et al., 2007). Maternal perinatal nutrition, a potential risk factor for adverse birth weight outcomes, was not evaluated as a confounder in these studies. The direction of any potential bias due to confounding by maternal nutrition depends on whether poor nutrition is associated with greater or less DBP exposure. Apart from some DBP exposures, other water contaminants were not evaluated as confounders in the studies evaluated for this report. Only two studies examined multi-pollutant DBP models. Hoffman et al. (2008a) did adjust associations between term birth weight and specific THMs for other THMs. Their analyses did not find consistent evidence for an association between any DBP species and term birth weight, although the authors concluded that these analyses were limited due to small sample sizes. A recent study by Rivera-Núñez and Wright (2013) saw some evidence in mean birth weight reductions for HAA5 and BrTHM exposures with and without adjustment for other DBP surrogates. The largest reduction was noted for DBP9 exposures which may better represent a mixture metric of the predominant DBPs that many people are exposed to. In contrast, although the authors saw increased adjusted ORs for SGA for various DBP metrics, these diminished following further adjustment of other DBP surrogates (i.e., THM4 or HAA5). These studies highlight the exposure assessment complexities that warrant further research to better elucidate the relevance of previously studied DBP mixtures relative to toxicity demonstrated in animals or other lines of evidence.

The misclassification of health endpoints in this body of scientific evidence is less problematic, relative to the challenges posed by assessment of DBP exposures. Nevertheless, misclassification of fetal growth and development endpoints are subject to measurement error, which is, in the studies reviewed, likely to be non-differential with respect to exposure. For example, gestational age measurements are estimated by use of maternal self-report of last menstrual period, evaluation of ultrasound, clinician estimates, or a combination of these approaches. Each of these can be subject to measurement error which can lead to outcome misclassification when used to examine outcomes such as PTD, as well as the possibility of residual confounding in studies that

adjust for gestational age. Another concern regarding the outcomes examined in these studies is that having a low birth weight, or being SGA, may not necessarily be an indicator of intrauterine growth restriction (although SGA and IUGR are often used synonymously), as babies may simply be born constitutionally small. Thus, the use of outcome measures that incorporate gestational age and other factors such as ethnicity into the definition (e.g., SGA) in most of these studies should help focus on infants that are pathologically growth restricted.

Although possible, selection bias was a limited concern in the epidemiologic studies reviewed for this analysis. Many of the existing studies use retrospective cohort designs which can comprehensively capture whole populations. These studies have a low probability of selection bias, since the study inclusion criteria are not likely to be differentially related to DBP exposures. Prospective cohort studies of birth outcomes also inherently have a low likelihood of selection bias due to minimal loss to follow-up given the short study duration. All of the case-control studies reviewed here also took documented steps to maximize the degree to which their control group represented the population that gave rise to the cases. Nevertheless, the studies almost exclusively assessed reproductive outcomes only among live births. In the case-control studies, control participants, too, were selected from among live births. In these studies, then, a selection bias would be induced if DBP exposure or the reproductive endpoint being evaluated influence the risk of fetal death (or elective termination of pregnancy). In such scenarios, selection bias may induce a false negative association if a true association between DBP and the reproductive outcome exists.

Many of the positive associations that were observed between DBP exposure indicators and adverse reproductive outcomes in the articles assessed for this analysis were not statistically significant. That is to say, under the assumption that there is truly no association between DBP exposure and adverse reproductive endpoints, one expects to observe associations as large as those that were observed, or associations of larger magnitude, greater than 5 percent of the time due to chance alone. The statistical power of some of the studies assessed in this analysis was limited by low DBP levels that were limited in range. Assessments of outcomes such as specific congenital anomalies studies were further limited by small study populations and correspondingly small numbers of cases. Although limited statistical power was a general weakness of the epidemiologic studies reviewed, the meta-analyses conducted for several reproductive endpoints were able to leverage the power of multiple studies to more precisely estimate associations with THM4.

The presence of exposure-response trends, indicated as either positive associations with continuously distributed DBP exposure metrics or as monotonically increasing RRs associated with ordinal categories of DBP exposure (e.g., quantiles), may be evidence for there being a causal association between DBP exposures and reproductive health endpoints. Such trends were formally hypothesized and assessed statistically in some studies although, often, investigators only addressed exposure-response trends informally or left consideration of exposure-response trends to be evaluated by the reader. Setting aside statistical evidence of exposure-response trends, even monotonically increasing RRs of reproductive endpoints with increasing levels of DBP exposure were infrequently and inconsistently observed. Even more seldom were such trends observed and found to be statistically significant. As noted before, the lack of exposure-response relationships in many studies might be partially due to some sources of bias such as information bias (resulting from exposure misclassification) or limited exposure contrasts which

preclude distinct characterization of differentially exposed groups. For categorical exposures comparisons, an additional limitation of some studies is the inability to examine a referent population that is lowly exposed or unexposed.

Finally, it is noted that DBP levels measured in most of the studies reviewed for this report were low and largely below current regulatory standards. Although it is important to be assessing potential DBP health effects at such levels, the relative lack of variability and limited range of DBP exposure constrains the statistical power of these studies, relative to studies where the DBP exposure range is broader.

Taken together, the limitations of the epidemiologic literature assessed in this document constrain conclusions that can be drawn. Because of these limitations, observed associations between DBP exposure and reproductive endpoints could be higher, or lower, than the corresponding "true" associations.

A.1.3 Mixtures of Organic Chlorination DBPs

The intent of Stage 1 and Stage 2 D/DBPRs was not only to reduce exposure to the four THMs and five HAAs included specifically under the MCLs, but also to reduce exposure to the mixture of organic chlorination DBPs as a group. This section provides information on animal studies and mixtures of DBPs and an update on research that has been conducted to further understand the toxicity of mixtures of DBPs. These mixtures include but are not limited to the nine substances addressed by the Stage 2 D/DBPR MCLs.

In 1998, an ILSI expert panel determined that the single-chemical testing approach was not sufficient to assess the cancer risk from DBPs (ILSI, 1998). The panel recommended a three-tiered testing approach, focusing first on simple, defined mixtures of fewer than 10 DBPs, then on complex mixtures which simulate disinfection scenarios, and lastly, on samples of real drinking water. The panel suggested using three levels of studies (*in vitro*, short-term screening tests or 90-day animal studies and long-term chronic bioassays), along with studies related to chemical structure-activity relationships and mechanism of action.

After publication of the ILSI report, a collaborative research effort was undertaken by EPA's National Center for Environmental Assessment and National Health and Environmental Effects Research Laboratory, Virginia Commonwealth University and Tulane University (Teuschler et al., 2000). The goal of their collective research efforts was to determine the toxicity and carcinogenicity of mixtures of DBPs in support of human health risk assessments. This collaborative approach resulted in new data collection, statistical analysis and methods development. Three approaches were recommended for future research on DBP mixtures: toxicological studies of simple defined mixtures, toxicological studies using reproducible disinfection scenario samples and toxicological or epidemiologic studies on direct drinking water samples.

As part of this collaborative research, two studies focused on a threshold additivity model and on a proportional-response addition model. The threshold additivity model assessed the hepatotoxic interactions between the THMs included in THM4. The response of specific mixtures of THMs in water samples from 35 water treatment facilities was predicted under dose-addition based on

the dose-response curves for the individual THMs. CD-1 mice were exposed to the water samples by gavage for 14 days, and the results of biochemical markers of liver toxicity of the mixtures fell within 95 percent of those predicted by dose-addition, demonstrating that threshold additivity is a reasonable assumption for mixtures risk assessment. The proportional-response addition model used a generic definition of additivity that was not dependent on mechanism of action. The proportional-response additivity model was used to estimate the proportional risks for developmental effects from the HAA and haloacetonitrile components of two water samples, one from the Mississippi River and one from the Ohio River. The model showed that the concentration of the individual DBPs may not be sufficient to result in adverse effects, but the activity of the mixture may result in additive or greater-than-additive effects.

Andrews et al. (2004) explored the developmental toxicity interactions between three HAAs – dichloroacetic acid, dibromoacetic acid and bromochloroacetic acid - using the whole embryo culture assay. In this *in vitro* assay, rat embryos at GD 9 were exposed for 48 hours to various concentrations (50–5000 micromolar (µM)) of the HAAs individually or in combination and evaluated for mortality and anomalies. Individually, the HAAs resulted in a significant increase in malformations consisting of rotational defects, heart defects, delayed caudal development, visceral arch defects, eye defects and a low incidence of neural tube defects. There was also a significant increase in embryo lethality at the higher doses. Of the three HAAs, dichloroacetic acid was the least embryotoxic, exhibiting 37 percent abnormalities at 5000 µM; dibromoacetic acid exhibited 64 percent at 400 µM; and bromochloroacetic acid exhibited 70 percent at 300 µM. The authors predicted that the combined embryo toxicity of the HAAs would be additive, and the results confirmed this prediction. Embryo toxicity from combinations of the compounds was additive in all binary combinations as well as in the mixture of the three compounds.

Yang et al. (2014) studied the impact of two disinfectants, free chlorine vs. monochloramine, and the impact of bromide (Br^-) and iodide (I^-) on mammalian cell toxicity of finished drinking water. The Chinese Hamster Ovary (CHO) cell line was used for mammalian cell toxicity studies and the CHO cell single cell gel electrophoresis (SCGE) assay was used to measure genomic DNA damage from drinking water samples. The water disinfected with chlorine was less cytotoxic than the water disinfected with chloramine but it was more genotoxic. The results of the CHO cell cytotoxicity assay showed that the lowest levels of cytotoxicity were associated with disinfection by monochloramine or free chlorine alone, and the addition of bromide and iodide significantly increased the cytotoxicity of the chloramine or chlorine disinfection. Similarly, the results of the SCGE assay demonstrated that the addition of bromide and iodide significantly increased the genotoxicity of the chloramine or chlorine disinfection. The authors concluded that the agents which resulted in cytotoxicity and genotoxicity were the generated brominated and iodinated DBPs rather than the formation of chlorinated DBPs.

A.2 Regulated Inorganic DBPs

A.2.1 Bromate

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

Bromate was carcinogenic when administered in drinking water to male and female rats. DeAngelo et al. (1998) administered potassium bromate in drinking water to male F344 rats and male B6C3F1 mice. Mesotheliomas, which originated from the testis, spread throughout the peritoneal cavity. Kidney and thyroid tumors were observed in the rats. Kurokawa et al. (1986a, 1986b) conducted a study with potassium bromate in drinking water administered to male and female F344 rats and female B6C3F1 mice. They also observed peritoneal mesotheliomas, but did not specify the origin. Kidney and thyroid tumors were observed in male rats and kidney tumors in female rats. It was not carcinogenic in female mice.

Mutagenicity/Genotoxicity

Mixed results were reported for bromate for *in vitro* mutagenicity studies in *S. typhimurium*. Positive results were reported in *in vitro* studies on chromosomal aberrations, chromatid breaks and micronuclei formation in mammalian cells and for positive results in the comet assay indicative of DNA strand breaks. *In vivo* studies in mice reported cytogenic effects on bone marrow cells, micronuclei formation and increases in micronucleated polychromatic erythrocytes (Health Canada, 1998; USEPA, 2001b).

Reproductive/Developmental

USEPA (2001b) reviewed the following study on bromate:

Wolf and Kaiser (1996) administered bromate to male and female rats at doses up to 22 mg/kg/day in drinking water for various times during a 35-day period. A significant decrease in epididymal sperm density was observed in males at 22 mg/kg/day and no effects were noted on female reproductive end points. A reproductive NOAEL of 7.7 mg/kg/day and LOAEL of 22 mg/kg/day were identified based on the effects on sperm.

Other

Nakano et al. (1989) reported necrotic changes in the kidneys, increased blood urea nitrogen and abnormalities in the cortical tubules of the kidneys of rats at 30 mg/kg/day in drinking water for 15 months. A LOAEL of 30 mg/kg/day was identified based on these effects (USEPA, 2001b). DeAngelo et al. (1998) reported renal urothelial hyperplasia at 7.9 mg/kg/day in a 100-week drinking water study in rats. A NOAEL of 1.1 mg/kg/day and a LOAEL of 7.9 mg/kg/day were identified from this study (USEPA, 2001b).

A.2.2 Chlorite

Information Available During Development of Stage 1 and Stage 2 D/DBPRs

Cancer

Kurokawa et al. (1986b) administered sodium chlorite to F344 rats and B6C3F1 mice in drinking water for 85 or 80 weeks. No chlorite-related increases in tumor incidence were observed in the rats and a high mortality rate in the control mice made statistical comparisons between controls and treated mice difficult to interpret. EPA concluded that the study was inadequate for assessing carcinogenicity due to the relatively short exposure (80 weeks) and the high incidence of early mortality in the control mice (USEPA, 2000b). IARC (1991) evaluated the carcinogenicity data on sodium chlorite and concluded that there was inadequate evidence for the carcinogenicity of sodium chlorite in experimental animals.

Mutagenicity/Genotoxicity

Positive results were reported for mutagenicity of chlorite in *in vitro* studies in *S. typhimurium*, both with and without metabolic activation. *In vivo* studies reported negative results for chromosomal aberrations in micronucleus assays, in bone marrow cells and in the sperm-head abnormality assay following gavage administration of chlorite in mice. Positive results were reported in one micronucleus assay in bone marrow cells of mice after intraperitoneal injection of chlorite (USEPA, 2000b).

Reproductive/Developmental

The following studies on chlorite were reviewed in USEPA (2000b) and Health Canada (2008b):

Moore et al. (1980) administered sodium chlorite to pregnant A/J mice at approximately 22 mg/kg/day in drinking water throughout gestation and lactation. No significant effects were noted on gestation length, litter size, or number of pups dead at birth; however, significant decreases were observed in average pup weaning weight and birth-to-weaning growth rate. A developmental LOAEL of 22 mg/kg/day was determined.

Couri et al. (1982) conducted a developmental study in pregnant Sprague-Dawley rats exposed to sodium chlorite in drinking water at doses up to 610 mg/kg/day on GD 8–15. Another group of pregnant rats received 200 mg/kg/day via gavage on GD 8–15, which resulted in 100 percent mortality. An increase in the number of resorbed and dead fetuses and decreases in crown-rump length were reported at all dose levels, with no effects reported on postnatal growth or incidences of soft tissue and skeletal malformations. A frank effect level of 70 mg/kg/day for resorbed and dead fetuses and decreases in crown-rump length was determined.

Suh et al. (1983) administered chlorite to pregnant Sprague-Dawley rats at approximately 0, 0.1 or 1 mg/kg/day for 2.5 months before mating them with unexposed males, as well as during GD 0–20. No significant effects were noted on resorptions, fetus survival, fetal body weights, or incidence of skeletal abnormalities. A developmental NOAEL of 1 mg/kg/day was determined.

Carlton and Smith (1985) and Carlton et al. (1987) conducted a series of reproductive/ developmental studies. In a first set of studies, male Long-Evans rats were administered doses up to 7.5 mg/kg/day chlorite in drinking water for 56 days before mating and throughout the 10-day mating period. Female rats were administered the same dose of sodium chlorite for 14 days before mating, during the mating periods and throughout gestation and lactation. No dose-related changes in fertility or in sperm parameters were observed in the parental rats; however, significant decreases in T3 and T4 levels were observed in the offspring of rats administered 7.5 mg/kg/day. A developmental NOAEL of 0.75 mg/kg/day and LOAEL of 7.5 mg/kg/day based on decreased hormone levels were determined. In a second set of studies, Long-Evans rats were administered doses of chlorite of up to 27 mg/kg/day in drinking water for 72–76 days. A significant increase in abnormal sperm was observed, with abnormalities including frayed tails, open hooks and amorphous sperm heads. A reproductive NOAEL of 0.75 mg/kg/day and LOAEL of 7.5 mg/kg/day were determined.

Mobley et al. (1990) exposed female Sprague-Dawley rats to approximately 3 and 6 mg/kg/day chlorite for 10 days before mating them with unexposed males and during gestation and lactation. Significant decreases in exploratory activity were observed in the rat pups, with a developmental NOAEL of 3 mg/kg/day and a LOAEL of 6 mg/kg/day identified.

Harrington et al. (1995a) conducted a developmental study in New Zealand white rabbits, administering doses up to 40 mg/kg/day chlorite in drinking water for GD 7–20. The authors concluded that there were no treatment-related effects on pregnancy incidence, number of implantations, number of pre-implantation losses, fetal sex ratio, number of live fetuses or fetal visceral or structural abnormalities. Mean fetal weights were slightly decreased at 26 and 40 mg/kg/day, and skeletal variants related to incomplete fetal bone ossification were increased at 26 mg/kg/day. EPA identified a developmental NOAEL of 10 mg/kg/day and a LOAEL of 26 mg/kg/day, based on decreased fetal weight and delayed skeletal ossification (USEPA, 2000b).

The Chemical Manufacturers Association (1996) conducted reproductive/developmental studies in Sprague-Dawley rats. Rats received drinking water containing up to 20 mg/kg/day chlorite for males and 28.6 mg/kg/day chlorite for females for 10 weeks. Males were exposed throughout mating, and females were exposed through mating, pregnancy and lactation for two generations. The F1 pups were mated twice to produce the F2a and F2b generations. Reduced absolute and relative liver weights in F0 females and F1 males and females, reduced pup survival, reduced body weights at birth in F1 and F2 rats, lower spleen and thymus weights in F1 and F2 rats, and lowered incidence of pups exhibiting normal righting reflex and response to an auditory startle stimulus were observed. A developmental and toxicity NOAEL of 2.9 mg/kg/day and LOAEL of 5.9 mg/kg/day were determined based on reduced organ weights and lowered auditory startle amplitude in the pups.

Other

Subchronic and chronic oral administration of chlorite in animals results in effects on the stomach and organ weights, and hematotoxicity. Oral studies in rats, mice and monkeys ranging from 30 days to 13 weeks reported hematological effects from chlorite administration (Abdel-Rahman et al., 1984; Couri and Abdel-Rahman, 1980; Moore and Calabrese, 1982; Bercz et al., 1982). However, USEPA (2000b) assessed the hematological effects from Abdel-Rahman et al.

(1984) and Couri and Abdel-Rahman (1980) studies and stated "The lack of a consistent dose-effect relationship, small numbers of animals, and small magnitude of effects complicate interpretation of the results" (USEPA, 2000b). Harrington et al. (1995b) administered sodium chlorite by gavage to Crl:CD (SD) BR rats for 13 weeks. A NOAEL of 7.4 mg/kg/day and a LOAEL of 19 mg/kg/day for stomach lesions and increases in spleen and adrenal weights in rats were identified from this study (USEPA, 2000b). The stomach lesions consisted of hyperplasia, hyperkeratosis, ulceration, chronic inflammation and edema and were considered by EPA to be noncancerous.

A.3 Regulated Disinfectants

A.3.1 Chlorine

Information Available During the Development of Stage 1 and Stage 2 D/DBPRs

Cancer

Chlorine was administered to F344/N rats and B6C3F1 mice in drinking water for two years (NTP, 1992a). NTP concluded that there was no evidence of carcinogenicity in male rats or male and female mice, and equivocal evidence in female rats, based on an increase in the incidence of mononuclear cell leukemia.

Reproductive/Developmental

NTP reviewed the following two reproductive and developmental studies on chlorine (NTP, 1992a):

Abdel-Rahman et al. (1982) administered female Sprague-Dawley rats up to 100 mg/L chlorine in drinking water for 2.5 months before conception and throughout gestation. No increase in fetal resorptions was observed at any doses, although some soft-tissue defects were noted at 100 mg/L.

Carlton et al. (1986) conducted a reproductive/developmental study in Long-Evans rats. Chlorine was administered by gavage at doses up to 5 mg/kg/day before breeding and throughout the 10-day breeding cycle. No effects were noted on sperm count, sperm motility or sperm morphology or on fertility, fetal viability or litter size.

Other

No treatment related effects were reported following 13-week drinking water studies with chlorine in Sprague-Dawley rats at 25, 100, 175 or 200 mg/L (Daniel et al., 1990). In 90-day drinking water studies (Daniel et al., 1991) some reductions in organ weights in B6C3Fi mice were observed in the liver, heart and lung in male mice and in the liver, heart and spleen in female mice at 100 and 200 mg/L (11.1 and 15.6 mg/kg/day in males and 12.9 and 15.8 mg/kg/day in females). Spleen and liver weights were reduced in male and female Sprague-Dawley rats at 9 mg/kg/day in males and 12.1 mg/kg/day in females.

A.3.2 Chloramines

Information Available During the Development of Stage 1 and Stage 2 D/DBPRs

Cancer

Chloramine was administered to F344/N rats and B6C3F1 mice in drinking water for two years (NTP, 1992a). NTP concluded that there was no evidence of carcinogenicity in male rats or male and female mice, and equivocal evidence in female rats, based on an increase in the incidence of mononuclear cell leukemia.

Reproductive/Developmental

NTP (1992a) reviewed the following two reproductive and developmental studies on chloramine:

Abdel-Rahman et al. (1982) administered female Sprague-Dawley rats up to 100 mg/L chloramine in drinking water for 2.5 months before conception and throughout gestation. No effects were observed at any dose.

Carlton et al. (1986) conducted a reproductive/developmental study in Long-Evans rats. Chloramine was administered by gavage at doses up to 10 mg/kg/day for 56 days before breeding and throughout the 10-day breeding cycle. No effects were noted on sperm count, sperm motility or sperm morphology or on fertility, fetal viability or litter size.

Other

No treatment related effects were reported following 13-week drinking water studies with chloramine in Sprague-Dawley rats at 25, 50, 100 or 200 mg/L (Daniel et al., 1990).

A.3.3 Chlorine dioxide

Information Available During the Development of Stage 1 and Stage 2 D/DBPRs

Reproductive/Developmental

The following studies on chlorine dioxide were reviewed in USEPA (2000b) and Health Canada (2008b):

Suh et al. (1983) administered chlorine dioxide to Sprague-Dawley rats at doses up to 10 mg/kg/day in drinking water for 2.5 months before mating and during GD 0–20. Total fetal weights and male fetal weights were significantly increased at 10 mg/kg/day and there was a significant trend for decreasing number of implants per litter and number of live fetuses per dam. A developmental NOAEL and LOAEL of 1 mg/kg/day and 10 mg/kg/day, respectively, were determined.

Orme et al. (1985) conducted a developmental study in Sprague-Dawley rats exposed to doses up to 14 mg/kg/day chlorine dioxide in drinking water for two weeks before mating and throughout gestation and lactation. Additional 5-day old pups (not exposed in utero) were exposed to 14

mg/kg/day by gavage on PND 5–20. In the pups exposed to 14 mg/kg/day by gavage, locomotor activity was significantly decreased, and in the pups exposed to 100 mg/L (14 mg/kg/day) in utero, there were significant decreases in T3 and T4 levels. A developmental NOAEL of 3 mg/kg/day and a LOAEL of 14 mg/kg/day were identified.

Taylor and Pfohl (1985) administered approximately 14 mg/kg/day chlorine dioxide in drinking water to female Sprague-Dawley rats for 14 days before breeding and throughout gestation and lactation. A significant decrease in whole brain weight, cerebellar total DNA content and exploratory behavior were observed in the offspring of the treated rats. The developmental LOAEL was 14 mg/kg/day.

Toth et al. (1990) administered daily gavage doses of 14 mg/kg/day chlorine dioxide by gavage to Sprague-Dawley rat pups on PND 1–20. No gross lesions, loss of myelin or cell changes in the brain were observed in the pups. However, forebrain weights, protein content and DNA content were significantly reduced in the brain at 14 mg/kg/day. A LOAEL of 14 mg/kg/day was identified.

Mobley et al. (1990) conducted a developmental study in female Sprague-Dawley rats administered 14 mg/kg/day chlorine dioxide in drinking water for 10 days before mating and during the gestation and lactation periods. No significant effects were observed on litter size, but decreased litter weights and decreased exploratory activity were observed in the offspring of the treated rats. The developmental LOAEL was 14 mg/kg/day.

Carlton et al. (1991) administered chlorine dioxide at doses up to 10 mg/kg/day in drinking water to Long-Evans rats for 56 days before mating and 10 days during the mating period. No significant effects were noted on mortality, clinical signs, fertility, sperm parameters, length of gestation, prenatal deaths, mean litter size or mean pup weights. A developmental/reproductive NOAEL of 10 mg/kg/day was determined.

Other

Subchronic and chronic drinking water studies ranging from 30 days to 2 years resulted in nasal lesions, ααalterations in thyroid hormone levels and hematological effects. Daniel et al. (1990) reported a significant increase in nasal lesions at 2 mg/kg/day in Sprague-Dawley rats; however, the toxicological significance of the nasal effect is not known and may be an artifact of treatment (USEPA, 2000b). Bercz et al. (1982) noted a significant decrease in serum T4 levels after administration of 9.5 mg/kg/day to monkeys for six weeks. Couri and Abdel-Rahman (1980) found significant increases in blood glutathione (GSH) reductase levels and significant decreases in erythrocyte GSH levels in Sprague-Dawley rats administered 0.1 – 100 mg/kg/day for one year.

Appendix B. Additional Information for Occurrence and Exposure to Regulated and Unregulated Disinfection Byproducts (DBPs) (Appendix to Chapter 6)

This appendix summarizes information relevant to occurrence and exposure to regulated and unregulated disinfection byproducts (DBPs), supplementing information provided in Chapter 6. Section B.1 provides what was known at the time of the development of the Stage 2 Disinfectants and Disinfection Byproducts Rule (D/DBPR) as well as new information related to DBP formation. Section B.2 provides historical and new information related to occurrence of DBP precursors available since the promulgation of the Stage 2 D/DBPR. Section B.3 presents historical information on DBP occurrence, presents the results of new occurrence analyses using the data on regulated DBPs from the Third Six-Year Review Information Collection Request (SYR3 ICR) and discusses new occurrence information available for unregulated DBPs. Lastly, Section B.4 describes additional quality assurance and quality control (QA/QC) process conducted on the SYR3 ICR DBP dataset.

B.1 DBP Formation

This section summarizes what was known about DBP formation at the time of the development of the Stage 2 D/DBPR and presents new, peer-reviewed information relevant to the SYR3 process. Note that in some cases no supplemental information is available.

B.1.1 Summary of Stage 1 and 2 D/DBPR Information

No additional information is provided in this appendix.

B.1.2 New Information since the Stage 2 D/DBPR

No additional information is provided in this appendix.

B.1.2.1 DBP Types

No additional information is provided in this appendix.

B.1.2.2 Disinfection Practices

This section describes disinfection methods and doses as well as contact time.

Disinfectant Types and Doses

Reactions between NOM and chlorine form a variety of halogenated DBPs, the most abundant of which are trihalomethanes (THMs) and haloacetic acids (HAAs). Chlorine also causes the formation of some non-halogenated DBPs, such as aldehydes and ketones. Because disinfectant is generally the limiting reagent, dose has a large effect on DBP formation. The combination of high doses and long residence times after booster disinfection can lead to areas of high DBP concentrations.

Studies have documented that chloramines produce significantly lower DBP levels than free chlorine (USEPA, 2005l).

The Information Collection Rule (ICR) was the main source of data for the Stage 1 and Stage 2 D/DBPRs. This database (referred to in this document as the "DBP ICR database") contains the information collected from a survey of 296 systems comprising 512 plants (which includes 11 plants with blended source water) serving more than 100,000 people, conducted over 18 months, from July 1997 to December 1998. It represented the largest and most comprehensive national occurrence estimates of DBPs at that time. In addition to DBP occurrence concentrations, the DBP ICR database also contained extensive information regarding treatment, source water characteristics and disinfectant type. The DBP ICR database characterized the water quality at each plant's source, at several steps in the treatment process and at several points in the distribution system (reflecting finished water).

The DBP ICR results showed that the amount of DBP formation by chloramines was between 5 and 35 percent of the DBP formation by chlorine depending on the individual DBP species. Studies at the time found that direct reaction between chloramines and NOM produces few DBPs, although dichloroacetic acid (DCAA) and cyanogen chloride were produced at higher concentrations than with the use of free chlorine (USEPA, 2005l). There was no clear evidence at the time that the reaction of NOM with chloramines leads to the formation of THMs. Most DBPs that form during chloramination are a result of reactions between free chlorine and NOM. The free chlorine can originate from its addition prior to ammonia or from the hydrolysis of chloramines. Prior to promulgation of the Stage 2 D/DBPR, little was known about the unidentified halogenated organics except that they were more hydrophilic and had a higher molecular weight than halogenated organics produced by free chlorine.

Studies prior to promulgation of the Stage 2 D/DBPR had studied the mechanism of the formation of *N*-nitrosodimethylamine (NDMA) from the use of chloramines in drinking water. However, there was not enough information to draw conclusions regarding increases in NDMA formation as systems switched from free chlorine to chloramines (USEPA, 2006a).

Chlorine dioxide does not produce significant amounts of organic halogenated DBPs. The inorganic DBPs chlorite and chlorate, however, are byproducts of chlorine dioxide use. Both chlorite and chlorate can be byproducts of the generation process for chlorine dioxide or can be produced by reactions with chlorine dioxide after its addition to source water containing NOM. Chlorite was regulated with the Stage 1 D/DBPR; chlorate was not regulated.

Research prior to the Stage 2 D/DBPR showed that ozone by itself does not form halogenated DBPs. Ozone alters the nature of NOM and forms oxygenated DBPs such as aldehydes and organic acids. The smaller molecules formed by ozone can be removed by biological filtration. If chlorine is added before these smaller more reactive molecules are removed, then they can react with chlorine to form DBPs. Ozone can also react with bromide to form bromate or hypobromous acid, which can react to form brominated DBPs. Brominated DBPs formed after ozonation include bromoform and cyanogen bromide, although two-thirds of the brominated DBPs formed during ozonation had not been identified at the time.

At the time of the Stage 2 D/DBPR, no evidence suggested that the use of ultraviolet light (UV) as a disinfectant resulted in the formation of DBPs, although little research had been performed in the area.

The Stage 2 D/DBPR Economic Analysis (USEPA, 2005g) provided a summary of what was known about disinfectant use based on DBP ICR data. Free chlorine only was used as a disinfectant in 53.7 percent of plants. Chloramines preceded by free chlorine contact time were used in 23.1 percent of plants, while 6.5 percent of plants used free chlorine as a primary disinfectant followed by chloramines in the distribution system. Chloramine was used both as a primary and residual disinfectant in 5.1 percent of plants. Only 2.7 percent of plants used chlorine dioxide as a primary disinfectant followed by chlorine, while another 3.7 percent used chlorine dioxide followed by chloramines. Three percent of plants used ozone followed by chloramines, and another 2.1 percent used ozone followed by chlorine.

Contact Time

Information prior to the Stage 2 D/DBPR showed that DBPs form as long as disinfectant residual and reactive DBP precursors are present. Generally, the longer the contact time, the greater the DBP formation potential. In the presence of a disinfectant residual, both THMs and HAAs had generally high stabilities and persisted after formation. HAAs, however, were known to biodegrade over time when disinfectant residual was low.

B.1.2.3 Source Water Quality Research

This section describes source water characteristics that affect DBP formation, including organic precursors, inorganic precursors such as bromide and iodide, temperature and pH.

Organic Precursors

At the time of the Stage 2 D/DBPR, studies conducted with different fractions of NOM found that NOM with high aromatic content tended to form more DBPs than NOM with low aromatic content. Since UV absorbance at 254 nm wavelength is correlated with aromatic content of organics, this led to the use of specific ultraviolet absorbance (SUVA)[2] as an indicator of THM and HAA formation in source water. Waters with high SUVA were known to be more easily treated with coagulation (USEPA, 2005l).

Inorganic Precursors

Bromide in source water affects the formation of DBPs. Free chlorine can oxidize bromide to hypobromite or hypobromous acid, which can react with NOM to form brominated DBPs. Research at the time had shown that the rate of THM formation was higher in waters with

[2] SUVA is the ultraviolet absorption at 254 nanometers divided by the concentration of dissolved organic carbon (DOC).

increased bromide concentration. Bromine can also substitute into chlorinated DBPs in the presence of hypobromous acid (USEPA, 2005l).

Temperature

The rate of THM formation increases with temperature. Research also showed that HAA formation increased with temperature, although the effect was less pronounced. Therefore, the highest THM and HAA concentrations were thought to occur in the summer months. In addition, high temperatures can accelerate chlorine depletion, resulting in less DBP formation and biodegradation of HAA (USEPA, 2005l).

pH

Research prior to the Stage 2 D/DBPR found that THM formation increases with increasing pH, while formation of HAA and other DBPs decreases with increasing pH. The formation of more THM at higher pH was likely due to base-catalyzed reactions. HAA formation may be altered at high pH due to hydrolysis of precursors.

The rate of DBP formation from ozone is not affected by pH; although, the rate of ozone decomposition increases at higher pH. Increased pH results in decreased aldehydes; although in some situations, carbonyls could increase at higher pH. Low pH in ozonated water increases formation of brominated DBPs. This occurs because the hypobromous acid and hypobromite formed by reaction of bromide and ozone shift more to hypobromous acid at lower pH. Hypobromous acid is more reactive than hypobromite in the formation of brominated DBPs (USEPA, 2005l).

B.1.2.4 Distribution System Conditions

No additional information provided in this appendix.

B.1.2.5 DBP Formation Modeling

Since promulgation of the Stage 2 D/DBPR, numerous studies have developed predictive models for DBP formation. This section provides background on the Surface Water Analytical Tool (SWAT) model, including its formulas for chlorination and chloramination.

Background on SWAT

Based on the research and the related national datasets available at the time, a computer program called the SWAT was created to predict formation of four regulated THMs (THM4) and five HAAs (HAA5) for all surface water systems serving 100,000 or more people. The program used empirical formulas to calculate THM4, HAA5, bromate and chlorite formation at the finished water point, average residence time and maximum residence time sites (USEPA, 2005g). For additional details on SWAT, refer to USEPA (2005g; see Appendix A of that document).

SWAT was developed with the assistance of the M/DBP Federal Advisory Committee to model DBP formation on a national level. The intent was that parametric inputs for many systems could be used to develop national distributions of DBPs that in turn could be used for predicting

national compliance forecasts for different regulatory options. The predictive equations contained in SWAT were calibrated with the national datasets generated from the DBP ICR using a central tendency approach. SWAT was not intended to provide reliable DBP formation predictions for specific systems, but rather to characterize national-level occurrence distributions.

Chlorination

SWAT's empirical formulas for the formation of THM4 and HAA5 used total organic carbon (TOC), UV_{254}, chlorine dose, bromide concentration, temperature, pH and time as variables to determine THM4 concentration. SWAT used different equations for THM4 and HAA5 formation depending on whether the water was raw or treated. For treated water, the equation used the product of TOC and UV_{254} to determine DBP formation. The equations used in SWAT are as follows (see Appendix A in USEPA, 2005g):

$$THM4_{raw} = 0.0412TOC^{1.098}\, Cl_2^{0.152}\, Br_{raw}^{0.068} T^{0.609} pH_{raw}^{1.601}\, t^{0.263}$$

$$THM4_{treated} = 23.9(TOC*UV_{254})^{0.403}\, Cl_2^{0.225}\, Br^{0.141}\, 1.027^{T-20}\, 1.156^{pH-7.5}\, t^{0.264}$$

SWAT also predicted the concentration of the sum of HAA5. The equations for HAA5 were:

$$HAA5_{raw} = 30TOC^{0.997}\, Cl_2^{0.278}\, Br_{raw}^{-0.138}\, T^{0.341}\, pH_{raw}^{-0.799}\, t^{1.69}$$

$$HAA5_{treated} = 41.6(TOC*UV_{254})^{0.238}\, Cl_2^{0.585}\, Br^{-0.12}\, 1.021^{T-20}\, 0.932^{pH-7.5}\, t^{0.150}$$

Where:

THM4 = total trihalomethanes in µg/L

HAA5 = total 5 haloacetic acids in µg/L

TOC = TOC concentration in mg/L

Cl_2 = chlorine dose in mg/L

Br = bromide concentration in µg/L

T = temperature in degrees Celsius

t = time in hours

UV_{254} = UV absorbance at 254 nm

Chloramination

Empirical predictive correlations for DBP formation for systems using chloramines were not available at the time of the Stage 2 D/DBPR. Therefore, the SWAT model assumed that THM4 formation by chloramines was 30 percent of what would have formed by chlorination and HAA5 formation was 35 percent of what would have formed by chlorination (USEPA, 2005g). Empirical formulas were included in SWAT for THM4 and HAA5, but were not identified for chlorite or bromate.

B.2 Occurrence of DBP Precursors

This section summarizes historical and new occurrence information on organic and inorganic DBP precursors and precursor mixtures.

B.2.1 Organic Precursors

This section provides additional information from the Stage 1 and Stage 2 D/DBPRs and new information available since the promulgation of the Stage 2 D/DBPR.

B.2.1.1 Summary of Stage 1 and Stage 2 D/DBPR Information

This section summarizes occurrence data that were available prior to the promulgation of the Stage 2 D/DBPR related to organic DBP precursors. DOC and total organic nitrogen (TON) were not measured as part of DBP ICR monitoring, thus, national-level occurrence data for these precursors was not reviewed during the development of the Stage 2 D/DBPR.

TOC is used as an indicator of the amount of organic carbon available to react with disinfectants to form organic DBPs. The main source of TOC data for large water systems serving at least 100,000 people was the DBP ICR database. The DBP ICR applied to surface and ground water systems and represented data collected between July 1997 and December 1998 (USEPA, 2005l). Exhibit B.1 summarizes DBP ICR data for water treatment plant influent TOC. Exhibit B.1 also summarizes DBP ICR data on UV_{254}, a potential predictor of the tendency of a source water to form THMs and HAAs (USEPA, 2005l) and alkalinity, which affects the treatability of the organic precursors.

Exhibit B.1: DBP ICR Large System Influent TOC, UV254 and Alkalinity Data

Parameter	Source Type	Number of Plants	Mean of Plant Means	Median of Plant Means	90th Percentile of Plant Means	Range of Plant Means
Total Organic Carbon (mg/L as C)						
	Surface	307	3.14	2.71	5.29	0.0 – 21.4
	Ground	103	1.46	0.19	3.36	0.0 – 16.1
UV_{254} (cm^{-1})						
	Surface	306	0.098	0.079	0.176	0.0 – 0.880
	Ground	104	0.062	0.009	0.266	0.0 – 0.606
Alkalinity (mg/L as $CaCO_3$)						
	Surface	336	81	79	165	2.75 – 273
	Ground	121	159	156	264	1.00 – 415

Source: ICR AUX1 Database (USEPA, 2005l)

Notes: From the ICR AUX1 database (USEPA, 2000e). Represents distribution of plant mean data as calculated using ICR monthly data from the last 12 months of the ICR (January 1998 - December 1998). Only plants with reported data for at least 9 of the 12 months are included in this analysis. Does not include blended, mixed or

purchased water plants. Values below the minimum reporting level (MRL) were converted to zero to calculate plant means.

Data for systems serving fewer than 100,000 people were available from the National Rural Water Association (NRWA), supplemental surveys (SS) and Waterstats. Exhibit B.2 summarizes TOC, UV_{254} and alkalinity data for these systems.

Exhibit B.2: Medium and Small System Influent TOC, UV_{254} and Alkalinity Data

Data Source/Size Category	N	Mean of Plant Means	Median of Plant Means	90th Percentile of Plant Means	Range of Plant Means
Source Water TOC (mg/L as C)					
NRWA Small SW Plants	96	3	2.6	5.4	0.3 - 9.0
ICR SS Medium SW Plants	40	3.6	3.7	5.5	0.2 - 7.9
ICR SS Small SW Plants	38	2.4	2.1	4.5	0.1 - 7.1
WATER:\STATS Medium SW Plants	102	5.6	3.2	6.4	0 - 200
WATER:\STATS Medium GW Plants	51	2.3	0.79	7	0 - 25
Source Water UV-254 (cm^{-1})					
NRWA Small SW Plants	96	0.082	0.074	0.127	0.01 - 0.23
ICR SS Medium SW Plants	40	0.093	0.083	0.171	0.03 - 0.21
ICR SS Small SW Plants	38	0.074	0.051	0.113	0.02 - 0.44
Source Water Alkalinity (mg/L as $CaCO_3$)					
NRWA Small Surface Water (SW) Plants	95	81	74	146	0 - 281
ICR Supplemental Survey (ICR SS) Medium SW Plants	40	82	74	159	4.8 - 240
ICR SS Small SW Plants	38	66	55	123	4.4 - 249

Source: USEPA, 2005l

Note: ICR SS data are the plant means for plants that took at least three-fourths of the total possible samples for each parameter. Only plants that had both a winter and summer sample are included in the NRWA data for this analysis.

Exhibit B.3 shows the percent of monthly samples over the final 12 months of the DBP ICR monitoring period (January to December 1998) that fall into specified source water TOC and alkalinity categories. These categories are used under the Stage 1 D/DBPR to specify source water TOC removal requirements as part of a treatment technique (TT) for DBP precursor removal for plants using conventional treatment. Due to seasonal variation and other factors affecting source water, the percentage removal requirements for each plant may have changed from month to month as the influent TOC and alkalinity varied. Many samples are close to the limits for a percentage removal group, indicating that the treatment requirements of a plant can easily change (USEPA, 2005l).

Exhibit B.3: Distribution of Monthly Influent TOC (mg/L) and Monthly Influent Alkalinity (mg/L) Samples Based on ICR Data for All Large Plants

Source Water TOC Range (mg/L)	Percentage			
	Alkalinity (mg/L)			Total
	< 60	60 - 120	> 120	
< 2.0	14%	10%	16%	39%
2.0 - 4.0	14%	14%	13%	41%
4.0 - 8.0	5%	5%	6%	16%
> 8.0	1%	0%	2%	4%

Source: ICR AUX1 Database (USEPA, 2005l)

B.2.1.2 New Information since the Stage 2 D/DBPR

This section provides new information on organic precursor occurrence from recent studies published since the promulgation of the Stage 2 D/DBPR and presents summary inventory information on TOC and alkalinity in the SYR3 ICR database.

Potter and Wimsatt (2012) used EPA Method 415.3 to quantify TOC, DOC and SUVA in seven different source waters. Samples came from five surface water sources and two ground water sources. Samples were tested on five different machines in order to determine method accuracy. Mean TOC concentrations ranged from 0.42 to 3.64 mg/L. Mean DOC concentrations ranged from 0.42 to 3.38 mg/L and mean SUVA values ranged from 1.95 to 3.37 L/mg-m.

Samson et al. (2013) used three case studies to develop monthly TOC thresholds defined as the highest TOC concentration of source water that allows a conventional surface water treatment plant to meet the DBP regulations at the maximum residence time location in the distribution system. Statistical models were developed to relate TOC threshold exceedances with variables including precipitation, temperature and vegetation indices.

Mikkelson et al. (2013) analyzed water-quality data from quarterly reports submitted as part of Stage 1 and Stage 2 D/DBPR compliance by Colorado treatment plants, including five plants impacted by the mountain pine beetle and four control plants. Mean TOC concentrations from control sites were 0.70 mg/L and 0.62 mg/L for the years 2004 to 2008 and 2009 to 2011, respectively. Mean TOC concentrations for infested sites were 2.5 mg/L and 2.7 mg/L for the years 2004 to 2008 and 2009 to 2011, respectively.

Writer et al. (2014) studied the Cache la Poudre River Watershed in Colorado after the 2012 High Park Wildfire. Following the wildfire, thunderstorms in the Poudre River Watershed caused mudslides, which resulted in sediment, ash and debris being deposited into the river. DOC concentrations after four thunderstorms measured within the burned area at the Poudre River drinking water intake ranged from 3.5 mg/L to 13.7 mg/L. DOC concentrations from monthly monitoring following the thunderstorm events at both locations upstream and downstream from the affected area ranged from 2.1 to 2.8 mg/L.

Emelko et al. (2013) studied seven watersheds that were affected by the 2003 Lost Creek Wildfire. From 2004 to 2012, Emelko et al. studied burned, burned and salvage logged, prescribed burned and undisturbed watersheds using instrumentation in the watersheds, climate stations and hydrometric stations. DOC was found to increase with flow and level of disturbance. The variation in DOC peaks was greater for disturbed catchments, ranging from about 2 to 17 mg/L.

Wang et al. (2015) analyzed the water-extractable organic matter (WEOM) from burned detritus of both moderate and high severity compared to a non-burned control. WEOM from both types of ash had lower reactivity at 55 percent of control for THM formation and 67 percent of control for HAA5 formation. Due to consumption of organic matter by the wildfire, the ashes contained decreased extractable organic carbon and organic nitrogen at 27 percent of control and 19 percent of control, respectively.

B.2.2 Precursor Inventory Analyses

B.2.2.1 TOC

The results of system and population inventories of the SYR3 ICR TOC dataset in 2006-2011 are included below in Exhibit B.4 through Exhibit B.6. Exhibit B.4 depicts the distribution of systems and population among the different system types, and **Error! Reference source not found.**includes the same information but distributed based on source water type. The source types are split by ground water (includes purchasing systems), surface water (includes purchasing systems), and purchased and non-purchased ground water under the direct influence of surface water (GWUDI) systems. Exhibit B.6 depicts the distribution of systems and population by both source water type, system type and aggregated by population size.

Exhibit B.4: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset with TOC Records, by System Type (2006 – 2011)

Year	System Type	Systems		Population	
		Number	Percent	Number	Percent
2006	Community	1,819	89.9%	54,759,578	99.8%
	Non-transient Non-community	204	10.1%	94,418	0.2%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**2,023**	**100.0%**	**54,853,996**	**100.0%**
2007	Community	1,762	92.9%	56,135,166	99.9%
	Non-transient Non-community	135	7.1%	66,133	0.1%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**1,897**	**100.0%**	**56,201,299**	**100.0%**
2008	Community	1,853	92.8%	59,719,015	99.9%
	Non-transient Non-community	144	7.2%	77,828	0.1%
	Transient Non-community	0	0.0%	0	0.0%

Year	System Type	Systems		Population	
		Number	Percent	Number	Percent
	Total	**1,997**	**100.0%**	**59,796,843**	**100.0%**
2009	Community	1,842	92.4%	60,738,439	99.9%
	Non-transient Non-community	151	7.6%	72,917	0.1%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**1,993**	**100.0%**	**60,811,356**	**100.0%**
2010	Community	1,833	93.4%	61,858,371	99.9%
	Non-transient Non-community	129	6.6%	71,938	0.1%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**1,962**	**100.0%**	**61,930,309**	**100.0%**
2011	Community	1,775	93.9%	62,322,706	99.9%
	Non-transient Non-community	116	6.1%	65,806	0.1%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**1,891**	**100.0%**	**62,388,512**	**100.0%**
All Years	Community	2,479	87.4%	69,562,352	99.8%
	Non-transient Non-community	357	12.6%	145,851	0.2%
	Transient Non-community	0	0.0%	0	0.0%
	Total	**2,836**	**100.0%**	**69,708,203**	**100.0%**

Exhibit B.5: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset (2006 – 2011) with TOC Records, by Source Water Type

Year	Source Water Type	Systems		Population	
		Number	Percent	Number	Percent
2006	Ground Water	345	17.1%	4,807,197	8.8%
	GWUDI	47	2.3%	402,823	0.7%
	Surface Water	1,631	80.6%	49,643,976	90.5%
	Total	**2,023**	**100.0%**	**54,853,996**	**100.0%**
2007	Ground Water	284	15.0%	5,414,297	9.6%
	GWUDI	42	2.2%	360,106	0.6%
	Surface Water	1,571	82.8%	50,426,896	89.7%
	Total	**1,897**	**100.0%**	**56,201,299**	**100.0%**
2008	Ground Water	280	14.0%	4,625,754	7.7%
	GWUDI	55	2.8%	442,967	0.7%
	Surface Water	1,662	83.2%	54,728,122	91.5%

Year	Source Water Type	Systems		Population	
		Number	Percent	Number	Percent
	Total	**1,997**	**100.0%**	**59,796,843**	**100.0%**
2009	Ground Water	254	12.7%	4,163,551	6.8%
	GWUDI	60	3.0%	532,411	0.9%
	Surface Water	1,679	84.2%	56,115,394	92.3%
	Total	**1,993**	**100.0%**	**60,811,356**	**100.0%**
2010	Ground Water	244	12.4%	4,637,952	7.5%
	GWUDI	60	3.1%	523,222	0.8%
	Surface Water	1,658	84.5%	56,769,135	91.7%
	Total	**1,962**	**100.0%**	**61,930,309**	**100.0%**
2011	Ground Water	179	9.5%	5,068,752	8.1%
	GWUDI	63	3.3%	528,104	0.8%
	Surface Water	1,649	87.2%	56,791,656	91.0%
	Total	**1,891**	**100.0%**	**62,388,512**	**100.0%**
All Years	Ground Water	775	27.3%	7,980,533	11.4%
	GWUDI	95	3.3%	639,322	0.9%
	Surface Water	1,966	69.3%	61,088,348	87.6%
	Total	**2,836**	**100.0%**	**69,708,203**	**100.0%**

Note: Purchased systems are included in each category.

Exhibit B.6: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset (2006 – 2011) with TOC Records, by System Size and System Type

Year	Population Served System Size	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
Community Water Systems							
2006	<101	53	3,094	91	3,067	144	6,161
	101 – 500	63	17,105	118	33,381	181	50,486
	501 – 1,000	15	12,313	98	76,057	113	88,370
	1,001 – 3,300	34	67,859	327	683,408	361	751,267
	3,301 – 10,000	22	131,679	387	2,337,185	409	2,468,864
	10,001 – 50,000	27	600,603	383	8,938,899	410	9,539,502
	50,001 – 100,000	7	503,993	82	5,885,904	89	6,389,897
	100,001 – 1 million	18	3,430,697	91	23,713,039	109	27,143,736
	> 1 million	-	-	3	8,321,295	3	8,321,295

Year	Population Served System Size	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	Total	239	4,767,343	1,580	49,992,235	1,819	54,759,578
2007	<101	36	2,105	80	2,157	116	4,262
	101 – 500	44	11,515	93	26,547	137	38,062
	501 – 1,000	17	13,829	94	72,687	111	86,516
	1,001 – 3,300	42	83,577	324	679,333	366	762,910
	3,301 – 10,000	28	175,027	390	2,343,825	418	2,518,852
	10,001 – 50,000	27	585,318	384	8,987,188	411	9,572,506
	50,001 – 100,000	8	592,865	81	5,804,558	89	6,397,423
	100,001 – 1 million	20	3,932,154	91	24,501,186	111	28,433,340
	> 1 million	-	-	3	8,321,295	3	8,321,295
	Total	222	5,396,390	1,540	50,738,776	1,762	56,135,166
2008	<101	35	2,147	85	2,401	120	4,548
	101 – 500	53	13,835	93	26,603	146	40,438
	501 – 1,000	19	15,261	102	79,043	121	94,304
	1,001 – 3,300	36	75,602	338	707,321	374	782,923
	3,301 – 10,000	23	146,486	432	2,610,247	455	2,756,733
	10,001 – 50,000	23	488,334	407	9,530,494	430	10,018,828
	50,001 – 100,000	6	450,166	89	6,310,501	95	6,760,667
	100,001 – 1 million	16	3,413,160	92	24,386,119	108	27,799,279
	> 1 million	-	-	4	11,461,295	4	11,461,295
	Total	211	4,604,991	1,642	55,114,024	1,853	59,719,015
2009	<101	30	1,753	80	2,219	110	3,972
	101 – 500	42	10,907	86	25,443	128	36,350
	501 – 1,000	5	4,125	104	80,926	109	85,051
	1,001 – 3,300	30	60,645	346	720,497	376	781,142
	3,301 – 10,000	25	152,778	441	2,669,582	466	2,822,360
	10,001 – 50,000	21	479,047	414	9,619,660	435	10,098,707
	50,001 – 100,000	6	425,321	96	6,755,256	102	7,180,577
	100,001 – 1 million	15	3,007,239	97	25,261,746	112	28,268,985
	> 1 million	-	-	4	11,461,295	4	11,461,295
	Total	174	4,141,815	1,668	56,596,624	1,842	60,738,439

Year	Population Served System Size	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
2010	<101	25	1,490	75	1,932	100	3,422
	101 – 500	46	11,901	85	25,252	131	37,153
	501 – 1,000	16	12,578	100	78,299	116	90,877
	1,001 – 3,300	31	58,171	343	719,308	374	777,479
	3,301 – 10,000	23	153,367	435	2,630,180	458	2,783,547
	10,001 – 50,000	21	479,717	414	9,580,779	435	10,060,496
	50,001 – 100,000	8	563,881	94	6,640,872	102	7,204,753
	100,001 – 1 million	15	3,336,565	98	26,102,784	113	29,439,349
	> 1 million	-	-	4	11,461,295	4	11,461,295
	Total	185	4,617,670	1,648	57,240,701	1,833	61,858,371
2011	<101	16	970	74	2,185	90	3,155
	101 – 500	22	5,997	89	25,863	111	31,860
	501 – 1,000	16	13,015	98	76,394	114	89,409
	1,001 – 3,300	22	42,194	339	710,311	361	752,505
	3,301 – 10,000	14	92,891	430	2,622,616	444	2,715,507
	10,001 – 50,000	20	506,456	415	9,634,912	435	10,141,368
	50,001 – 100,000	8	630,238	92	6,482,543	100	7,112,781
	100,001 – 1 million	18	3,763,850	98	26,250,976	116	30,014,826
	> 1 million	-	-	4	11,461,295	4	11,461,295
	Total	136	5,055,611	1,639	57,267,095	1,775	62,322,706
All Years	<101	117	6,982	119	3,956	236	10,938
	101 – 500	144	37,711	156	44,433	300	82,144
	501 – 1,000	53	41,459	129	100,418	182	141,877
	1,001 – 3,300	76	154,908	398	829,104	474	984,012
	3,301 – 10,000	57	340,617	479	2,909,488	536	3,250,105
	10,001 – 50,000	48	1,149,366	445	10,314,231	493	11,463,597
	50,001 – 100,000	17	1,203,451	102	7,194,345	119	8,397,796
	100,001 – 1 million	27	4,974,839	108	28,795,749	135	33,770,588
	> 1 million	-	-	4	11,461,295	4	11,461,295
	Total	539	7,909,333	1,940	61,653,019	2,479	69,562,352

Year	Population Served System Size	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
Non-Transient Non-Community Water Systems							
2006	<101	48	2,866	24	1,418	72	4,284
	101 – 500	48	10,098	36	8,737	84	18,835
	501 – 1,000	5	2,805	21	16,470	26	19,275
	1,001 – 3,300	1	2,275	16	24,139	17	26,414
	3,301 – 10,000	4	21,810	1	3,800	5	25,610
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**106**	**39,854**	**98**	**54,564**	**204**	**94,418**
2007	<101	37	1,943	16	871	53	2,814
	101 – 500	19	4,434	22	5,455	41	9,889
	501 – 1,000	3	2,279	19	15,191	22	17,470
	1,001 – 3,300	2	3,251	15	22,909	17	26,160
	3,301 – 10,000	1	6,000	1	3,800	2	9,800
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**62**	**17,907**	**73**	**48,226**	**135**	**66,133**
2008	<101	35	1,846	17	868	52	2,714
	101 – 500	26	6,102	23	6,629	49	12,731
	501 – 1,000	5	3,564	19	15,513	24	19,077
	1,001 – 3,300	2	3,251	14	21,755	16	25,006
	3,301 – 10,000	1	6,000	2	12,300	3	18,300
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**69**	**20,763**	**75**	**57,065**	**144**	**77,828**

Year	Population Served System Size	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
2009	<101	47	2,630	14	745	61	3,375
	101 – 500	26	4,986	22	6,368	48	11,354
	501 – 1,000	3	1,940	19	15,513	22	17,453
	1,001 – 3,300	3	6,180	15	24,755	18	30,935
	3,301 – 10,000	1	6,000	1	3,800	2	9,800
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**80**	**21,736**	**71**	**51,181**	**151**	**72,917**
2010	<101	34	1,823	12	680	46	2,503
	101 – 500	18	4,048	22	6,368	40	10,416
	501 – 1,000	3	2,160	20	16,053	23	18,213
	1,001 – 3,300	3	6,251	15	24,755	18	31,006
	3,301 – 10,000	1	6,000	1	3,800	2	9,800
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**59**	**20,282**	**70**	**51,656**	**129**	**71,938**
2011	<101	21	977	14	769	35	1,746
	101 – 500	18	3,869	22	6,368	40	10,237
	501 – 1,000	2	1,244	21	16,973	23	18,217
	1,001 – 3,300	1	1,051	15	24,755	16	25,806
	3,301 – 10,000	1	6,000	1	3,800	2	9,800
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**43**	**13,141**	**73**	**52,665**	**116**	**65,806**
All Years	<101	116	6,467	31	1,811	147	8,278

Year	Population Served System Size	Ground Water		Surface Water		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	101 – 500	98	21,040	44	11,815	142	32,855
	501 – 1,000	12	8,228	26	20,416	38	28,644
	1,001 – 3,300	6	13,655	18	28,309	24	41,964
	3,301 – 10,000	4	21,810	2	12,300	6	34,110
	10,001 – 50,000	-	-	-	-	-	-
	50,001 – 100,000	-	-	-	-	-	-
	100,001 – 1 million	-	-	-	-	-	-
	> 1 million	-	-	-	-	-	-
	Total	**236**	**71,200**	**121**	**74,651**	**357**	**145,851**

Note: GWUDI systems are included in SW, and purchased systems are included in each category as well.

Exhibit B.7 displays the results for the inventory analyses of TOC surface water CWSs over the entire period of the SYR3 ICR database (2006-2011). The inventory results were split via raw water and finished water for comparison of sample locations relevant to the TT requirement. Altogether, there are more than 215,000 records, with slightly more finished water records available than raw water (about 119,000). A total of 3,471 surface water CWSs are included in the dataset, and as was the case with the record count, more systems reported finished water than raw water data. Almost 114 million people are served by the surface water CWSs reporting the TOC data.

States/primacy entities that were not included in TOC analyses (either because they did not provide information or because none of their data passed QA/QC) were: American Samoa; Arizona; Arkansas; Colorado; Delaware; Washington, DC; Georgia; Hawaii; Idaho; Louisiana; Maryland; Massachusetts; Mississippi; Missouri; Nebraska; New Hampshire; New Mexico; Oregon; Rhode Island; South Dakota; Tennessee; Texas; Washington and Wisconsin.

Exhibit B.7: SYR3 ICR Inventory Analysis for TOC (2006-2011; Surface Water CWSs)

State	TOC from Surface Water Systems All Years, CWS only								
	Number of Records			Number of Systems			Population Served		
	Total	Raw Water	Finished Water	Total	Raw Water	Finished Water	Total	Raw Water	Finished Water
Alabama	10,455	5,124	5,331	145	72	73	5,611,047	2,801,736	2,809,311
Alaska	1,414	755	659	93	24	69	661,971	317,407	344,564
American Samoa	-	-	-	-	-	-	-	-	-
Arizona	6	0	6	1	0	1	28,022	0	28,022
Arkansas	-	-	-	-	-	-	-	-	-

State	TOC from Surface Water Systems All Years, CWS only								
	Number of Records			Number of Systems			Population Served		
	Total	Raw Water	Finished Water	Total	Raw Water	Finished Water	Total	Raw Water	Finished Water
California	18,920	10,749	8,171	438	238	200	25,025,974	12,004,468	13,021,506
Colorado	59	29	30	2	1	1	4,040	2,020	2,020
Connecticut	20	0	20	4	0	4	168,163	0	168,163
Delaware	-	-	-	-	-	-	-	-	-
District of Columbia	-	-	-	-	-	-	-	-	-
Florida	4	3	1	3	2	1	224,000	122,000	102,000
Georgia	-	-	-	-	-	-	-	-	-
Hawaii	-	-	-	-	-	-	-	-	-
Idaho	-	-	-	-	-	-	-	-	-
Illinois	12,527	6,262	6,265	194	97	97	9,722,450	4,861,225	4,861,225
Indiana	2,649	1,360	1,289	74	37	37	4,159,416	2,079,708	2,079,708
Iowa	4,675	2,232	2,443	61	31	30	1,735,443	909,101	826,342
Kansas	4	0	4	1	0	1	146,453	0	146,453
Kentucky	21,753	10,854	10,899	278	139	139	6,011,074	3,005,537	3,005,537
Louisiana	-	-	-	-	-	-	-	-	-
Maine	981	512	469	55	28	27	629,633	314,959	314,674
Maryland	-	-	-	-	-	-	-	-	-
Massachusetts	-	-	-	-	-	-	-	-	-
Michigan	655	0	655	26	0	26	434,465	0	434,465
Minnesota	2,091	1,174	917	34	20	14	2,212,028	1,170,029	1,041,999
Mississippi	-	-	-	-	-	-	-	-	-
Missouri	-	-	-	-	-	-	-	-	-
Montana	4,399	2,145	2,254	78	37	41	714,856	352,490	362,366
Nebraska	-	-	-	-	-	-	-	-	-
Nevada	523	248	275	22	7	15	1,336,394	660,759	675,635
New Hampshire	-	-	-	-	-	-	-	-	-
New Jersey	8,406	4,194	4,212	52	26	26	8,079,530	4,039,765	4,039,765
New Mexico	-	-	-	-	-	-	-	-	-
New York	6,693	3,426	3,267	190	101	89	1,944,194	981,061	963,133
North Carolina	22,030	10,218	11,812	263	130	133	10,245,116	5,111,316	5,133,800
North Dakota	2,694	1,351	1,343	42	21	21	593,524	296,762	296,762
Ohio	86	1	85	9	1	8	246,607	51,000	195,607
Oklahoma	25,528	316	25,212	177	5	172	2,610,655	217,541	2,393,114

State	TOC from Surface Water Systems All Years, CWS only								
	Number of Records			Number of Systems			Population Served		
	Total	Raw Water	Finished Water	Total	Raw Water	Finished Water	Total	Raw Water	Finished Water
Oregon	-	-	-	-	-	-	-	-	-
Pennsylvania	23,002	12,118	10,884	490	257	233	15,781,924	7,968,998	7,812,926
Rhode Island	-	-	-	-	-	-	-	-	-
South Carolina	7,637	3,792	3,845	98	49	49	4,253,920	2,126,960	2,126,960
South Dakota	148	74	74	2	1	1	50	25	25
Tennessee	-	-	-	-	-	-	-	-	-
Texas	-	-	-	-	-	-	-	-	-
Utah	3,203	1,637	1,566	62	30	32	1,203,940	600,996	602,944
Vermont	193	93	100	21	7	14	114,233	45,835	68,398
Virginia	16,324	8,152	8,172	245	122	123	7,771,442	3,768,611	4,002,831
Washington	-	-	-	-	-	-	-	-	-
West Virginia	16,087	8,027	8,060	258	129	129	1,961,348	972,698	988,650
Wisconsin	-	-	-	-	-	-	-	-	-
Wyoming	2,405	1,248	1,157	53	27	26	339,664	170,847	168,817
Total	**215,571**	**96,094**	**119,477**	**3,471**	**1,639**	**1,832**	**113,971,576**	**54,953,854**	**59,017,722**

B.2.2.2 Representativeness of the SYR3 ICR Precursor Data

Exhibit B.8 shows the TOC inventory for the year 2011 for SW CWSs in all states and primacy agencies that participated in the SYR3 ICR. The inventory results were split via raw water and finished water for comparison of sample locations relevant to the TT requirement. Additionally, in Exhibit B.8, EPA compared the SYR3 ICR TOC inventory data for SW CWSs to inventory data from EPA's Safe Drinking Water Information System (SDWIS)[3] to determine how well systems that submitted TOC data through the ICR represented the total number of CWSs in a state, as well as how well the SYR3 systems represented the nation as a whole. EPA compared data from 2011 for both data sources (2011 was the most recent and complete year in the SYR3 ICR database). Inventory data show that the SYR3 ICR TOC data are generally representative of the national occurrence of organic precursors in both raw and finished water, as described below.

In Exhibit B.8, the SDWIS counts represent active CWSs in 2011 that were served by SW (includes SW, SWP, GU and GUP). It is important to recognize that SDWIS does not contain information on what National Primary Drinking Water Regulations (NPDWRs), state regulations and/or alternative criteria a system must comply with. Moreover, SDWIS does not contain information on system treatment characteristics (e.g., conventional or direct filtration) used to determine if a system is subject to the Stage 1 D/DBPR TT (historical data from the DBP ICR

[3] SDWIS contains information about PWSs and their violations of EPA's drinking water regulations, as reported to EPA by the states.

indicated that the majority of SW plants used conventional treatment; McGuire et al., 2002). While EPA recognizes these limitations, it believes that the TOC data in the SYR3 ICR are useful for informing a perspective on the national occurrence of TOC for SYR.

Exhibit B.8: SYR3 ICR Inventory Analysis for TOC (2011; SW CWSs)

State	TOC from SW CWSs, 2011										
	Number of Records			Number of Systems			Population Served				
	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]	Total SDWIS[2]	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]	Total SDWIS[2]	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]
Alabama	1,984	968	1,016	237	72	71	72	3,980,408	2,780,811	2,773,236	2,780,811
Alaska	221	110	111	118	15	14	15	387,940	295,876	291,126	295,876
American Samoa	-	-	-	9	-	-	-	56,524	-	-	-
Arizona	6	-	6	45	1	-	1	3,637,061	28,022	-	28,022
Arkansas	-	-	-	290	-	-	-	1,830,199	-	-	-
California	3,059	1,742	1,317	896	162	149	129	34,884,701	12,917,851	9,452,073	11,011,391
Colorado	8	4	4	352	1	1	1	4,884,315	2,020	2,020	2,020
Connecticut	1	-	1	73	1	-	1	2,398,731	7,784	-	7,784
Delaware	-	-	-	5	-	-	-	486,555	-	-	-
District of Columbia	-	-	-	5	-	-	-	606,730	-	-	-
Florida	1	1	-	69	1	1	-	3,925,963	20,000	20,000	-
Georgia	-	-	-	226	-	-	-	6,753,370	-	-	-
Hawaii	-	-	-	10	-	-	-	164,854	-	-	-
Idaho	-	-	-	67	-	-	-	261,721	-	-	-
Illinois	2,119	1,060	1,059	578	94	94	94	8,961,544	4,837,511	4,837,511	4,837,511
Indiana	921	475	446	117	36	36	36	2,482,746	2,074,508	2,074,508	2,074,508
Iowa	795	361	434	147	30	28	30	1,314,746	826,342	819,885	826,342
Kansas	1	-	1	367	1	-	1	1,939,470	146,453	-	146,453
Kentucky	3,604	1,805	1,799	311	137	137	137	4,056,392	3,000,636	3,000,636	3,000,636

State	TOC from SW CWSs, 2011										
	Number of Records			Number of Systems			Population Served				
	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]	Total SDWIS[2]	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]	Total SDWIS[2]	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]
Louisiana	-	-	-	90	-	-	-	2,028,904	-	-	-
Maine	201	100	101	53	24	24	24	443,240	169,936	169,936	169,936
Maryland	-	-	-	66	-	-	-	4,566,722	-	-	-
Massachusetts	-	-	-	186	-	-	-	7,711,391	-	-	-
Michigan	133	-	133	298	18	-	18	5,940,183	333,761	-	333,761
Minnesota	355	201	154	41	20	20	14	1,407,994	1,170,029	1,170,029	1,041,999
Mississippi	-	-	-	12	-	-	-	245,401	-	-	-
Missouri	-	-	-	226	-	-	-	3,307,131	-	-	-
Montana	846	428	418	95	37	33	35	391,119	358,265	343,063	357,349
Nebraska	-	-	-	26	-	-	-	828,019	-	-	-
Nevada	57	26	31	29	11	6	10	2,311,044	391,855	385,759	387,480
New Hampshire	-	-	-	58	-	-	-	529,428	-	-	-
New Jersey	1,485	742	743	139	25	25	25	6,354,868	3,977,840	3,977,840	3,977,840
New Mexico	-	-	-	48	-	-	-	878,918	-	-	-
New York	925	469	456	799	64	60	46	13,892,396	780,056	736,224	741,503
North Carolina	3,529	1,656	1,873	435	125	124	125	6,078,505	5,101,395	5,085,249	5,101,395
North Dakota	424	213	211	86	20	20	20	319,889	295,516	295,516	295,516
Ohio	16	-	16	300	3	-	3	7,630,724	65,875	-	65,875
Oklahoma	4,234	53	4,181	620	167	5	167	2,926,470	2,384,939	217,541	2,384,939
Oregon	-	-	-	228	-	-	-	2,823,664	-	-	-
Pennsylvania	3,626	1,920	1,706	498	235	235	214	9,416,267	7,911,762	7,911,762	7,782,215

State	TOC from SW CWSs, 2011										
	Number of Records			Number of Systems			Population Served				
	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]	Total SDWIS[2]	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]	Total SDWIS[2]	Total SYR3 ICR	SYR3 ICR RW[1]	SYR3 ICR FN[1]
Rhode Island	-	-	-	28	-	-	-	848,400	-	-	-
South Carolina	1,268	634	634	206	49	49	49	3,299,324	2,126,960	2,126,960	2,126,960
South Dakota	26	13	13	143	1	1	1	434,488	25	25	25
Tennessee	-	-	-	311	-	-	-	4,897,088	-	-	-
Texas	-	-	-	1,218	-	-	-	19,487,622	-	-	-
Utah	312	152	160	111	25	23	23	2,006,571	525,644	523,696	516,295
Vermont	25	12	13	94	2	1	2	265,874	10,043	9,956	10,043
Virginia	2,705	1,341	1,364	370	117	116	117	6,205,709	3,589,459	3,355,239	3,589,459
Washington	-	-	-	193	-	-	-	3,684,203	-	-	-
West Virginia	2,402	1,196	1,206	309	124	123	121	1,263,392	978,991	960,669	949,291
Wisconsin	-	-	-	55	-	-	-	1,854,986	-	-	-
Wyoming	354	183	171	101	21	21	18	324,182	156,930	156,930	145,044
Total	**35,643**	**15,865**	**19,778**	**11,394**	**1,639**	**1,417**	**1,549**	**207,618,086**	**57,267,095**	**50,697,389**	**54,988,279**

[1] RW = Raw water; FN = Finished water

[2] These numbers were generated using the SDWIS Pivot Tables.

B.2.2.3 Alkalinity

Exhibit B.9 displays the results for the inventory analyses of alkalinity over the entire time period of the SYR3 ICR database. The inventory results presented below were filtered to only include SW (includes SW, SWP, GU and GUP) CWSs with raw water results, as only raw water samples from subpart H systems (SW or GWUDI systems) are required to be collected under the Stage 1 D/DBPR TT. Altogether, there are almost 95,000 records available for analysis from 1,540 SW CWSs, with the number of systems varying across states. Over 50 million people are served by the SW CWSs reporting the alkalinity data.

States/primacy entities that were not included in analyses (either because they did not provide information or because none of their data passed QA/QC) were: American Samoa; Arizona; Arkansas; California; Colorado; Delaware; Washington, DC; Georgia; Hawaii; Maryland; Massachusetts; Michigan; Mississippi; Nebraska; New Hampshire; South Dakota; Tennessee; Washington and Wisconsin.

Exhibit B.9: SYR3 ICR Inventory Analysis for Alkalinity (2006 – 2011; SW CWSs; Raw Water only)

State	Alkalinity in Raw Water from SW Systems All Years, CWS only		
	Number of Records	Number of Systems	Population Served
Alabama	5,129	72	2,801,736
Alaska	507	15	260,803
American Samoa	-	-	-
Arizona	2	1	28,022
Arkansas	-	-	-
California	-	-	-
Colorado	29	1	2,020
Connecticut	3,178	34	2,211,078
Delaware	-	-	-
District of Columbia	-	-	-
Florida	1	1	20,000
Georgia	-	-	-
Hawaii	-	-	-
Idaho	93	7	236,159
Illinois	6,329	99	4,909,225
Indiana	1,322	37	2,079,708
Iowa	1,249	19	712,155
Kansas	5,860	87	1,571,039
Kentucky	11,109	140	3,007,087
Louisiana	20	6	88,573

State	Alkalinity in Raw Water from SW Systems All Years, CWS only		
	Number of Records	Number of Systems	Population Served
Maine	394	27	178,822
Maryland	-	-	-
Massachusetts	-	-	-
Michigan	-	-	-
Minnesota	1	1	3,616
Mississippi	-	-	-
Missouri	3,592	67	2,505,357
Montana	1,371	27	297,242
Nebraska	-	-	-
Nevada	132	3	372,307
New Hampshire	-	-	-
New Jersey	5,864	27	4,040,419
New Mexico	219	8	106,738
New York	658	30	231,564
North Carolina	10,272	132	5,186,010
North Dakota	1,336	21	296,762
Ohio	2	1	2,491
Oklahoma	318	5	217,541
Oregon	1,911	74	772,185
Pennsylvania	11,023	226	7,806,882
Rhode Island	594	8	563,287
South Carolina	3,789	49	2,126,960
South Dakota	74	1	25
Tennessee	-	-	-
Texas	3	2	2,099,395
Utah	1,518	31	601,596
Vermont	63	1	9,956
Virginia	8,003	128	4,068,953
Washington	-	-	-
West Virginia	7,709	127	965,978
Wisconsin	-	-	-
Wyoming	1,158	25	161,054
Total	**94,832**	**1,540**	**50,542,745**

B.2.3 Inorganic Precursors

This section provides additional information on inorganic precursors from the period prior to promulgation of the Stage 1 and Stage 2 D/DBPRs.

B.2.3.1 Summary of Stage 1 and 2 D/DBPR Information

This section summarizes occurrence data on inorganic DBP precursors that were available prior to the promulgation of the Stage 2 D/DBPR. Iodide was not measured as part of ICR monitoring; thus, national-level occurrence data for iodide was not reviewed during the development of the Stage 2 D/DBPR. The main source of bromide data was the DBP ICR database. Exhibit B.10 summarizes ICR data for influent bromide. Data for systems serving fewer than 100,000 people were available from the NRWA and supplemental surveys. Exhibit B.11 summarizes bromide data for these systems.

Exhibit B.10: ICR Large System Influent Bromide Data (mg/L)

Source Type	Number of Plants	Mean of Plant Means	Median of Plant Means	90th Percentile of Plant Means	Range of Plant Means
Surface Water	320	0.055	0.027	0.115	ND – 1.325
Ground Water	118	0.103	0.066	0.19	ND – 1.325

Source: USEPA, 2005l.

Notes: These statistics were generated from the ICR AUX1 database (USEPA, 2000e). The database represents distribution of plant mean data as calculated using ICR monthly data from the last 12 months of the ICR (January 1998 - December 1998). Only plants with reported data for at least 9 of the 12 months are included in this analysis. Does not include blended, mixed or purchased plants. Values below the minimum reporting level (MRL) were converted to zero to calculate plant means.

Exhibit B.11: Medium and Small System Influent Bromide Data (mg/L)

Data Source/Size Category	N	Mean of Plant Means	Median of Plant Means	90th Percentile of Plant Means	Range of Plant Means
NRWA Small Surface Water (SW) Plants	95	0.063	0.021	0.107	0 - 1.72
ICR Supplemental Survey (ICR SS) Medium SW Plants	40	0.05	0.016	0.092	0 - 0.53
ICR SS Small SW Plants	38	0.02	0	0.044	0 - 0.27

Source: USEPA, 2005l

Note: ICR SS data are the plant means for plants that took at least three-fourths of the total possible samples for each parameter. Only plants that had both a winter and summer sample are included in the NRWA data for this analysis.

B.2.3.2 New Information since the Stage 2 D/DBPR

SYR3 National TOC Occurrence in 2006-2010

EPA reviewed the entire SYR3 ICR TOC dataset to evaluate plant means for TOC in raw and finished waters for given system size categories. Exhibit B.12 presents summary-level information on TOC data in 2006-2010. (Chapter 6 presents 2011 summary-level information as well as cumulative distributions of raw and finished water plant means for TOC data in that year.)

Exhibit B.12: Raw and Finished Water Plant Means from the SYR3 ICR TOC Dataset; SW Systems (2006-2010)

System Size	Year	Raw Water (mg/L)							Finished Water (mg/L)						
		Count of Plants	Median	Mean	90%ile	95%ile	% Plant Means > 2 mg/L	% Plant Means > 3 mg/L	Count of Plants	Median	Mean	90%ile	95%ile	% Plant Means > 2 mg/L	% Plant Means > 3 mg/L
Serving <10,000	2006	594	2.50	3.18	6.09	7.46	63%	37%	594	1.59	1.91	3.39	4.23	32%	13%
Serving 10,000 - <100,000	2006	364	2.50	3.05	5.49	6.56	73%	38%	364	1.62	1.72	2.70	3.09	27%	6%
Serving ≥100,000	2006	99	2.75	3.40	6.78	7.56	76%	42%	99	1.65	1.86	3.01	3.30	30%	11%
All	**2006**	**1,057**	**2.55**	**3.16**	**5.88**	**7.10**	**68%**	**38%**	**1,057**	**1.62**	**1.84**	**3.06**	**3.83**	**30%**	**11%**
Serving <10,000	2007	598	2.57	3.16	5.95	7.36	67%	38%	598	1.62	1.88	3.37	4.09	33%	14%
Serving 10,000 - <100,000	2007	364	2.56	3.02	5.51	6.53	72%	37%	364	1.63	1.68	2.59	3.09	24%	6%
Serving ≥100,000	2007	106	2.65	3.24	5.98	7.24	76%	41%	106	1.64	1.77	2.91	3.24	28%	9%
All	**2007**	**1,068**	**2.57**	**3.12**	**5.81**	**7.00**	**69%**	**38%**	**1,068**	**1.63**	**1.80**	**3.08**	**3.72**	**30%**	**11%**
Serving <10,000	2008	652	2.55	3.09	5.73	7.20	67%	37%	652	1.63	1.80	3.00	3.58	33%	10%
Serving 10,000 - <100,000	2008	385	2.68	3.19	5.73	7.20	75%	41%	385	1.63	1.75	2.79	3.23	29%	7%
Serving ≥100,000	2008	113	2.76	3.56	6.82	7.51	74%	40%	113	1.66	1.87	3.16	3.46	28%	12%
All	**2008**	**1,150**	**2.64**	**3.17**	**5.81**	**7.27**	**70%**	**39%**	**1,150**	**1.64**	**1.79**	**2.92**	**3.50**	**31%**	**9%**
Serving <10,000	2009	669	2.51	3.06	5.87	7.15	64%	39%	669	1.58	1.72	2.93	3.56	32%	9%
Serving 10,000 - <100,000	2009	406	2.75	3.21	5.66	6.93	72%	44%	406	1.61	1.70	2.64	2.96	31%	4%
Serving ≥100,000	2009	117	3.20	3.80	7.01	7.92	78%	54%	117	1.76	1.97	3.25	3.68	38%	15%
All	**2009**	**1,192**	**2.66**	**3.18**	**5.90**	**7.15**	**68%**	**42%**	**1,192**	**1.60**	**1.74**	**2.87**	**3.37**	**32%**	**8%**
Serving <10,000	2010	667	2.60	3.09	5.78	6.85	67%	39%	667	1.61	1.73	2.88	3.36	32%	8%
Serving 10,000 - <100,000	2010	407	2.64	3.06	5.43	6.51	72%	42%	407	1.60	1.65	2.51	3.00	27%	5%
Serving ≥100,000	2010	116	2.87	3.58	6.40	6.66	77%	43%	116	1.65	1.78	2.94	3.26	27%	9%
All	**2010**	**1,190**	**2.64**	**3.13**	**5.82**	**6.77**	**70%**	**41%**	**1,190**	**1.61**	**1.71**	**2.78**	**3.24**	**30%**	**7%**

The 2 mg/L TOC level represents the level below which TOC removal is not required in the Stage 2 DBPR.

B.3 DBP Occurrence and Exposure

This section provides additional information on what was known at the time of the development of the Stage 2 D/DBPR on organic and inorganic DBP occurrence information, presents the results of new occurrence analyses using the SYR3 ICR data for regulated DBPs and discusses new occurrence information available for unregulated DBPs.

B.3.1 Overview of DBP Inventory Analyses

The results of system and population inventories of the entire SYR3 ICR DBP dataset are included below in Exhibit B.13 through Exhibit B.15. Exhibit B.13 depicts the distribution of systems and population among the different system types, and Exhibit B.14 includes the same information but distributed based on source water type. The source types are split by GW (includes GW and GWP), SW (includes SW and SWP), and purchased and non-purchased GWUDI systems. Exhibit B.15 depicts the distribution of systems and population by both source water type and aggregated by population size. The same conclusions noted for 2011 in Chapter 6 can be applied from all years of the data. The systems serving more than 100,000 people make up almost 50 percent of the population and are largely SW systems. The population served is roughly 70 percent of the 2011 population in SDWIS, indicating that the SYR3 ICR dataset covers a substantial amount of the potentially exposed population.

Exhibit B.13: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset with DBP Records, by System Type (2006 – 2011)

Year	System Type	Systems		Population	
		Number	Percent	Number	Percent
2006	Community	18,422	81.5%	190,759,362	99.0%
	Non-transient Non-community	4,161	18.4%	1,969,045	1.0%
	Transient Non-community	16	0.1%	1,403	0.0%
	Unknown	1	0.0%	35	0.0%
	Total	**22,600**	**100.0%**	**192,729,845**	**100.0%**
2007	Community	21,204	79.8%	194,804,662	98.8%
	Non-transient Non-community	5,339	20.1%	2,353,118	1.2%
	Transient Non-community	16	0.1%	3,902	0.0%
	Unknown	0	0.0%	0	0.0%
	Total	**26,559**	**100.0%**	**197,161,682**	**100.0%**
2008	Community	18,059	80.1%	197,169,751	99.0%
	Non-transient Non-community	4,469	19.8%	2,067,002	1.0%
	Transient Non-community	15	0.1%	2,969	0.0%

Year	System Type	Systems		Population	
		Number	Percent	Number	Percent
	Unknown	1	0.0%	35	0.0%
	Total	**22,544**	**100.0%**	**199,239,757**	**100.0%**
2009	Community	18,453	81.7%	200,590,738	99.0%
	Non-transient Non-community	4,118	18.2%	1,960,057	1.0%
	Transient Non-community	9	0.0%	2,370	0.0%
	Unknown	0	0.0%	0	0.0%
	Total	**22,580**	**100.0%**	**202,553,165**	**100.0%**
2010	Community	21,188	80.0%	200,350,388	98.8%
	Non-transient Non-community	5,297	20.0%	2,383,034	1.2%
	Transient Non-community	5	0.0%	601	0.0%
	Unknown	0	0.0%	0	0.0%
	Total	**26,490**	**100.0%**	**202,734,023**	**100.0%**
2011	Community	17,484	81.3%	199,318,093	99.0%
	Non-transient Non-community	4,015	18.7%	1,917,482	1.0%
	Transient Non-community	8	0.0%	910	0.0%
	Unknown	0	0.0%	0	0.0%
	Total	**21,507**	**100.0%**	**201,236,485**	**100.0%**
All Years	Community	32,909	78.1%	224,122,324	98.5%
	Non-transient Non-community	9,167	21.8%	3,501,819	1.5%
	Transient Non-community	54	0.1%	9,877	0.0%
	Unknown	1	0.0%	35	0.0%
	Total	**42,131**	**100.0%**	**227,634,055**	**100.0%**

Exhibit B.14: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset (2006 – 2011) with DBP Records, by Source Water Type

Year	Source Water Type	Systems		Population	
		Number	Percent	Number	Percent
2006	GW	15,571	68.9%	51,019,010	26.5%
	GWUDI	352	1.6%	1,613,975	0.8%
	SW	6,677	29.5%	140,096,860	72.7%

Year	Source Water Type	Systems		Population	
		Number	Percent	Number	Percent
	Total	**22,600**	**100.0%**	**192,729,845**	**100.0%**
2007	GW	19,399	73.0%	55,565,166	28.2%
	GWUDI	369	1.4%	1,643,280	0.8%
	SW	6,791	25.6%	139,953,236	71.0%
	Total	**26,559**	**100.0%**	**197,161,682**	**100.0%**
2008	GW	15,623	69.3%	52,453,489	26.3%
	GWUDI	362	1.6%	1,676,539	0.8%
	SW	6,559	29.1%	145,109,729	72.8%
	Total	**22,544**	**100.0%**	**199,239,757**	**100.0%**
2009	GW	15,641	69.3%	52,744,623	26.0%
	GWUDI	368	1.6%	1,773,259	0.9%
	SW	6,571	29.1%	148,035,283	73.1%
	Total	**22,580**	**100.0%**	**202,553,165**	**100.0%**
2010	GW	19,506	73.6%	55,854,994	27.6%
	GWUDI	387	1.5%	1,751,886	0.9%
	SW	6,597	24.9%	145,127,143	71.6%
	Total	**26,490**	**100.0%**	**202,734,023**	**100.0%**
2011	GW	14,558	67.7%	52,559,785	26.1%
	GWUDI	380	1.8%	1,755,985	0.9%
	SW	6,569	30.5%	146,920,715	73.0%
	Total	**21,507**	**100.0%**	**201,236,485**	**100.0%**
All Years	GW	33,508	79.5%	69,338,188	30.5%
	GWUDI	475	1.1%	1,856,122	0.8%
	SW	8,148	19.3%	156,439,745	68.7%
	Total	**42,131**	**100.0%**	**227,634,055**	**100.0%**

Note: Purchased systems are included in each category.

Exhibit B.15: Number of Systems and Population Served by Systems in the SYR3 ICR Dataset with DBP Records, by System Size and System Type (2006 – 2011)

Year	System Size (Population Served by the System)	GW		SW		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
Community Water Systems							
2006	<101	2,641	167,086	472	24,093	3,113	191,179
	101 – 500	3,902	989,428	1,063	297,775	4,965	1,287,203

Year	System Size (Population Served by the System)	GW		SW		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	501 – 1,000	1,358	1,006,988	639	483,049	1,997	1,490,037
	1,001 – 3,300	1,922	3,642,123	1,510	3,015,660	3,432	6,657,783
	3,301 – 10,000	951	5,377,586	1,330	8,125,246	2,281	13,502,832
	10,001 – 50,000	759	16,191,158	1,246	28,208,256	2,005	44,399,414
	50,001 – 100,000	110	7,247,390	222	15,444,516	332	22,691,906
	100,001 – 1 million	57	11,753,773	225	57,036,751	282	68,790,524
	> 1 million	2	3,200,000	13	28,548,484	15	31,748,484
	Total	**11,702**	**49,575,532**	**6,720**	**141,183,830**	**18,422**	**190,759,362**
2007	<101	3,299	206,745	465	23,398	3,764	230,143
	101–500	4,683	1,176,706	1,084	307,856	5,767	1,484,562
	501–1,000	1,654	1,223,255	667	505,306	2,321	1,728,561
	1,001–3,300	2,461	4,630,949	1,544	3,093,222	4,005	7,724,171
	3,301–10,000	1,295	7,274,944	1,369	8,353,921	2,664	15,628,865
	10,001–50,000	806	16,719,869	1,247	28,286,830	2,053	45,006,699
	50,001–100,000	113	7,464,471	219	15,170,961	332	22,635,432
	100,001–1 million	58	11,861,700	225	56,556,045	283	68,417,745
	>1 million	2	3,200,000	13	28,748,484	15	31,948,484
	Total	**14,371**	**53,758,639**	**6,833**	**141,046,023**	**21,204**	**194,804,662**
2008	<101	2,559	160,553	398	19,036	2,957	179,589
	101–500	3,698	939,032	917	263,591	4,615	1,202,623
	501–1,000	1,349	989,527	663	502,179	2,012	1,491,706
	1,001–3,300	1,853	3,533,927	1,537	3,083,606	3,390	6,617,533
	3,301–10,000	1,040	5,878,135	1,351	8,267,864	2,391	14,145,999
	10,001–50,000	797	16,833,564	1,256	28,383,845	2,053	45,217,409
	50,001–100,000	114	7,529,701	225	15,538,875	339	23,068,576
	100,001–1 million	58	11,861,156	228	58,296,676	286	70,157,832
	>1 million	2	3,200,000	14	31,888,484	16	35,088,484
	Total	**11,470**	**50,925,595**	**6,589**	**146,244,156**	**18,059**	**197,169,751**
2009	<101	2,392	148,002	399	18,766	2,791	166,768
	101–500	3,585	947,117	907	261,559	4,492	1,208,676
	501–1,000	1,612	1,191,081	652	491,639	2,264	1,682,720
	1,001–3,300	2,161	3,997,623	1,561	3,125,809	3,722	7,123,432
	3,301–10,000	1,073	6,119,897	1,361	8,307,088	2,434	14,426,985

Year	System Size (Population Served by the System)	GW		SW		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	10,001–50,000	839	17,718,572	1,261	28,447,458	2,100	46,166,030
	50,001–100,000	122	8,089,980	228	15,726,342	350	23,816,322
	100,001–1 million	54	11,024,340	230	59,886,981	284	70,911,321
	>1 million	1	2,100,000	15	32,988,484	16	35,088,484
	Total	**11,839**	**51,336,612**	**6,614**	**149,254,126**	**18,453**	**200,590,738**
2010	<101	2,960	184,228	408	18,992	3,368	203,220
	101–500	4,670	1,188,103	937	270,106	5,607	1,458,209
	501–1,000	1,890	1,388,470	643	485,148	2,533	1,873,618
	1,001–3,300	2,597	4,871,959	1,559	3,133,550	4,156	8,005,509
	3,301–10,000	1,394	7,806,349	1,374	8,371,675	2,768	16,178,024
	10,001–50,000	855	17,856,396	1,251	28,271,282	2,106	46,127,678
	50,001–100,000	119	7,882,678	229	15,796,816	348	23,679,494
	100,001–1 million	57	10,761,855	229	56,974,297	286	67,736,152
	>1 million	1	2,100,000	15	32,988,484	16	35,088,484
	Total	**14,543**	**54,040,038**	**6,645**	**146,310,350**	**21,188**	**200,350,388**
2011	<101	2,222	137,751	397	18,611	2,619	156,362
	101–500	3,267	836,532	932	265,835	4,199	1,102,367
	501–1,000	1,342	996,958	643	487,084	1,985	1,484,042
	1,001–3,300	1,843	3,465,602	1,528	3,072,766	3,371	6,538,368
	3,301–10,000	1,186	6,812,788	1,369	8,369,480	2,555	15,182,268
	10,001–50,000	849	17,725,805	1,255	28,285,116	2,104	46,010,921
	50,001–100,000	119	7,876,457	228	15,813,961	347	23,690,418
	100,001–1 million	57	11,279,556	231	58,785,307	288	70,064,863
	>1 million	1	2,100,000	15	32,988,484	16	35,088,484
	Total	**10,886**	**51,231,449**	**6,598**	**148,086,644**	**17,484**	**199,318,093**
All Years	<101	6,179	382,679	698	36,416	6,877	419,095
	101–500	8,517	2,141,680	1,499	423,822	10,016	2,565,502
	501–1,000	3,014	2,219,222	792	595,295	3,806	2,814,517
	1,001–3,300	3,921	7,300,050	1,796	3,587,515	5,717	10,887,565
	3,301–10,000	1,977	11,125,614	1,530	9,297,604	3,507	20,423,218
	10,001–50,000	942	19,485,082	1,346	30,288,043	2,288	49,773,125
	50,001–100,000	124	8,237,954	246	17,015,806	370	25,253,760
	100,001–1 million	62	12,378,117	249	63,418,941	311	75,797,058

Year	System Size (Population Served by the System)	GW		SW		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	>1 million	2	3,200,000	15	32,988,484	17	36,188,484
	Total	**24,738**	**66,470,398**	**8,171**	**157,651,926**	**32,909**	**224,122,324**
Non-Community Water Systems							
2006	<101	1,807	100,584	85	4,130	1,892	104,714
	101 – 500	1,411	349,282	117	29,899	1,528	379,181
	501 – 1,000	383	269,667	46	35,098	429	304,765
	1,001 – 3,300	224	386,796	47	80,450	271	467,246
	3,301 – 10,000	39	206,609	10	62,640	49	269,249
	10,001 – 50,000	4	130,505	2	39,450	6	169,955
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	-	-	1	203,375	1	203,375
	> 1 million	-	-	-	-	-	-
	Total	**3,868**	**1,443,443**	**309**	**527,005**	**4,177**	**1,970,448**
2007	<101	2,376	133,043	90	4,559	2,466	137,602
	101 – 500	1,794	455,885	124	32,105	1,918	487,990
	501 – 1,000	511	363,697	50	37,720	561	401,417
	1,001 – 3,300	300	523,045	46	82,021	346	605,066
	3,301 – 10,000	43	224,757	13	79,300	56	304,057
	10,001 – 50,000	4	106,100	2	39,450	6	145,550
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	**-**	**-**	**1**	**203,375**	**1**	**203,375**
	> 1 million	-	-	-	-	-	-
	Total	**5,028**	**1,806,527**	**327**	**550,493**	**5,355**	**2,357,020**
2008	<101	1,983	110,050	98	4,798	2,081	114,848
	101 – 500	1,501	377,926	125	31,821	1,626	409,747
	501 – 1,000	392	282,594	51	39,084	443	321,678
	1,001 – 3,300	236	408,019	42	76,771	278	484,790
	3,301 – 10,000	34	189,765	12	74,850	46	264,615
	10,001 – 50,000	6	159,505	2	39,450	8	198,955
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	-	-	1	203,375	1	203,375
	> 1 million	-	-	-	-	-	-
	Total	**4,152**	**1,527,859**	**332**	**542,112**	**4,484**	**2,069,971**

Year	System Size (Population Served by the System)	GW		SW		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
2009	<101	1,792	98,224	92	4,408	1,884	102,632
	101 – 500	1,356	339,894	124	30,404	1,480	370,298
	501 – 1,000	376	270,311	50	39,084	426	309,395
	1,001 – 3,300	238	414,696	41	71,585	279	486,281
	3,301 – 10,000	37	195,286	12	72,300	49	267,586
	10,001 – 50,000	3	89,600	4	61,297	7	150,897
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	-	-	1	203,375	1	203,375
	> 1 million	-	-	-	-	-	-
	Total	**3,802**	**1,408,011**	**325**	**554,416**	**4,127**	**1,962,427**
2010	<101	2,294	127,546	91	4,499	2,385	132,045
	101 – 500	1,802	455,907	135	33,663	1,937	489,570
	501 – 1,000	500	357,211	52	40,397	552	397,608
	1,001 – 3,300	319	548,834	43	79,835	362	628,669
	3,301 – 10,000	44	223,358	12	73,650	56	297,008
	10,001 – 50,000	4	102,100	4	61,297	8	163,397
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	-	-	1	203,375	1	203,375
	> 1 million	-	-	-	-	-	-
	Total	**4,963**	**1,814,956**	**339**	**568,679**	**5,302**	**2,383,635**
2011	<101	1,693	92,862	93	4,604	1,786	97,466
	101 – 500	1,370	339,302	136	33,874	1,506	373,176
	501 – 1,000	355	255,289	56	42,555	411	297,844
	1,001 – 3,300	219	368,505	45	82,485	264	450,990
	3,301 – 10,000	31	170,278	15	89,903	46	260,181
	10,001 – 50,000	4	102,100	4	61,297	8	163,397
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	-	-	1	203,375	1	203,375
	> 1 million	-	-	-	-	-	-
	Total	**3,672**	**1,328,336**	**351**	**590,056**	**4,023**	**1,918,392**
All Years	<101	4,273	233,139	136	6,570	4,409	239,709
	101 – 500	3,149	784,577	176	44,914	3,325	829,491
	501 – 1,000	823	588,765	61	46,571	884	635,336

Year	System Size (Population Served by the System)	GW		SW		Total	
		Number of Systems	Population Served	Number of Systems	Population Served	Number of Systems	Population Served
	1,001 – 3,300	454	769,564	55	97,898	509	867,462
	3,301 – 10,000	64	332,205	18	111,353	82	443,558
	10,001 – 50,000	6	159,505	4	61,297	10	220,802
	50,001 – 100,000	-	-	1	71,963	1	71,963
	100,001 – 1 million	-	-	1	203,375	1	203,375
	> 1 million	-	-	-	-	-	-
	Total	**8,769**	**2,867,755**	**452**	**643,941**	**9,221**	**3,511,696**

Note: There is one water system with data in 2006 and 2008 that has an unknown system type. That system is not counted in this table. In addition, GWUDI systems are included in SW, and purchased systems are included in each category as well.

B.3.2 Regulated Organic DBPs

This section provides new information since the promulgation of the Stage 2 D/DBPR.

B.3.2.1 Summary of Stage 1 and 2 D/DBPR Information

No additional information provided in this appendix.

B.3.2.2 New Information since the Stage 2 D/DBPRs

Inventory Analyses

Inventory analyses of the SYR3 ICR data were conducted to determine the number of records, number of systems and population served by those systems for each contaminant (or suite of contaminants, for THMs and HAAs) on a state-by-state basis. Summary inventory information tables for all years combined as well as just for 2011 are presented for each contaminant in the following sections. The results for other individual years are not presented here, but it is important to note that some systems did not have records in every year. In some cases, this may be due to reduced monitoring frequency requirements; in others, the data were not available as part of the SYR3 ICR due to differences in reporting frequency requirements. As a result, the number of systems and population included in all years will be greater than the number of systems and population in any given individual year. Note that no SYR3 ICR data were received from Colorado, Delaware, Georgia or Mississippi, but there may be Tribes or other primacy agencies with systems in those states and these data are included in the tables below. Other states may have reported SYR3 ICR data for chemical or radiological contaminants, but did not provide any information for DBPs. Furthermore, some states may have provided data for DBPs, but none of their data passed the QA/QC process as described in Appendix Section B.4.

Trihalomethanes

In this appendix, inventory information for the THMs are presented for all six years of the SYR3 ICR database (2006-2011) as well as just for 2011 (see the "representativeness of SYR3 ICR THM and HAA data" section below). States/primacy entities that were not included in analyses (either because they did not provide information or because none of their data passed QA/QC) were: Delaware, Georgia, Maryland, Massachusetts and New Hampshire.

Exhibit B.16 presents inventory information by state for all THM species within THM4 and approximately 70 percent of systems submitted THM4 and speciation information. Altogether, there are over 2.2 million THM records, with about 1.3 million records from SW systems. More than 42,000 systems are represented, of which about 80 percent are GW systems. Almost 226 million people are served water by these systems, with almost 70 percent of that population served by SW systems. Thus, the systems that provided THM data for the SYR3 ICR are predominantly small GW systems, but the largest population of people exposed is associated with SW systems. This is to be expected based on the requirements for disinfection and monitoring for DBPs and the national distribution of drinking water systems.

Exhibit B.16: SYR3 ICR Inventory Analysis for Trihalomethanes (2006-2011)

State	THMs								
	Number of Records			Number of Systems			Population Served		
	SYR3 Total	SYR3 GW	SYR3 SW	SYR3 Total	SYR3 GW	SYR3 SW	SYR3 Total	SYR3 GW	SYR3 SW
Alabama	59,522	14,543	44,979	569	316	253	5,586,574	1,507,488	4,079,086
Alaska	17,740	5,839	11,901	366	218	148	623,273	227,333	395,940
American Samoa	297	297	0	11	11	0	59,434	59,434	0
Arizona	18,139	10,478	7,661	882	818	64	6,572,188	2,946,069	3,626,119
Arkansas	58,136	19,765	38,371	556	381	175	2,130,131	810,735	1,319,396
California	187,438	114,041	73,397	566	245	321	24,608,939	2,250,807	22,358,132
Colorado	8	0	8	2	0	2	4,320	0	4,320
Connecticut	81,302	44,039	37,263	1,246	1,162	84	2,932,497	390,303	2,542,194
Delaware	-	-	-	-	-	-	-	-	-
District of Columbia	-	-	-	-	-	-	-	-	-
Florida	32,632	27,041	5,591	2,774	2,707	67	19,479,396	15,237,562	4,241,834
Georgia	-	-	-	-	-	-	-	-	-
Hawaii	7,589	4,779	2,810	123	110	13	1,426,542	1,260,976	165,566
Idaho	6,081	4,285	1,796	599	526	73	1,178,887	880,021	298,866
Illinois	134,811	22,733	112,078	1,868	1,275	593	12,223,036	3,246,101	8,976,935
Indiana	10,454	7,643	2,811	960	900	60	4,656,274	2,427,032	2,229,242
Iowa	53,027	16,206	36,821	1,028	868	160	2,806,779	1,445,471	1,361,308
Kansas	29,332	7,279	22,053	846	544	302	2,552,039	753,353	1,798,686
Kentucky	12,913	720	12,193	235	82	153	3,353,730	301,742	3,051,988

State	THMs								
	Number of Records			Number of Systems			Population Served		
	SYR3 Total	SYR3 GW	SYR3 SW	SYR3 Total	SYR3 GW	SYR3 SW	SYR3 Total	SYR3 GW	SYR3 SW
Louisiana	32,219	15,607	16,612	1,124	1,026	98	4,958,888	2,919,346	2,039,542
Maine	19,953	11,048	8,905	592	538	54	729,225	254,678	474,547
Maryland	-	-	-	-	-	-	-	-	-
Massachusetts	-	-	-	-	-	-	-	-	-
Michigan	13,976	9,181	4,795	474	416	58	1,847,194	912,666	934,528
Minnesota	6,569	5,418	1,151	344	325	19	1,169,656	936,264	233,392
Mississippi	52	52	0	4	4	0	5,976	5,976	0
Missouri	68,706	31,772	36,934	1,418	1,328	90	4,667,482	1,868,091	2,799,391
Montana	27,125	17,134	9,991	896	811	85	781,929	381,807	400,122
Nebraska	22,840	16,809	6,031	728	703	25	1,621,685	676,855	944,830
Nevada	27,741	11,707	16,034	341	302	39	2,653,608	279,128	2,374,480
New Hampshire	-	-	-	-	-	-	-	-	-
New Jersey	182,662	91,704	90,958	1,486	1,317	169	9,527,287	2,653,687	6,873,600
New Mexico	21,815	11,919	9,896	656	604	52	1,897,275	985,322	911,953
New York	138,390	47,427	90,963	2,523	1,858	665	18,511,404	4,392,260	14,119,144
North Carolina	124,286	64,810	59,476	2,751	2,241	510	7,859,530	1,709,599	6,149,931
North Dakota	11,878	4,801	7,077	332	232	100	652,313	247,809	404,504
Ohio	122,179	45,682	76,497	2,046	1,742	304	10,474,154	3,032,334	7,441,820
Oklahoma	73,875	23,117	50,758	939	531	408	3,272,082	624,701	2,647,381
Oregon	7,355	1,241	6,114	622	392	230	3,194,225	414,781	2,779,444
Pennsylvania	11,461	648	10,813	394	151	243	7,662,936	288,644	7,374,292
Rhode Island	1,388	131	1,257	38	23	15	870,797	133,443	737,354
South Carolina	47,068	8,282	38,786	359	263	96	3,080,026	493,738	2,586,288
South Dakota	1,641	681	960	341	240	101	698,028	295,293	402,735
Tennessee	16,568	802	15,766	463	179	284	6,296,075	1,421,965	4,874,110
Texas	344,097	113,371	230,726	5,422	4,124	1,298	25,868,677	6,043,316	19,825,361
Utah	8,323	2,379	5,944	341	240	101	2,605,901	671,946	1,933,955
Vermont	28,772	14,421	14,351	705	611	94	423,297	224,371	198,926
Virginia	93,153	28,801	64,352	1,834	1,413	421	7,496,747	623,867	6,872,880
Washington	62,619	35,319	27,300	1,323	1,134	189	5,002,822	2,624,229	2,378,593
West Virginia	38,381	8,015	30,366	582	310	272	1,448,938	276,570	1,172,368
Wisconsin	185	185	0	33	33	0	47,309	47,309	0
Wyoming	2,368	552	1,816	271	180	91	446,838	120,852	325,986
Total	**2,267,066**	**922,704**	**1,344,362**	**42,013**	**33,434**	**8,579**	**225,966,343**	**69,305,274**	**156,661,069**

Haloacetic Acids

This section presents the inventory results for HAAs during all six years of the SYR3 ICR database (2006-2011), as well as just for 2011 (see the "representativeness of SYR3 ICR THM and HAA data" section below). States/primacy entities that were not included in the analysis (either because they did not provide information or because none of their data passed QA/QC) were: Delaware; Washington, DC; Georgia; Maryland; Massachusetts; New Hampshire and Washington State.

Exhibit B.17 presents inventory information by state for HAAs records over the entire date range of the SYR3 ICR database. The inventory information summary shows the number of records, systems reporting and population served by those reporting for all states and primacy agencies that submitted data for the SYR3 ICR. The results presented below are from both GW (includes GW and GWP) and SW (includes SW, SWP, GU and GUP) systems. Altogether, there are more than 1.8 million HAA records, with about 1.4 million records from SW systems. More than 33,000 systems are represented, of which about 75 percent are GW. More than 208 million people are served water by these systems, with about 70 percent served by SW systems. As with THMs the systems that provided HAA data for the SYR3 ICR are predominantly small GW systems, but the largest population exposed is associated with SW systems. This is to be expected based on the requirements for disinfection and monitoring for DBPs and the national distribution of drinking water systems and is similar to the results for THMs.

Exhibit B.17: SYR3 ICR Inventory Analysis for Haloacetic Acids (2006-2011)

State	HAAs								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Alabama	42,932	3,310	39,622	566	314	252	5,583,002	1,503,916	4,079,086
Alaska	16,452	4,307	12,145	283	135	148	592,234	196,294	395,940
American Samoa	91	91	0	11	11	0	59,434	59,434	0
Arizona	16,202	9,223	6,979	851	787	64	6,545,150	2,919,040	3,626,110
Arkansas	49,300	9,486	39,814	556	381	175	2,130,131	810,735	1,319,396
California	11,563	871	10,692	326	142	184	15,443,164	630,230	14,812,934
Colorado	8	0	8	2	0	2	4,320	0	4,320
Connecticut	46,911	8,611	38,300	282	198	84	2,759,095	216,901	2,542,194
Delaware	-	-	-	-	-	-	-	-	-
District of Columbia	-	-	-	-	-	-	-	-	-
Florida	30,986	25,507	5,479	2,773	2,706	67	19,479,039	15,237,205	4,241,834
Georgia	-	-	-	-	-	-	-	-	-
Hawaii	8,737	5,378	3,359	123	110	13	1,426,542	1,260,976	165,566
Idaho	3,230	2,154	1,076	334	262	72	1,029,848	731,057	298,791
Illinois	159,729	27,251	132,478	1,869	1,276	593	12,223,535	3,246,600	8,976,935
Indiana	4,284	2,467	1,817	605	546	59	4,566,555	2,340,447	2,226,108
Iowa	63,633	19,436	44,197	1,029	868	161	2,807,286	1,445,471	1,361,815
Kansas	34,928	8,760	26,168	848	545	303	2,553,050	753,485	1,799,565

State	HAAs								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Kentucky	12,928	700	12,228	232	81	151	3,335,764	301,700	3,034,064
Louisiana	36,105	18,137	17,968	1,116	1,020	96	4,947,716	2,909,150	2,038,566
Maine	16,178	5,446	10,732	350	296	54	683,678	209,131	474,547
Maryland	-	-	-	-	-	-	-	-	-
Massachusetts	-	-	-	-	-	-	-	-	-
Michigan	10,996	6,263	4,733	395	353	42	1,290,591	813,958	476,633
Minnesota	2,780	1,478	1,302	139	122	17	493,888	262,446	231,442
Mississippi	52	52	0	5	5	0	6,176	6,176	0
Missouri	56,856	16,026	40,830	805	720	85	4,325,620	1,553,231	2,772,389
Montana	15,379	5,306	10,073	324	241	83	636,372	236,500	399,872
Nebraska	9,808	3,384	6,424	206	181	25	1,283,963	339,133	944,830
Nevada	23,238	6,116	17,122	253	215	38	2,632,748	258,548	2,374,200
New Hampshire	-	-	-	-	-	-	-	-	-
New Jersey	149,041	54,258	94,783	699	530	169	9,303,584	2,429,984	6,873,600
New Mexico	23,402	12,034	11,368	614	564	50	1,887,356	975,483	911,873
New York	140,462	34,107	106,355	2,478	1,819	659	18,472,569	4,354,384	14,118,185
North Carolina	108,493	44,707	63,786	2,486	1,977	509	7,830,446	1,680,515	6,149,931
North Dakota	14,155	5,735	8,420	332	232	100	652,313	247,809	404,504
Ohio	120,194	33,815	86,379	1,585	1,281	304	10,398,550	2,956,730	7,441,820
Oklahoma	61,550	7,841	53,709	843	436	407	3,177,265	577,032	2,600,233
Oregon	7,308	1,226	6,082	620	389	231	3,195,292	414,475	2,780,817
Pennsylvania	9,944	512	9,432	347	128	219	7,442,337	276,769	7,165,568
Rhode Island	1,336	85	1,251	30	15	15	869,459	132,105	737,354
South Carolina	51,334	6,171	45,163	354	260	94	3,068,324	493,003	2,575,321
South Dakota	1,583	634	949	335	234	101	693,112	290,377	402,735
Tennessee	16,470	798	15,672	463	179	284	6,296,075	1,421,965	4,874,110
Texas	352,895	96,191	256,704	5,388	4,091	1,297	25,848,449	6,023,088	19,825,361
Utah	8,684	2,306	6,378	317	217	100	2,579,285	646,738	1,932,547
Vermont	19,734	4,512	15,222	369	276	93	363,275	164,525	198,750
Virginia	82,463	13,435	69,028	1,237	830	407	7,361,824	491,722	6,870,102
Washington	-	-	-	-	-	-	-	-	-
West Virginia	45,246	9,120	36,126	580	310	270	1,446,142	276,570	1,169,572
Wisconsin	186	186	0	33	33	0	47,309	47,309	0
Wyoming	2,361	552	1,809	271	180	91	446,838	120,852	325,986
Total	**1,890,147**	**517,985**	**1,372,162**	**33,664**	**25,496**	**8,168**	**208,218,705**	**62,263,199**	**145,955,506**

Representativeness of SYR3 ICR THM4 and HAA5 Data

Exhibit B.18 and Exhibit B.19 shows the THM4 and HAA5 inventory analyses, respectively, for CWSs in 2011, the most recent and complete year of the SYR3 ICR database. The number of records, systems and population served by those systems is provided. Additionally, EPA considered SDWIS inventory data to provide baseline information on the number of systems and population served in a given state. In order to assess representativeness of the SYR3 ICR data, EPA compared the SDWIS inventory information with the SYR3 ICR inventory information to determine how well the SYR3 systems represented the total number of systems in each state, as well as how well the SYR3 systems represented the nation as a whole. SDWIS inventory tables were filtered to include all active CWSs (of all source water types) in 2011. As noted in the representativeness assessment for TOC (see Section 6.2.1.2 in Chapter 6), SDWIS does not contain information on what NPDWRs, state regulations and/or alternative criteria a system must comply with. Although all SW systems must monitor for THM4 and HAA5, not all GW systems disinfect. Non-disinfecting GW systems are not required to monitor for DBPs.

Exhibit B.18: SYR3 ICR Inventory Analysis for Trihalomethanes (2011; CWS Only)

State	THM; CWSs										
	Number of Records			Number of Systems				Population Served			
	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW
Alabama	9,505	2,256	7,249	528	467	227	240	5,515,724	5,366,315	1,316,447	4,049,868
Alaska	2,311	693	1,618	435	163	66	97	609,336	537,911	172,825	365,086
American Samoa	37	37	-	19	7	7	-	60,958	58,424	58,424	-
Arizona	2,506	1,286	1,220	780	446	402	44	6,225,100	6,047,141	2,428,674	3,618,467
Arkansas	9,279	2,934	6,345	710	435	282	153	2,709,389	1,998,452	716,868	1,281,584
California	37,558	22,607	14,951	3,027	227	80	147	40,956,858	19,560,514	1,352,522	18,207,992
Colorado	3	-	3	877	2	-	2	5,386,406	4,320	-	4,320
Connecticut	9,398	3,244	6,154	542	351	275	76	2,656,236	2,729,491	224,493	2,504,998
Delaware	-	-	-	216	-	-	-	899,801	-	-	-
District of Columbia	-	-	-	5	-	-	-	606,730	-	-	-
Florida	4,205	3,270	935	1,728	668	618	50	19,219,921	18,024,160	13,917,894	4,106,266
Georgia	-	-	-	1,776	-	-	-	8,432,935	-	-	-
Hawaii	945	254	691	110	55	45	10	1,460,540	1,249,353	1,084,499	164,854
Idaho	525	358	167	745	180	122	58	1,100,437	955,247	659,650	295,597
Illinois	15,192	2,225	12,967	1,751	912	335	577	12,128,970	10,983,115	2,027,030	8,956,085
Indiana	3,216	2,204	1,012	813	549	494	55	4,870,296	4,499,723	2,275,882	2,223,841
Iowa	6,276	1,773	4,503	1,122	399	258	141	2,741,931	2,110,974	795,738	1,315,236
Kansas	4,166	994	3,172	887	281	148	133	2,676,572	2,166,015	488,169	1,677,846
Kentucky	2,110	103	2,007	402	206	62	144	4,441,302	3,309,765	290,286	3,019,479
Louisiana	6,622	3,298	3,324	1,049	506	423	83	4,921,528	4,191,032	2,164,275	2,026,757
Maine	2,323	1,101	1,222	378	206	154	52	664,022	645,126	171,539	473,587
Maryland	-	-	-	474	-	-	-	5,192,667	-	-	-

State	THM; CWSs										
	Number of Records			Number of Systems				Population Served			
	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW
Massachusetts	-	-	-	527	-	-	-	9,317,400	-	-	-
Michigan	2,780	1,813	967	1,397	211	171	40	7,615,948	1,333,146	571,951	761,195
Minnesota	786	585	201	961	132	116	16	4,262,862	787,003	555,668	231,335
Mississippi	4	4	-	1,106	4	4	-	3,152,270	5,976	5,976	-
Missouri	10,040	3,437	6,603	1,474	433	356	77	5,171,584	3,836,124	1,090,051	2,746,073
Montana	2,989	1,672	1,317	698	263	213	50	713,698	536,195	163,925	372,270
Nebraska	3,690	2,590	1,100	589	306	281	25	1,479,705	1,447,961	503,131	944,830
Nevada	3,334	1,042	2,292	211	139	111	28	2,557,680	2,526,310	194,580	2,331,730
New Hampshire	-	-	-	705	-	-	-	855,402	-	-	-
New Jersey	26,490	10,908	15,582	612	517	356	161	8,998,715	8,968,237	2,221,337	6,746,900
New Mexico	2,508	1,075	1,433	600	176	140	36	1,810,927	1,540,529	642,266	898,263
New York	18,811	6,500	12,311	2,466	946	499	447	17,828,851	13,684,237	1,639,870	12,044,367
North Carolina	6,003	1,899	4,104	2,081	1,070	637	433	7,622,946	7,349,084	1,288,381	6,060,703
North Dakota	1,272	440	832	332	96	69	27	581,311	480,718	134,070	346,648
Ohio	16,755	4,586	12,169	1,240	723	445	278	10,411,689	9,612,658	2,231,066	7,381,592
Oklahoma	11,000	2,693	8,307	1,095	489	269	220	3,542,286	2,987,551	502,989	2,484,562
Oregon	1,133	188	945	875	365	150	215	3,374,323	3,073,431	300,423	2,773,008
Pennsylvania	3,150	135	3,015	2,061	189	31	158	10,744,868	6,766,712	83,180	6,683,532
Rhode Island	182	14	168	89	20	6	14	989,055	827,645	106,511	721,134
South Carolina	6,715	725	5,990	600	173	94	79	3,822,295	2,815,443	288,010	2,527,433
South Dakota	235	81	154	456	70	46	24	719,433	484,839	139,625	345,214
Tennessee	2,819	95	2,724	479	288	49	239	6,309,434	5,825,944	1,154,946	4,670,998
Texas	42,210	15,082	27,128	4,714	2,819	1698	1121	25,061,629	23,331,584	3,976,740	19,354,844
Utah	2,091	750	1,341	465	168	103	65	2,728,314	1,968,831	473,518	1,495,313
Vermont	3,369	1,639	1,730	439	309	233	76	446,339	335,035	140,580	194,455
Virginia	11,792	1,782	10,010	1,169	613	262	351	6,607,284	6,493,644	200,822	6,292,822
Washington	8,228	4,616	3,612	2,242	459	352	107	6,418,929	4,414,853	2,171,412	2,243,441
West Virginia	5,107	479	4,628	492	270	84	186	1,509,947	1,245,977	144,249	1,101,728
Wisconsin	28	28	-	1,070	25	25	-	4,015,261	44,374	44,374	-
Wyoming	282	73	209	313	104	66	38	449,992	249,703	69,382	180,321
Total	**309,980**	**113,568**	**196,412**	**49,932**	**17,437**	**10,864**	**6,573**	**292,598,036**	**197,410,822**	**51,184,248**	**146,226,574**

[1] These numbers were generated using the SDWIS Pivot Tables.

Exhibit B.19: SYR3 ICR Inventory Analysis for Haloacetic Acids (2011; CWS only)

State	HAA5; CWSs										
	Number of Records			Number of Systems				Population Served			
	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW
Alabama	6,807	432	6,375	528	355	118	237	5,515,724	4,902,540	865,938	4,036,602
Alaska	2,427	660	1,767	435	151	54	97	609,336	520,572	155,486	365,086
American Samoa	30	30	-	19	7	7	-	60,958	58,424	58,424	-
Arizona	2,098	1,107	991	780	435	391	44	6,225,100	6,038,180	2,419,713	3,618,467
Arkansas	7,811	1,428	6,383	710	290	137	153	2,709,389	1,783,544	501,960	1,281,584
California	1,824	63	1,761	3,027	94	32	62	40,956,858	7,803,736	69,087	7,734,649
Colorado	3	-	3	877	2	-	2	5,386,406	4,320	-	4,320
Connecticut	7,598	1,279	6,319	542	214	139	75	2,656,236	2,689,447	184,999	2,504,448
Delaware	-	-	-	216	-	-	-	899,801	-	-	-
District of Columbia	-	-	-	5	-	-	-	606,730	-	-	-
Florida	4,151	3,216	935	1,728	668	618	50	19,219,921	18,024,160	13,917,894	4,106,266
Georgia	-	-	-	1,776	-	-	-	8,432,935	-	-	-
Hawaii	1,111	292	819	110	52	42	10	1,460,540	1,244,496	1,079,642	164,854
Idaho	457	301	156	745	162	104	58	1,100,437	924,127	628,530	295,597
Illinois	18,097	2,682	15,415	1,751	910	335	575	12,128,970	10,979,398	2,024,914	8,954,484
Indiana	1,393	755	638	813	493	439	54	4,870,296	4,466,148	2,245,441	2,220,707
Iowa	7,526	2,108	5,418	1,122	399	258	141	2,741,931	2,110,974	795,738	1,315,236
Kansas	4,839	1,181	3,658	887	281	148	133	2,676,572	2,166,015	488,169	1,677,846
Kentucky	2,146	102	2,044	402	206	62	144	4,441,302	3,309,765	290,286	3,019,479
Louisiana	7,448	3,854	3,594	1,049	492	413	79	4,921,528	3,651,102	2,143,384	1,507,718
Maine	1,708	456	1,252	378	108	56	52	664,022	565,696	92,109	473,587
Maryland	-	-	-	474	-	-	-	5,192,667	-	-	-
Massachusetts	-	-	-	527	-	-	-	9,317,400	-	-	-
Michigan	2,205	1,219	986	1,397	142	113	29	7,615,948	830,488	462,004	368,484
Minnesota	506	260	246	961	81	65	16	4,262,862	420,439	189,104	231,335
Mississippi	4	4	-	1,106	4	4	-	3,152,270	5,976	5,976	-
Missouri	8,678	1,662	7,016	1,474	196	123	73	5,171,584	3,549,115	828,103	2,721,012
Montana	1,971	679	1,292	698	134	85	49	713,698	497,909	125,733	372,176
Nebraska	1,440	276	1,164	589	50	26	24	1,479,705	1,131,964	190,594	941,370
Nevada	3,208	583	2,625	211	102	74	28	2,557,680	2,472,740	141,010	2,331,730
New Hampshire	-	-	-	705	-	-	-	855,402	-	-	-
New Jersey	24,155	8,071	16,084	612	489	328	161	8,998,715	8,955,532	2,208,632	6,746,900
New Mexico	2,932	1,201	1,731	600	171	135	36	1,810,927	1,538,100	639,837	898,263
New York	17,980	3,276	14,704	2,466	876	429	447	17,828,851	12,655,616	583,249	12,072,367
North Carolina	5,978	1,901	4,077	2,081	1,072	639	433	7,622,946	7,349,321	1,288,618	6,060,703
North Dakota	1,510	521	989	332	95	68	27	581,311	480,443	133,795	346,648

State	HAA5; CWSs										
	Number of Records			Number of Systems				Population Served			
	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW	SDWIS Total[1]	SYR3 Total	SYR3 GW	SYR3 SW
Ohio	18,182	3,991	14,191	1,240	682	404	278	10,411,689	9,567,549	2,185,957	7,381,592
Oklahoma	10,409	1,380	9,029	1,095	411	195	216	3,542,286	2,913,745	434,877	2,478,868
Oregon	1,133	188	945	875	365	150	215	3,374,323	3,073,661	300,653	2,773,008
Pennsylvania	1,546	45	1,501	2,061	157	24	133	10,744,868	6,512,979	77,165	6,435,814
Rhode Island	182	14	168	89	20	6	14	989,055	827,645	106,511	721,134
South Carolina	8,056	870	7,186	600	173	94	79	3,822,295	2,815,443	288,010	2,527,433
South Dakota	226	74	152	456	63	40	23	719,433	475,445	130,356	345,089
Tennessee	2,815	95	2,720	479	288	49	239	6,309,434	5,825,944	1,154,946	4,670,998
Texas	38,268	10,686	27,582	4,714	2,110	1050	1060	25,061,629	21,432,756	2,350,024	19,082,732
Utah	2,254	744	1,510	465	156	92	64	2,728,314	1,947,299	453,486	1,493,813
Vermont	2,052	294	1,758	439	117	43	74	446,339	218,358	24,663	193,695
Virginia	12,460	1,163	11,297	1,169	522	171	351	6,607,284	6,454,437	161,615	6,292,822
Washington	-	-	-	2,242	-	-	-	6,418,929	-	-	-
West Virginia	6,069	564	5,505	492	269	83	186	1,509,947	1,245,869	144,141	1,101,728
Wisconsin	28	28	-	1,070	25	25	-	4,015,261	44,374	44,374	-
Wyoming	282	73	209	313	104	66	38	449,992	249,703	69,382	180,321
Total	**252,003**	**59,808**	**192,195**	**49,932**	**14,193**	**7,934**	**6,259**	**292,598,036**	**174,735,494**	**42,684,529**	**132,050,965**

[1] These numbers were generated using the SDWIS Pivot Tables.

Cumulative Distributions of Mean Concentrations for THM4 and HAA5

Using the SYR3 ICR data for THM4 and HAA5, EPA compared the occurrence of these analytes in systems of different sizes and source water types. In this analysis, average THM4 and HAA5 concentrations were calculated in for each year between 2006 and 2011. Exhibit B.20 and Exhibit B.21 below present summary information for the average THM4 and HAA5 value per system, respectively.

Exhibit B.20: System Means from the SYR3 ICR THM4 Data; 2006-2011

System Size	Year	THM4 System Means; Ground Water Systems					THM4 System Means; Surface Water Systems				
		Count of Systems	Mean	90%ile	95%ile	% System Means > 80 µg/L	Count of Systems	Mean	90%ile	95%ile	% System Means > 80 µg/L
<=10,000	2011	10,052	14.5	44.4	61.6	1.9%	5,067	43.58	73.0	85.6	6.9%
>10,000	2011	982	17.6	46.8	57.4	0.3%	1,707	35.23	58.9	65.2	0.9%
<=10,000	2010	14,763	12.2	38.0	56.5	1.7%	5,157	44.0	74.0	89.1	7.1%

System Size	Year	THM4 System Means; Ground Water Systems					THM4 System Means; Surface Water Systems				
		Count of Systems	Mean	90%ile	95%ile	% System Means > 80 µg/L	Count of Systems	Mean	90%ile	95%ile	% System Means > 80 µg/L
>10,000	2010	1,004	17.1	46.9	58.4	0.2%	1,703	35.9	57.9	65.8	1.1%
<=10,000	2009	9,953	15.6	46.0	62.6	1.9%	5,065	45.0	75.8	91.0	7.9%
>10,000	2009	980	17.3	47.1	57.9	0.5%	1,716	35.9	59.3	65.7	1.2%
<=10,000	2008	10,188	14.5	45.5	62.8	2.1%	5,058	46.3	78.4	98.0	9.3%
>10,000	2008	937	16.9	47.8	57.8	0.4%	1,696	37.0	61.9	69.7	1.8%
<=10,000	2007	14,233	12.4	38.8	58.9	1.9%	5,341	48.4	83.6	106.0	11.6%
>10,000	2007	947	16.9	48.1	58.2	0.6%	1,680	37.6	61.9	70.0	2.0%
<=10,000	2006	9,803	16.1	48.0	68.3	3.1%	5,175	48.6	83.8	109.2	11.7%
>10,000	2006	893	16.4	46.6	57.8	0.7%	1,679	36.4	60.8	67.4	1.3%

Exhibit B.21: System Means from the SYR3 ICR HAA5 Data; 2006-2011

System Size	Year	HAA5 System Means; Ground Water Systems					HAA5 System Means; Surface Water Systems				
		Count of Systems	Mean	90%ile	95%ile	% System Means > 60 µg/L	Count of Systems	Mean	90%ile	95%ile	% System Means > 60 µg/L
<=10,000	2011	8,931	6.4	17.5	29.5	0.7%	4,943	23.7	44.0	52.6	2.7%
>10,000	2011	899	7.2	21.8	28.3	0.2%	1,622	21.1	38.8	46.0	1.0%
<=10,000	2010	13,314	5.1	14.8	24.9	0.7%	5,016	25.1	46.8	55.0	3.4%
>10,000	2010	925	6.7	21.0	28.5	0.1%	1,620	21.5	39.0	45.6	0.7%
<=10,000	2009	9,027	7.0	19.9	31.2	1.0%	4,922	26.2	48.5	58.4	4.5%
>10,000	2009	897	7.1	21.0	29.6	0.0%	1,635	21.9	40.9	46.3	1.0%
<=10,000	2008	9,255	6.6	18.3	30.0	1.2%	4,921	27.8	50.2	61.6	5.2%
>10,000	2008	867	6.8	21.0	27.9	0.0%	1,611	22.1	39.9	45.6	0.7%
<=10,000	2007	12,828	6.5	16.1	29.0	1.2%	5,166	27.8	52.6	64.7	6.2%
>10,000	2007	868	6.9	21.1	28.2	0.1%	1,596	22.9	42.7	48.6	1.3%
<=10,000	2006	9,040	7.9	21.6	35.4	1.6%	5,024	28.0	53.2	66.1	7.0%
>10,000	2006	827	7.0	20.6	28.2	0.1%	1,593	23.2	42.8	48.9	1.4%

Highest Value Measurements of THM4 and HAA5

A fundamental question is how much DBP exposure/risk reduction we can anticipate to the U.S. population following the implementation of the D/DBPRs. The primary difference between the Stage 1 and Stage 2 D/DBPRs was the incorporation of a locational running annual average (LRAA) compliance monitoring requirement, which was intended to limit the repeated occurrence of high DBP levels at a given location in a distribution system. Using the SYR3 ICR DBP dataset, EPA analyzed the highest reported values for THM4 and HAA5 to determine their occurrence and related exposure throughout 2006–2011. For the purposes of this analysis, the highest regulated organic DBP value for each CWS and non-transient non-community water system (NTNCWSs) was used to generate summary information by system size, source water type and year. Statistical endpoints include the median of all highest values, the mean of all highest values, the 95th and 99th percentiles of all highest values, the percentage of systems whose highest DBP result is greater than the MCL, and the percentage of the population served by systems whose highest DBP level is greater than the MCL. Results are presented for all systems as well as GW, SW, GWP and SWP systems. Additionally, results are presented for all years as well as just 2011.

It is expected that the highest levels of the individual THM4 and HAA5 species can also be reviewed using the SYR3 ICR data; however, the DBP group analytical results are reported for compliance and thus only the analyses reflecting THM4 and HAA5 are presented below. In this analysis, the non-detection records were substituted with zero for all average concentration calculations. For those systems and plants that only reported non-detection records within a given year, the highest value would be equal to zero, as all non-detections were set equal to zero for this analysis. For those instances where 95th percentiles were based on less than 20 system means, and where 99th percentiles were based on less than 100 system means, EPA chose to not present these results because they were not believed to be reliable estimates. As previously mentioned, the NPDWR for THM4 and HAA5 under the Stage 1 D/DBPR is based on a RAA of monitoring samples, and the summary statistics within the tables below are not an indication of any MCL violations. Further, EPA anticipates that many of these peak concentrations will have been significantly lowered based on a number of factors, including system treatment changes made to more easily comply with the Stage 1 D/DBPR and the implementation of the 2006 Stage 2 D/DBPR, which was designed, in part, to lower such occurrences.

The population served is an overestimation of the true population exposed because of the way this estimate was derived. In this estimate, the entire retail population served by a system was counted for each system included in the analysis. Only the highest THM4/HAA5 value per system was used for analysis. In these cases, the true population exposed to such elevated concentrations would more appropriately be considered as those consumers associated with the specific sampling location where the highest THM4/HAA5 value was measured. However, the population served associated with specific sampling locations is often difficult to know and is not reported along with other SYR3 ICR compliance monitoring records. Given these constraints, this evaluation considered the total retail population as an upper-bound for potential exposure to these contaminants.

In addition to the highest value tables for CWSs in all years, additional tables below show the summary statistics of the highest THM4 and HAA5 values per NTNCWS across all years of the SYR3 ICR database as well as just for 2011.

Trihalomethanes

Exhibit B.22 presents the results from the THM4 highest value analysis for CWSs for 2011 split up by system size, and Exhibit B.23 presents the results from the THM4 highest value analysis for CWSs for the entire 2006-2011 period split up by year. Exhibit B.24 and Exhibit B.25 present similar information for NTNCWSs.

Exhibit B.22: Highest THM4 Value for CWSs (2011)

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	>=500K	67.7	89.6	143.3	--	29.4%	36.7%
	100K - <500K	58.8	69.6	129.1	246.4	32.7%	35.6%
	10K - <100K	71.0	77.1	126.0	175.9	37.7%	36.5%
	500 - <10K	63.0	66.1	142.0	201.7	33.0%	34.2%
	<500	36.8	53.6	151.0	273.0	21.8%	27.0%
	All sizes	**61.9**	**67.6**	**137.2**	**218.6**	**32.5%**	**36.2%**
SWP	>=500K	--	--	--	--	--	--
	100K - <500K	56.0	53.7	80.4	--	5.0%	2.7%
	10K - <100K	57.9	62.2	113.4	160.6	26.2%	25.7%
	500 - <10K	60.3	67.3	131.0	181.0	29.7%	28.9%
	<500	54.9	60.7	121.2	204.3	25.9%	29.0%
	All	**58.2**	**64.7**	**125.0**	**180.9**	**27.9%**	**20.2%**
GW	>=500K	67.6	61.6	--	--	37.5%	31.3%
	100K - <500K	37.0	37.6	88.4	--	6.3%	7.0%
	10K - <100K	22.2	31.8	92.7	134.0	8.5%	9.4%
	500 - <10K	11.7	27.6	97.9	169.6	8.6%	9.5%
	<500	2.0	13.3	67.0	128.0	3.6%	4.6%
	All	**6.8**	**21.8**	**88.0**	**149.4**	**6.3%**	**11.6%**
GWP	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	37.5	35.1	--	--	0.0%	0.0%
	500 - <10K	18.6	28.9	84.4	130.1	6.9%	7.1%
	<500	20.2	31.5	90.9	203.9	7.8%	6.7%
	All	**20.0**	**30.3**	**87.0**	**135.8**	**7.0%**	**3.5%**
All Sources	>=500K	67.7	84.3	118.3	--	31.0%	35.9%
	100K - <500K	51.0	58.2	123.0	171.8	22.1%	25.5%
	10K - <100K	45.2	51.8	115.9	160.0	21.1%	21.9%
	500 - <10K	32.1	43.6	120.0	184.0	18.0%	20.3%
	<500	5.0	22.7	95.2	162.1	7.8%	9.9%

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	All sizes and sources	**22.2**	**37.6**	**112.0**	**177.5**	**14.9%**	**26.4%**

On average, the maximum THM4 value reported by SW and SWP systems was around 60 µg/L, below the MCL of 80 µg/L. The percentage of GW systems that reported a maximum THM4 concentration above the MCL was far lower than the percentage of SW systems that reported a maximum concentration above the MCL, indicating that relatively higher THM4 values were commonly associated with SW systems. A particularly interesting statistic is the percent of systems with maximum values greater than the MCL. In nearly all SW system size categories, more than 25 percent of systems had at least one maximum THM4 value greater than the MCL. Comparatively, only one size category of GW systems had more than 25 percent of systems reporting a THM4 value above 80 µg/L. The difference between the source water types is considerable, as most GW categories had less than 10 percent of systems with detections greater than the MCL.

Exhibit B.23: Highest THM4 Value per CWS (2006-2011)

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	2006	66.0	73.0	155.3	265.4	36.1%	45.4%
	2007	65.0	73.2	164.5	277.0	36.6%	37.0%
	2008	66.6	72.6	157.9	257.0	38.0%	36.6%
	2009	63.6	69.2	146.0	226.8	33.9%	27.8%
	2010	63.5	68.8	146.0	236.3	34.6%	33.7%
	2011	61.9	67.6	137.2	218.6	32.5%	36.2%
SWP	2006	66.1	71.3	154.6	243.9	36.5%	29.0%
	2007	65.8	70.7	150.0	239.7	35.0%	26.5%
	2008	63.0	68.5	142.0	217.3	33.3%	27.3%
	2009	61.6	66.3	127.0	190.9	30.3%	23.0%
	2010	61.0	64.5	128.7	185.3	27.8%	25.2%
	2011	58.2	64.7	125.0	180.9	27.9%	20.2%
GW	2006	6.8	24.1	98.0	190.8	7.7%	12.7%
	2007	4.1	19.1	85.8	164.1	5.7%	13.8%
	2008	6.0	22.5	91.8	161.9	6.7%	13.4%
	2009	7.8	23.2	90.5	154.1	6.7%	15.2%
	2010	5.0	17.7	78.8	135.7	4.7%	14.6%

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	2011	6.8	21.8	88.0	149.4	6.3%	11.6%
GWP	2006	16.0	35.1	133.3	272.7	12.3%	7.9%
	2007	15.2	30.6	109.2	215.8	9.9%	14.1%
	2008	17.2	34.2	104.4	251.6	10.6%	5.4%
	2009	17.0	33.4	102.0	216.8	9.7%	17.5%
	2010	15.4	28.2	90.4	158.7	7.1%	7.7%
	2011	20.0	30.3	87.0	135.8	7.0%	3.5%
All	**2006**	**24.0**	**41.7**	**128.4**	**226.0**	**18.1%**	**32.6%**
	2007	**12.9**	**35.0**	**122.0**	**210.0**	**14.7%**	**27.6%**
	2008	**22.0**	**39.7**	**124.6**	**201.0**	**17.1%**	**27.7%**
	2009	**23.5**	**39.1**	**117.0**	**186.0**	**15.7%**	**23.1%**
	2010	**13.0**	**31.7**	**109.0**	**171.0**	**12.3%**	**26.1%**
	2011	**22.2**	**37.6**	**112.0**	**177.5**	**14.9%**	**26.4%**

Exhibit B.23 shows that, over these six years, there have been decreases in both the percent of systems with detections above the MCL and the population served by systems with detections greater than the MCL. The summary table for 2006-2011 demonstrates that higher levels of THM4 occurred in GWP systems as opposed to GW systems (with 2011 being the only exception to this), which could be a result of increased water residence time in purchased systems. Additionally, the yearly means in the SW and SWP categories show no considerable differences. Over time, there have been decreases in both the percent of systems with detections above the MCL and the population served by systems with detections greater than the MCL. This could be the outcome of a number of changes over the six-year period, such as changes in disinfection practices, or other factors.

Exhibit B.24: Highest THM4 Value per NTNCWS (2011)

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	--	--	--	--	--	--
	500 - <10K	66.7	71.0	131.7	--	35.9%	36.6%
	<500	41.9	48.7	109.9	193.9	18.0%	14.5%
	All	**50.0**	**56.1**	**129.6**	**217.3**	**24.0%**	**32.3%**
SWP	>=500K	--	--	--	--	--	--
	100K - <500K	14.4	14.4	--	--	0.0%	0.0%

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	10K - <100K	84.7	82.4	--	--	60.0%	37.1%
	500 - <10K	49.5	50.0	98.2	--	14.7%	27.7%
	<500	26.2	47.2	117.0	--	16.9%	17.3%
	All	**46.1**	**49.3**	**113.7**	**142.0**	**18.0%**	**17.1%**
GW	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	6.8	6.6	--	--	0.0%	0.0%
	500 - <10K	4.7	16.2	67.2	161.1	3.5%	4.9%
	<500	2.3	19.6	69.9	187.5	3.8%	3.5%
	All	**2.8**	**18.9**	**69.9**	**184.5**	**3.7%**	**4.1%**
GWP	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	--	--	--	--	--	--
	500 - <10K	38.9	35.9	--	--	0.0%	0.0%
	<500	10.0	28.3	127.3	--	8.3%	13.3%
	All	**19.1**	**30.0**	**104.5**	--	**6.5%**	**3.9%**
All S	>=500K	--	--	--	--	--	--
	100K - <500K	14.4	14.4	--	--	0.0%	0.0%
	10K - <100K	55.0	48.7	--	--	33.3%	21.0%
	500 - <10K	8.0	24.7	99.8	176.0	7.8%	10.2%
	<500	3.3	22.6	81.1	189.7	5.2%	5.0%
	All Sizes and Sources	**4.3**	**23.1**	**86.7**	**190.2**	**5.9%**	**9.6%**

There were limited data available for analysis from the larger NTNCWSs. With this said, it is clear that there were no averages or medians above the MCL of 80 µg/L across all size categories, with the exception of medium-sized SWP systems (10K-<100K; mean reported concentration is 82.4 µg/L). A notable observation is that GWP systems had much higher concentrations for the mean concentration and 95 percent percentile when compared to GW, which could be explained by the increased residence time of water in purchased systems.

Exhibit B.25: Highest THM4 Value per NTNCWS (2006-2011)

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	2006	50.2	58.4	140.0	262.5	28.7%	37.8%
	2007	43.0	55.9	153.2	265.3	23.8%	35.7%
	2008	46.8	57.2	159.2	275.3	24.1%	30.7%
	2009	51.0	59.1	146.2	198.6	28.4%	38.7%

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	2010	46.7	52.0	130.6	190.8	22.1%	35.6%
	2011	50.0	56.1	129.6	217.3	24.0%	32.3%
SWP	2006	42.0	56.1	133.0	--	20.0%	1.4%
	2007	51.2	65.7	182.9	--	25.0%	7.4%
	2008	39.1	55.8	124.8	--	25.8%	7.0%
	2009	38.5	49.9	113.6	--	19.6%	5.0%
	2010	35.4	44.4	113.8	124.9	12.5%	3.9%
	2011	46.1	49.3	113.7	142.0	18.0%	17.1%
GW	2006	2.9	18.2	80.1	216.6	5.0%	2.8%
	2007	3.1	14.3	67.4	143.2	3.4%	3.2%
	2008	2.7	16.7	74.2	173.0	4.3%	3.7%
	2009	3.0	19.5	67.4	167.4	4.1%	3.9%
	2010	3.6	15.8	69.1	170.0	3.5%	3.8%
	2011	2.8	18.9	69.9	184.5	3.7%	4.1%
GWP	2006	32.3	50.4	182.5	--	20.0%	7.3%
	2007	34.0	58.1	109.9	--	18.2%	1.8%
	2008	18.4	25.2	61.0	--	3.3%	0.7%
	2009	22.6	27.4	91.3	--	9.1%	4.3%
	2010	19.0	27.5	83.3	--	9.1%	3.3%
	2011	19.1	30.0	104.5	--	6.5%	3.9%
All	**2006**	**4.5**	**23.1**	**97.2**	**223.6**	**7.6%**	**4.7%**
	2007	**4.1**	**18.6**	**84.3**	**176.8**	**5.4%**	**5.7%**
	2008	**4.0**	**21.2**	**95.5**	**188.2**	**6.5%**	**6.3%**
	2009	**5.2**	**24.3**	**90.2**	**176.4**	**6.8%**	**6.5%**
	2010	**4.5**	**18.9**	**79.6**	**170.6**	**4.9%**	**5.6%**
	2011	**4.3**	**23.1**	**86.7**	**190.2**	**5.9%**	**9.6%**

The results of the THM4 highest value analysis for NTNCWS shows that there has been very little change in system high-value averages over the course of 2006 to 2011, with the exception of the GWP systems (from 50.4 µg/L in 2006 to 30.0 µg/L in 2011). Additionally, there is little variation in the averages between purchased and non-purchased systems. The largest variations are demonstrated by the percentile statistics, where there are fluctuations across years as well as across purchased and non-seller systems. When taking all results into account, there is little difference in the median and mean concentrations across all years, and some improvement within the percentile statistics which could be a result of early adoption of the Stage 2 D/DBPR or other factors.

Haloacetic Acids

Exhibit B.26 presents the results from the HAA5 highest value analysis for CWSs for 2011 split up by system size and Exhibit B.27 presents the results from the HAA5 highest value analysis for CWSs for the entire 2006-2011 period split up by year. Exhibit B.28 and Exhibit B.29 present similar information for NTNCWSs.

Exhibit B.26: Highest HAA5 Value for CWSs (2011)

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	>=500K	36.5	38.5	75.7	--	22.6%	34.0%
	100K - <500K	35.7	41.1	87.7	131.6	15.9%	15.8%
	10K - <100K	41.1	49.7	94.3	140.0	22.9%	21.7%
	500 - <10K	38.0	42.4	94.2	157.3	21.4%	21.8%
	<500	24.0	36.3	109.3	229.3	17.3%	19.7%
	All	**37.0**	**43.3**	**95.0**	**161.2**	**20.9%**	**24.8%**
SWP	>=500K	--	--	--	--	--	--
	100K - <500K	39.0	41.2	--	--	21.1%	13.9%
	10K - <100K	29.0	36.4	81.9	122.7	12.1%	11.7%
	500 - <10K	30.6	34.6	78.4	103.4	12.1%	12.4%
	<500	25.0	32.1	71.0	103.6	9.3%	9.6%
	All	**29.0**	**34.2**	**76.9**	**107.5**	**11.4%**	**12.4%**
GW	>=500K	29.9	26.7	--	--	12.5%	26.4%
	100K - <500K	18.9	20.7	48.8	--	0.0%	0.0%
	10K - <100K	7.5	14.9	53.8	87.7	3.4%	4.0%
	500 - <10K	3.8	11.7	46.2	85.6	2.5%	2.7%
	<500	0.0	6.9	31.5	71.8	1.5%	1.9%
	All	**2.1**	**10.1**	**43.0**	**84.2**	**2.2%**	**6.2%**
GWP	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	14.7	22.0	--	--	0.0%	0.0%
	500 - <10K	4.3	9.8	34.9	51.3	1.1%	0.5%
	<500	4.2	11.5	41.0	94.2	2.6%	2.4%
	All	**4.6**	**11.0**	**41.0**	**88.7**	**1.7%**	**0.4%**
All Sources	>=500K	36.5	36.1	75.4	--	20.5%	32.7%
	100K - <500K	31.7	35.5	78.0	116.3	12.0%	12.1%
	10K - <100K	20.7	30.3	81.6	121.3	11.6%	12.0%
	500 - <10K	14.0	23.2	73.3	115.7	8.7%	10.3%
	<500	1.7	12.9	55.0	103.0	4.0%	4.7%

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	All sizes and sources	**9.5**	**20.9**	**70.6**	**115.4**	**7.6%**	**17.4%**

The mean highest HAA5 values are less than the MCL of 60 µg/L for all source water and system size categories; however, relatively high levels of HAA5 occur primarily in SW systems. Similar to THM4, there are slight reductions in HAA5 levels when comparing SW and SWP systems, however, mean levels were higher in GWP systems as opposed to GW systems. The "All" category shows that HAA5 concentrations greater than the MCL were detected more often in large systems than small systems.

Exhibit B.27: Highest HAA5 Value per CWS (2006-2011)

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	2006	41.4	49.3	112.5	223.8	28.2%	32.3%
	2007	40.3	49.6	115.1	237.5	28.3%	32.9%
	2008	40.0	47.0	108.2	191.9	25.4%	28.4%
	2009	39.3	47.0	107.0	194.4	25.3%	24.7%
	2010	39.0	44.8	104.2	172.5	23.3%	26.4%
	2011	37.0	43.3	95.0	161.2	20.9%	24.8%
SWP	2006	33.1	40.2	93.4	161.5	18.4%	16.4%
	2007	34.8	40.0	93.3	150.2	17.7%	14.5%
	2008	34.1	39.7	92.5	150.3	17.6%	13.6%
	2009	32.2	38.6	91.1	146.8	16.2%	13.6%
	2010	30.9	35.7	83.7	130.0	12.8%	12.9%
	2011	29.0	34.2	76.9	107.5	11.4%	12.4%
GW	2006	2.4	11.8	51.6	110.0	3.4%	3.6%
	2007	0.0	10.4	46.5	110.0	3.0%	3.6%
	2008	1.8	10.9	49.6	96.0	3.2%	6.6%
	2009	2.7	11.2	49.0	96.9	3.2%	6.7%
	2010	1.0	7.8	39.0	76.5	1.9%	2.6%
	2011	2.1	10.1	43.0	84.2	2.2%	6.2%
GWP	2006	4.7	14.8	58.0	133.3	4.6%	1.9%

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	2007	3.2	13.5	53.7	157.4	4.6%	4.3%
	2008	4.6	14.0	48.5	134.7	3.8%	8.9%
	2009	4.0	13.2	45.7	116.5	3.2%	1.2%
	2010	3.5	9.9	35.2	86.5	1.8%	0.6%
	2011	4.6	11.0	41.0	88.7	1.7%	0.4%
All	**2006**	**10.4**	**24.2**	**83.0**	**148.0**	**10.9%**	**20.9%**
	2007	**5.1**	**21.1**	**79.3**	**150.0**	**9.3%**	**20.8%**
	2008	**9.6**	**22.9**	**80.0**	**136.5**	**10.0%**	**19.7%**
	2009	**10.6**	**22.9**	**78.0**	**131.5**	**9.8%**	**17.8%**
	2010	**4.7**	**17.5**	**68.3**	**119.0**	**6.8%**	**16.7%**
	2011	**9.5**	**20.9**	**70.6**	**115.4**	**7.6%**	**17.4%**

Over the course of the six years, system maximum HAA5 concentrations have decreased from approximately 148 µg/L in 2006 to 115 µg/L in 2011. These reductions shown in the 99th percentile column could be a result of system changes relative to the Stage 2 D/DBPR, however it is unknown how many systems have made changes in preparation for Stage 2 during the 2006-2011 time period. There are minimal differences between purchased and non-purchased GW systems, however there is some reduction across all statistical endpoints for SW and SWP systems. Overall, average HAA5 maximum concentrations are lower than maximum THM4 concentrations in each year.

Exhibit B.28: Highest HAA5 Value per NTNCWS (2011)

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	--	--	--	--	--	--
	500 - <10K	34.2	39.0	113.1	--	18.8%	12.0%
	<500	14.5	30.2	97.2	130.0	16.2%	16.9%
	All	**21.7**	**33.3**	**102.2**	**133.6**	**17.1%**	**12.9%**
SWP	>=500K	--	--	--	--	--	--
	100K - <500K	20.9	20.9	--	--	0.0%	0.0%

Source Type	System Size	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
	10K - <100K	43.7	48.8	--	--	20.0%	7.5%
	500 - <10K	20.2	26.1	63.9	--	5.9%	7.4%
	<500	13.4	18.2	51.6	--	2.8%	2.8%
	All	**15.9**	**22.0**	**53.8**	**84.3**	**4.5%**	**3.8%**
GW	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	0.3	0.5	--	--	0.0%	0.0%
	500 - <10K	1.0	6.7	32.6	71.1	1.8%	1.8%
	<500	1.1	8.9	38.0	87.0	2.2%	1.8%
	All	**1.0**	**8.4**	**37.1**	**82.8**	**2.1%**	**1.6%**
GWP	>=500K	--	--	--	--	--	--
	100K - <500K	--	--	--	--	--	--
	10K - <100K	--	--	--	--	--	--
	500 - <10K	4.0	5.4	--	--	0.0%	0.0%
	<500	0.0	6.0	20.7	--	0.0%	0.0%
	All	**1.9**	**5.9**	**19.4**	--	**0.0%**	**0.0%**
All	>=500K	--	--	--	--	--	--
	100K - <500K	20.9	20.9	--	--	0.0%	0.0%
	10K - <100K	36.4	27.3	--	--	11.1%	4.3%
	500 - <10K	2.3	11.8	52.5	110.5	4.1%	3.4%
	<500	1.6	10.7	46.8	97.1	3.1%	3.0%
	All	**1.8**	**11.0**	**49.0**	**98.0**	**3.4%**	**3.0%**

Much like THM4, there were limited HAA5 SYR3 ICR data available for analysis from larger NTNCWSs in 2011. The 2011 SYR3 ICR data shows that the SW and SWP systems have higher HAA5 values across the statistical endpoints when compared to GW and GWP systems. Additionally, there are only minor differences between the purchased and non-purchased systems. Median and mean concentrations were also relatively low (when compared to the HAA5 MCL of 60 µg/L) for all systems that reported HAA5 data.

Exhibit B.29: Highest HAA5 Value per NTNCWS (2006-2011)

Source Type	Year	Median (µg/L)	Mean (µg/L)	95%ile (µg/L)	99%ile (µg/L)	Percent of Systems with Highest Value > MCL	Percent of Population Served by Systems with Highest Value > MCL
SW	2006	24.4	35.9	90.1	243.3	16.5%	20.6%
	2007	20.0	31.1	101.8	156.9	13.7%	15.4%
	2008	24.0	59.4	95.9	192.3	15.0%	23.9%
	2009	22.0	32.2	92.0	223.9	13.5%	15.4%
	2010	21.7	27.3	76.0	113.4	10.0%	6.7%
	2011	21.7	33.3	102.2	133.6	17.1%	12.9%
SWP	2006	26.0	31.5	74.5	--	12.6%	8.3%
	2007	28.1	33.1	81.9	--	14.9%	4.1%
	2008	21.8	29.6	84.9	--	11.4%	1.8%
	2009	22.5	26.4	58.4	--	4.1%	3.7%
	2010	19.3	23.3	68.7	101.4	6.7%	2.1%
	2011	15.9	22.0	53.8	84.3	4.5%	3.8%
GW	2006	1.4	10.2	46.2	143.1	3.7%	1.3%
	2007	1.0	8.8	38.3	102.6	2.5%	1.9%
	2008	1.1	10.5	43.5	126.2	3.0%	1.4%
	2009	1.4	9.2	42.6	96.0	2.8%	1.3%
	2010	1.6	8.4	35.1	100.5	2.3%	1.4%
	2011	1.0	8.4	37.1	82.8	2.1%	1.6%
GWP	2006	10.0	19.1	--	--	5.3%	0.2%
	2007	9.0	30.4	62.9	--	9.5%	0.3%
	2008	4.0	10.0	31.7	--	3.4%	0.7%
	2009	3.8	7.4	18.8	--	0.0%	0.0%
	2010	5.0	7.9	24.3	--	0.0%	0.0%
	2011	1.9	5.9	19.4	--	0.0%	0.0%
All	**2006**	**2.3**	**13.2**	**61.5**	**152.3**	**5.1%**	**4.5%**
	2007	**1.5**	**11.0**	**50.9**	**114.0**	**3.6%**	**3.0%**
	2008	**1.7**	**15.0**	**53.1**	**140.0**	**4.2%**	**3.1%**
	2009	**2.3**	**12.0**	**53.8**	**114.6**	**3.8%**	**2.9%**
	2010	**2.2**	**10.0**	**44.0**	**104.8**	**2.9%**	**1.9%**
	2011	**1.8**	**11.0**	**49.0**	**98.0**	**3.4%**	**3.0%**

Over the course of all years and within all system size categories, the median and mean concentrations never exceed the MCL of 60 µg/L. Instead, the values were found to be below approximately 3.0 µg/L for the median and 15.0 µg/L for the mean concentration. Generally speaking, higher HAA5 concentrations are found within surface water monitoring results, as

demonstrated across all statistical endpoints. There are also significantly more non-purchased systems than purchasing systems, the biggest differences in the count of systems can be seen when comparing the GW and GWP categories. Importantly, each year in the "All" category for 99th percentile had values greater than the MCL for HAA5. It is possible that these values occurred in distribution system monitoring locations that produced high concentrations of DBPs due to water chemistry. The reduction in these 99th percentile values (152.3 µg/L in 2006, 98.0 µg/L in 2011) may indicate that high levels of HAA5 do not occur as frequently now as they once did in the past.

B.3.3 Regulated Inorganic DBPs

B.3.3.1 Summary of Stage 1 and 2 D/DBPR Information

No additional information provided in this appendix.

B.3.3.2 New Information since the Stage 2 D/DBPR

Inventory Analyses

Exhibit B.30 and Exhibit B.31 display the SYR3 ICR inventory information for bromate and chlorite, respectively, including the number of records, systems reporting and population served by those reporting for all states and primacy agencies that submitted data for the SYR3 ICR. The results presented below are from both GW (includes GW and GWP) and SW (includes SW, SWP, GU and GUP) systems.

States/primacy entities that were not included in the bromate analysis (either because they did not provide information or because none of their data passed QA/QC) were: Alabama; American Samoa; Colorado; Delaware; Washington, DC; Florida; Georgia; Hawaii; Iowa; Kentucky; Maryland; Massachusetts; Mississippi; New Hampshire; New Jersey; Rhode Island; South Carolina; South Dakota; Tennessee; Texas; Vermont; Washington and Wisconsin.

States/primacy entities that were not included in the chlorite analysis (either because they did not provide information or because none of their data passed QA/QC) were: Alaska; American Samoa; Delaware; Washington, DC; Florida; Georgia; Hawaii; Indiana; Louisiana; Maryland; Massachusetts; Minnesota; Mississippi; New Hampshire; North Dakota; South Carolina; South Dakota; Tennessee; Texas; Utah; Vermont; Washington State; West Virginia and Wisconsin.

Exhibit B.30: SYR3 ICR Inventory Analysis for Bromate (2006–2011)

State	Bromate								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Alabama	-	-	-	-	-	-	-	-	-
Alaska	400	159	241	10	4	6	6,365	1,664	4,701
American Samoa	-	-	-	-	-	-	-	-	-
Arizona	401	25	376	11	5	6	2,442,462	44,030	2,398,432

State	Bromate								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Arkansas	95	-	95	2	-	2	14,883	-	14,883
California	2,961	679	2,282	76	26	50	13,421,783	62,889	13,358,894
Colorado	-	-	-	-	-	-	-	-	-
Connecticut	103	-	103	3	-	3	543,130	-	543,130
Delaware	-	-	-	-	-	-	-	-	-
District of Columbia	-	-	-	-	-	-	-	-	-
Florida	-	-	-	-	-	-	-	-	-
Georgia	-	-	-	-	-	-	-	-	-
Hawaii	-	-	-	-	-	-	-	-	-
Idaho	93	54	39	5	2	3	83,488	82,357	1,131
Illinois	299	217	82	8	6	2	27,859	12,359	15,500
Indiana	141	141	-	5	5	-	17,315	17,315	-
Iowa	-	-	-	-	-	-	-	-	-
Kansas	413	-	413	8	-	8	439,459	-	439,459
Kentucky	-	-	-	-	-	-	-	-	-
Louisiana	1	1	-	1	1	-	7,769	7,769	-
Maine	68	-	68	4	-	4	140,110	-	140,110
Maryland	-	-	-	-	-	-	-	-	-
Massachusetts	-	-	-	-	-	-	-	-	-
Michigan	92	1	91	6	1	5	121,790	2,360	119,430
Minnesota	19	19	-	1	1	-	50	50	-
Mississippi	-	-	-	-	-	-	-	-	-
Missouri	65	48	17	4	2	2	1,172,244	21,544	1,150,700
Montana	104	51	53	11	7	4	11,451	8,401	3,050
Nebraska	53	-	53	1	-	1	258,300	-	258,300
Nevada	1,003	68	935	9	2	7	33,711	6,050	27,661
New Hampshire	-	-	-	-	-	-	-	-	-
New Jersey	-	-	-	-	-	-	-	-	-
New Mexico	91	35	56	3	1	2	611,314	1,239	610,075
New York	89	8	81	10	8	2	14,913	5,320	9,593
North Carolina	507	71	436	8	1	7	1,036,854	17,429	1,019,425
North Dakota	64	-	64	1	-	1	105,549	-	105,549
Ohio	23	2	21	3	2	1	11,887	205	11,682
Oklahoma	479	74	405	7	2	5	836,161	1,544	834,617

State	Bromate								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Oregon	196	1	195	6	1	5	116,504	450	116,054
Pennsylvania	2	1	1	2	1	1	2,450	900	1,550
Rhode Island	-	-	-	-	-	-	-	-	-
South Carolina	-	-	-	-	-	-	-	-	-
South Dakota	-	-	-	-	-	-	-	-	-
Tennessee	-	-	-	-	-	-	-	-	-
Texas	-	-	-	-	-	-	-	-	-
Utah	9	-	9	2	-	2	-	-	-
Vermont	-	-	-	-	-	-	-	-	-
Virginia	832	-	832	9	-	9	1,593,586	-	1,593,586
Washington	-	-	-	-	-	-	-	-	-
West Virginia	45	45	-	1	1	-	11,999	11,999	-
Wisconsin	-	-	-	-	-	-	-	-	-
Wyoming	236	36	200	5	1	4	88,232	2,000	86,232
Total	**8,884**	**1,736**	**7,148**	**222**	**80**	**142**	**23,171,618**	**307,874**	**22,863,744**

Exhibit B.31: SYR ICR Inventory Analysis for Chlorite (2006–2011)

State	Chlorite								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Alabama	985	-	985	17	-	17	1,321,904	-	1,321,904
Alaska	-	-	-	-	-	-	-	-	-
American Samoa	-	-	-	-	-	-	-	-	-
Arizona	427	4	423	6	2	4	2,190,680	1,690	2,188,990
Arkansas	848	-	848	7	-	7	57,643	-	57,643
California	693	2	691	16	2	14	3,057,712	31	3,057,681
Colorado	93	-	93	1	-	1	2,020	-	2,020
Connecticut	315	-	315	3	-	3	57,693	-	57,693
Delaware	-	-	-	-	-	-	-	-	-
District of Columbia	-	-	-	-	-	-	-	-	-
Florida	-	-	-	-	-	-	-	-	-
Georgia	-	-	-	-	-	-	-	-	-
Hawaii	-	-	-	-	-	-	-	-	-

State	Chlorite								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Idaho	3	-	3	2	-	2	488	-	488
Illinois	1,014	33	981	14	1	13	180,905	41,508	139,397
Indiana	-	-	-	-	-	-	-	-	-
Iowa	1,840	483	1,357	14	4	10	190,482	89,892	100,590
Kansas	1,937	287	1,650	19	2	17	511,104	6,086	505,018
Kentucky	1,117	-	1,117	8	-	8	162,940	-	162,940
Louisiana	-	-	-	-	-	-	-	-	-
Maine	111	-	111	2	-	2	33,340	-	33,340
Maryland	-	-	-	-	-	-	-	-	-
Massachusetts	-	-	-	-	-	-	-	-	-
Michigan	93	2	91	7	2	5	122,122	2,692	119,430
Minnesota	-	-	-	-	-	-	-	-	-
Mississippi	-	-	-	-	-	-	-	-	-
Missouri	3,890	-	3,890	23	-	23	1,249,811	-	1,249,811
Montana	1	1	-	1	1	-	1,001	1,001	-
Nebraska	108	75	33	2	1	1	28,350	25,000	3,350
Nevada	1	1	-	1	1	-	250	250	-
New Hampshire	-	-	-	-	-	-	-	-	-
New Jersey	912	99	813	4	1	3	430,389	2,000	428,389
New Mexico	124	-	124	1	-	1	8,092	-	8,092
New York	194	8	186	13	8	5	340,740	5,320	335,420
North Carolina	367	-	367	3	-	3	177,719	-	177,719
North Dakota	-	-	-	-	-	-	-	-	-
Ohio	382	175	207	7	1	6	125,943	18,665	107,278
Oklahoma	2,849	-	2,849	24	-	24	826,012	-	826,012
Oregon	1	-	1	1	-	1	1,000	-	1,000
Pennsylvania	6,273	270	6,003	9	2	7	1,657,310	1,178	1,656,132
Rhode Island	528	-	528	3	-	3	97,987	-	97,987
South Carolina	-	-	-	-	-	-	-	-	-
South Dakota	-	-	-	-	-	-	-	-	-
Tennessee	-	-	-	-	-	-	-	-	-
Texas	-	-	-	-	-	-	-	-	-
Utah	-	-	-	-	-	-	-	-	-
Vermont	-	-	-	-	-	-	-	-	-

State	Chlorite								
	Number of Records			Number of Systems			Population Served		
	Total	GW	SW	Total	GW	SW	Total	GW	SW
Virginia	848	-	848	10	-	10	568,985	-	568,985
Washington	-	-	-	-	-	-	-	-	-
West Virginia	-	-	-	-	-	-	-	-	-
Wisconsin	-	-	-	-	-	-	-	-	-
Wyoming	35	-	35	2	-	2	58,672	-	58,672
Total	**25,989**	**1,440**	**24,549**	**220**	**28**	**192**	**13,461,294**	**195,313**	**13,267,159**

B.3.4 Additional Considerations

No additional information provided in this appendix.

B.4 DBP Compliance Monitoring Data Quality and Analysis Reported under the SYR3 ICR

In February 2011, EPA's Office of Management and Budget approved an extension through 2013 of the ICR. The ICR was updated to reflect the expansion of the NPDWRs and included information pertaining to the surface water treatment rules, D/DBPRs, ground water rule and the filter backwash recycling rule. These data were obtained as part of SYR3.

The data call resulted in over 47 million compliance and water quality records delivered to EPA. The records within the SYR3 ICR database were collected and analyzed using a rigorous QA/QC process, which is described in detail in *The Data Management and Quality Assurance/Quality Control Process for the Third Six-Year Review Information Collection Rule Dataset* (USEPA, 2016i). See that report for the full details of the QA/QC process, as well as data acquisition, storage, management and preparation (for analysis).

For the purposes of reviewing the D/DBPRs during SYR3, EPA compiled the state compliance monitoring datasets containing the records for 13 DBP contaminants: THMs, HAAs, chlorite and bromate. (The datasets for THMs and HAAs included both individual speciation data as well as the regulatory endpoints of TTHM and HAA5). Additionally, EPA compiled a dataset for TOC and alkalinity monitoring records. For the purposes of this document, EPA will refer to these datasets as DBP and TOC datasets, respectively. The following sections provide an overview of the data management steps, highlighting when different approaches were used for the contaminants and water quality parameters analyzed in this report (as opposed to the chemical contaminants regulated under the Chemical Phase Rules and radionuclide contaminants). As described below, a thorough QA/QC process was undertaken to evaluate these DBP and TOC datasets.

B.4.1 Data Management Steps

A number of data management tasks were necessary to prepare the SYR3 datasets for QA/QC review and, ultimately, for data analysis. Due to the fact that some states submitted their data using the EPA-provided SDWIS extract tool and other states submitted their data in different

formats, the two groups of datasets (SDWIS states and Non-SDWIS states) were managed separately. Data for regulated contaminants were reported by states that used the SDWIS extract tool and by non-SDWIS states, while the data on unregulated contaminants were reported only by non-SDWIS states. The following sections provide information on the various data management tasks completed for each state dataset submitted through the ICR.

In order to promote usability, EPA restructured the data submitted from states not using the SDWIS extract tool and eventually consolidated all contaminant monitoring data into one database, including the data for THM4, HAA5, bromate, chlorite, TOC and alkalinity. Primary restructuring steps included importing all datasets into a single database; populating rows to ensure that there was one row of data for every sample analytical result (for example, some states summarized the results of a single method with an "non-detect" or "zero" for all contaminants not detected and individual samples only for those contaminants with a positive result); and "mapping" all data fields from the non-extract states to the final data structure. For more details on these data management steps, see USEPA (2016i).

In addition to the fields provided by the states as part of the SYR3 ICR, EPA added fields to help further characterize the records and/or more easily conduct analyses.

B.4.1.1 Water Source Characterization

To further inform the occurrence analyses, the records were examined as a whole and by system water source type. A field titled "GW_OR_SW" was created to simplify the water source type codes found in the "D_FED_PRIM_SRC_CD" (a code indicating a system's primary source water) field into just two different options. Systems denoted as "GW" were either ground water systems or purchased ground water systems (originally GW or GWP), whereas those denoted as "SW" could be surface water, purchased surface water, ground water under the direct influence of surface water or purchased ground water under the direct influence of surface water systems (originally SW, SWP, GU or GUP).

B.4.1.2 Sample Year Characterization

To facilitate analyses based on yearly trends, the "Sample_Year" field was created to simplify the information listed in "COLLLECTION_END_DT" (the sample collection date) from a date and time to a year format.

B.4.1.3 Flagged Fields

As part of a DBP-specific data processing and QA protocol, three additional fields were created in the database. "Filter_Flag" provides a field to flag records excluded using dataset-specific filters for certain types of records. "Outlier_Flag" provides a field to flag records excluded as outliers, also described as part of Section B.4.3. "Analyze" is analogous to the "Analyze" field included for all the SYR3 contaminants (Chemical Phase Rule contaminants, radionuclides, DBPs, etc.), but also incorporates the other flagged fields to indicate a final decision for including or excluding a record in the occurrence analyses.

B.4.2 SYR3 ICR Data Elements

The SYR3 ICR database includes data collected from states and primacy agencies. There are many different data elements to track items such as laboratory sample results, water system characteristics, and QA/QC processes. A more detailed description of the data and collection efforts is available in USEPA (2016i).

For the purposes of conducting occurrence analyses, the data elements were grouped into several tables and combined using queries to create a coherent and usable dataset. The occurrence analyses often differ between the SYR3 contaminants, and certain elements were used in the DBP and TOC analyses that may not be useful or relevant to other contaminants, and vice versa. Exhibit B.32 lists each of the data elements used for conducting DBP and TOC occurrence analyses, along with a brief description and if the field was used for analytical purposes or only during QA/QC procedures. Any fields that were included in the original datasets but are not listed below were not relevant to conducting the occurrence analyses.

Exhibit B.32: List of the Primary SYR3 ICR Elements Used for Occurrence Analyses

Field Name	Description	Use
Analyte ID	4-digit SDWIS analyte code	Analyses
Analyte Name	Analyte name	Analyses
State Code	Used to identify the state in which a system is located, including tribal systems.	Analyses
PWSID	Public water system identification number (PWSID).	Analyses
System Name	Water system name.	Analyses
System Type	Water system type according to federal requirements. C = Community water system NC = Non-community water system NTNC = Non-transient non-community water system NP = Non-public water system	Analyses
Retail Population Served	Retail population served by the water system.	Analyses
Source Water Type	Primary water source for the water system. GU = Ground water under direct influence of surface water GUP = Purchased GU GW = Ground water GWP = Purchased GW SW = Surface water SWP = Purchased SW	Analyses
Water Facility ID	Unique identifier for each water system facility.	Analyses
Water Facility Type	Type of the water system facility. CC = consecutive connection; CH = common headers; CS = cistern; CW = clear well; DS = distribution system; IG = infiltration gallery; IN = intake; NP = non-piped, purchased;	QA Only

Field Name	Description	Use
	OT = other; PC = pressure control; PF = pumping facility; RS = reservoir; SP = spring; SS = sampling station; ST = storage; TM = transmission main (manifold); TP = treatment plant; WH = well head; WL = well; XX = unknown	
Sampling Point ID	Unique identifier for each sample point.	Analyses
Sampling Point Type	Location type of a sampling point. DS = distribution system; EP = entry point; FC = first customer; FN = finished water; LD = lowest disinfectant residual; MD = midpoint in the DS; MR = point of maximum residence; PC = process control; RW = raw water source; SR = source water point; UP = unit process; WS = water system facility point	QA Only
Source Type	The type of water source, based on whether treatment has taken place. FN = Finished, treated; RW = Raw, untreated; XX = Unknown	Analyses
Sample Type Code	Sample type code. CO = confirmation; DU = duplicate; FB = field blank; MR = maximum residence time; MS = matrix spike; OT = other; RP = repeat; RT = routine; RW = raw water; SB = shipping blank; SP = special; TE = technical evaluation	QA Only
Six Year ID	Unique identifier for each sample analytical result. Used as primary key to link multiple tables.	Analyses
Sample Collection Date	Sample collection date.	Analyses
Detection limit value	Limit below which the specific lab indicated they could not reliably measure results for a contaminant with the methods and procedures used by the lab.	Analyses
Detection limit unit	Units of the detection limit value	Analyses
Detection limit code	Indicates the type of Detection Limit reported in the Detection Limit Value column (e.g., the Minimum Reporting Level, Laboratory Reporting Level, etc.)	Analyses
Detect	Added by EPA to indicate whether the result was a detection record (1) or a non-detection record (0), based off of the sample analytical result fields in the raw datasets.	Analyses
Value	Actual numeric (decimal) value of the concentration for the chemical result. This value is equal to zero if the analytical result is less than the contaminant's MRL.	Analyses
Units	Unit of measurement for the analytical results reported. All DBP records were converted to µg/L for analytical purposes. All TOC and alkalinity records were converted to mg/L for analytical purposes. Added by EPA.	Analyses
Analyze[1]	If record was flagged during initial QA/QC process, field contains "Y" or "N" indicating whether the record should be included in occurrence analyses or not. Added by EPA.	Analyses
GW_or_SW[2]	Added by EPA to aid in analyses based on of source water type, derived from the "Source Water Type" field.	Analyses
Sample_Year[2]	Added by EPA to aid in analyses based on year, derived from the "Sample Collection Date" field.	Analyses
Filter_Flag[3]	Flags records for occurrence analysis inclusion or exclusion based on the filter criteria outlined in Section B.4.3.	QA Only

Field Name	Description	Use
Outlier_Flag[3]	Flags records for occurrence analysis inclusion or exclusion based on the outlier criteria outlined in Section B.4.3.	QA Only

[1] The "Analyze" data element is not being posted online. However, only data where "Analyze" = "Y" (i.e., data that passed QA) are being posted.

[2] Although these data elements were used in the analyses, they are not being posted with the data online. The data elements from which they are derived are being posted, however.

[1] These data elements are not being posted online, as they were used for "QA only."

B.4.3 QA/QC Steps

The SYR3 QA/QC effort encountered a range of data quality issues across contaminants and states. Quality control measures were established to identify records that fit certain criteria using a two-step process. The first round of QA/QC was established at the time of data submission, when flags fitting exclusion criteria were run against a state's data submission. During this first round of QA/QC, flagged records were sent back to the state for input on the accuracy of the flagged records. These QA/QC steps were applied to all regulated contaminant monitoring data in the SYR3 ICR database. See USEPA (2016i) for complete details on the first round of the SYR3 QA/QC process. The second round of QA/QC procedures allows for the exclusion (via filters, see below) of contaminant specific records that do not fit within the contaminant's rule requirement context.

EPA created several automated data QA checks within the state SDWIS Query Extract Tool to identify potential common entry errors or numerical inconsistencies. These QA checks identified (or "flagged") records of potential data quality concerns. EPA sent out a detailed report to each state describing their flagged records; EPA requested that each state provide the appropriate disposition (delete, make corrections, etc.) of these records. Exhibit B.33 lists all of the QA/QC flags and respective descriptions for the SYR3 ICR database. See USEPA (2016i) for complete details on the records flagged for potential data quality concerns.

Exhibit B.33: Description of the SYR3 ICR QA/QC Flags

Flag Code	Description	Decision/Action
Outside date range	Identified all data from outside the date range of the SYR3 (i.e., prior to 1/1/2006 or after 12/31/2011).	All records from outside of the SYR3 date range were flagged to be excluded from the analysis.
Duplicate	Identified all detection records with the same PWSID, sample point ID, analyte, sample collection date and concentration.	As is consistent with SYR2, all contaminant records identified as potential duplicates were included in the analysis unless the state responded to say that the records were indeed duplicates and one set should be excluded from the analysis.
Missing Inventory	Identified all data from systems with missing inventory data (i.e., source water type or population served).	All records from systems with missing inventory data were flagged to be excluded from the analysis.

Flag Code	Description	Decision/Action
Non-compliance samples	Identified any non-compliance samples (i.e., samples with COMPL_PURP_IND_CD (compliance purpose indicator code) equal to "N").	All records flagged as not being "for compliance" were flagged to be excluded from the analysis.
Non-public water systems	Identified all data from non-public water systems.	All records from non-public water systems were flagged to be excluded from the analysis.
Sample Type Code (Non-routine)	Identified records that are compliance monitoring samples but have a sample type code of something not for compliance purposes in [TSASAMPL_TYPE_CODE].	Samples that were not for compliance purposes, such as special samples or for performance evaluation, were excluded.
Transient	Identified records from transient systems (i.e. system type equal to "NC" (non-community)).	Unless a state responded to say that the system in question used to be a CWS and NTNCWS at the time of sampling (and thus the records should be included), all data from transients was excluded from the occurrence analysis (except for rules that transients are required to monitor).
Units	Identified all records when the units reported are not one of the standard units used for the particular contaminant	All records in non-standard units were flagged to be excluded from the analysis unless there was strong evidence of the correct standard unit to use (e.g., obvious data entry error, concentration was within the range of standard units and all other records from the state are reported in the standard units).
Outlier Analysis and Removal[2]	Identified all detected concentrations that were greater than four times the contaminant's Maximum Contaminant Level (MCL), 10xMCL and 100xMCL. Also, identified all detected concentrations that were less than the contaminant's minimum Method Detection Limit (MDL), 1/10xMDL and 1/100xMDL.	Any changes suggested by the states were implemented for these records. For example, some states wrote back to say there were "no errors" in their high detect concentrations or that they had "no reason or evidence to show these data to be invalid." Other states responded that "all of the high results were due to using mg/L when they should have been ug/L." EPA's occurrence analyses for DBPs utilized the upper and lower outlier thresholds of 100xMCL and 1/100xMDL, respectively. EPA used the 100xMCL threshold for national, multi-year occurrence analyses for DBPs. For the TOC dataset, all TOC results greater than 100 mg/L and all alkalinity results greater than 1,500 mg/L were excluded from occurrence analyses, as this was consistent to the highest values evaluated from the DBP ICR Database. Additionally, EPA used low level thresholds of 0.1 mg/L and 1.0 mg/L for TOC and alkalinity, respectively; the reasoning behind these thresholds being that they were representative of the lower levels reported by multiple EPA-approved methods.
Sampling Point Location Type & Water Facility Type[1]	Removed any DBP records with sampling point location types not clearly associated with DBP compliance and the distribution system, such as raw water sources.	This step was based on two fields, TSASMPPT_TYPE_CODE and TYPE_CODE. This step removes any records with sampling point location types not clearly associated with DBP compliance and the distribution system, such as raw water sources. For records whose sampling point location type was either null or labeled as a generic "Water System Facility Point," an additional filter was added to make sure any records with a water system facility type that was likely associated with the distribution system were not excluded. After this process, the records remaining are only those that were likely sampled at points relevant to the D/DBPR compliance regulations.

[1] This field was created and used only in the DBP datasets.

[2] TOC and Alkalinity inventory analyses in Chapter 6 and this appendix do not reflect the exclusion data less than the low-level outlier thresholds. However, the low-level outliers were removed for all occurrence analyses presented.

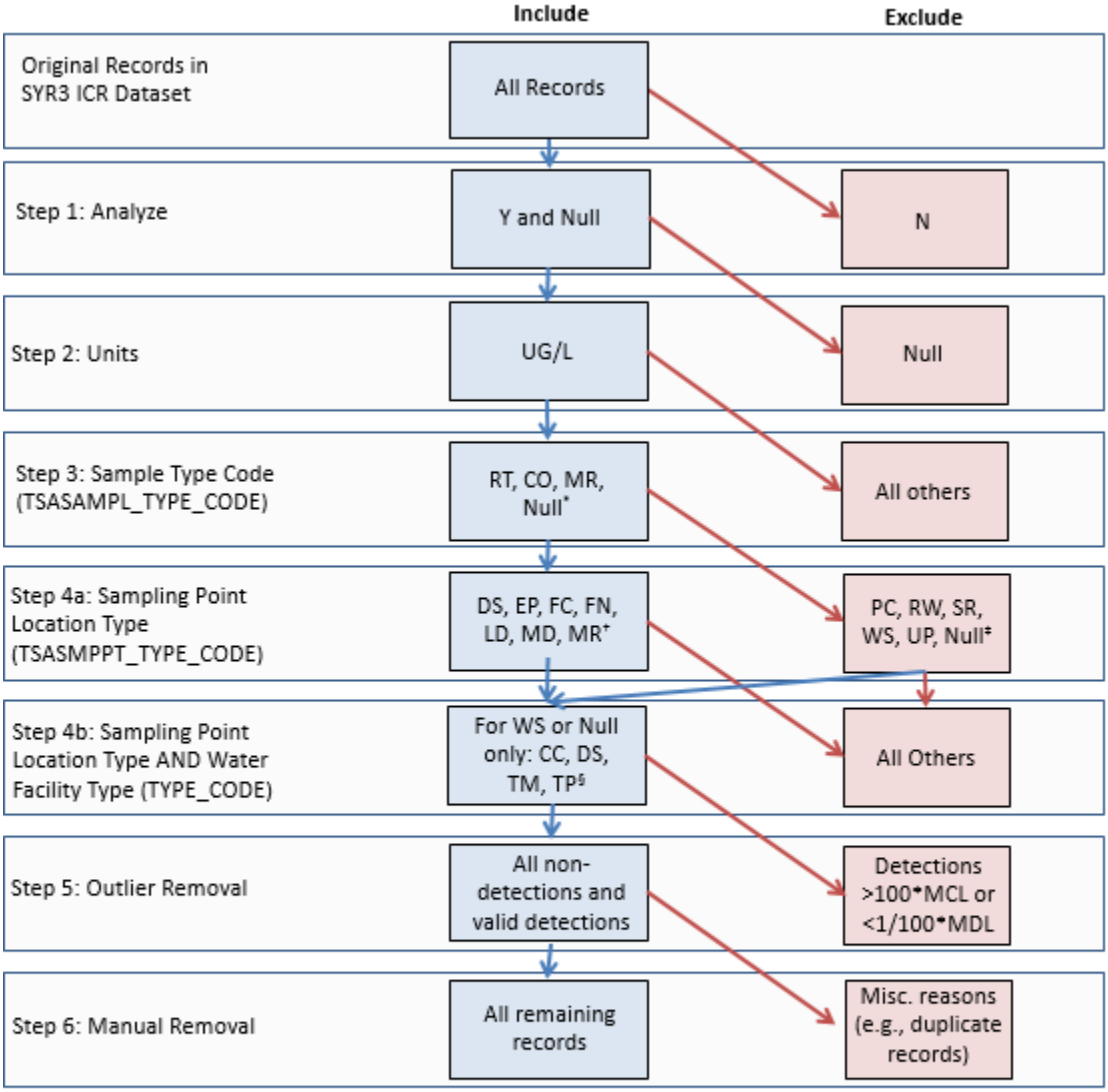
B.4.4 Filters

Following the rigorous QA/QC efforts, records that did not pass the QA/QC evaluation outlined above were excluded from the occurrence analyses. The following sections provide the specific criteria used to determine records to include in the DBP and TOC analyses.

B.4.4.1 Filters for the SYR3 DBP and TOC Datasets

EPA determined that several other fields could be used to filter out records from the occurrence analyses for various reasons, such as any records from a sampling location point that occur prior to disinfection and thus have no relevance to the D/DBPR compliance statutes. These criteria are specific to the Stage 1 and 2 D/DBPRs and were not used for any other contaminants in the SYR3 ICR database (i.e., the contaminants regulated under the Phase Chemical Rules, the radionuclide contaminants or TOC). A logic flowchart was developed, as depicted in Exhibit B.34, to filter out certain records from the occurrence analyses.

Exhibit B.34: Logic Flowchart for Filtering Records in the SYR3 ICR DBP and TOC Datasets[1]



*RT: routine; CO: confirmation; MR: maximum residence time
†DS: distribution system; EP: entry point; FC: first customer; FN: finished; LD: lowest disinfectant residual; MD: midpoint of distribution system; MR: maximum residence time
‡PC: process control; RW: raw water source; SR: source water point; WS: water system facility point; UP: unit process
§CC: consecutive connection; DS: distribution system; TM: transmission main; TP: treatment plant

[1] Each step indicates which fields were used, and the relevant criteria for including or excluding records are denoted in the blue and red boxes. Note that not all filters/steps were applied to the TOC dataset.

The logic for each step in the filtering process is indicated as follows:

Step 1: Analyze: EPA created the "Analyze" field to record the results of a rigorous QA/QC process and feedback from states on whether or not certain records should be excluded from the occurrence analyses for reasons described in Section B.4.3. EPA excluded any records that were flagged for exclusion in this field and fit the decision-making criteria to remove from the

analyses. This field does not include any criteria specific to the DBP and TOC datasets. For more information on the QA/QC process and feedback from states, please see USEPA (2016i).

Step 2: Units: All records with missing or unusual units in the SYR3 ICR DBP dataset were sent back to states for input. However, not all of these records were evaluated by the submitter due to time and resource limitations. In these cases, EPA converted all DBP records to µg/L and excluded all records with no units indicated, since the values could not be guaranteed to be in the specific unit of measure.

For records within the SYR3 ICR TOC dataset, there was a limited effort to send questionable records back to states for input (comparative to the DBP data). As was the case with the SYR3 ICR DBP dataset, not all of the records were evaluated by the submitter due to time and resource limitations. In these cases, EPA converted all TOC and alkalinity records to mg/L and excluded all records with no units indicated, since the values could not be guaranteed to be in the specific unit of measure.

Step 3: Sample Type Code: Samples that were not for compliance purposes, such as special samples or performance evaluation, were excluded in the DBP and TOC datasets. Additionally, non-routine records were excluded for the DBP and TOC datasets.

Step 4a: Location Type of Sampling Point: While the occurrence of DBPs could theoretically occur anywhere in a given water system, EPA is primarily focused on the occurrence in the distribution system. As such, EPA excluded any DBP records with a location sampling point type that was not obviously a part of the distribution system, such as sampling results from raw or source waters (see Step 4b for the fields used to filter out these records). Note that excluding any raw water sources for the DBP contaminants meant EPA did not undergo a comparison of raw and finished water samples as was done for the chemical and radiological contaminants in a separate but related SYR3 effort (see USEPA (2016i) for more details).

For the TOC occurrence analyses, EPA only included those records that had sampling point locations reported as raw water or finished water.

Step 4b: Sapling Point Location Type and Water Facility Type: This step was based on two fields, TSASMPPT_TYPE_CODE and TYPE_CODE. The primary filter in Step 4a was based on TSASMPPT_TYPE_CODE and excluded any records with sampling point location types not clearly associated with DBP compliance and the distribution system, such as raw water sources. However, some of the codes appeared vague. To be more conservative, for records whose sampling point location type was either null or labeled as a generic "Water System Facility Point," an additional filter in Step 4b using TYPE_CODE was added to make sure any records with a water system facility type that was likely associated with the distribution system were not excluded. At the end of Step 4, the records remaining are only those that were likely sampled at points relevant to the D/DBPR compliance regulations.

This filtering step was not applied to the TOC dataset.

Step 5: Outlier Removal: Following the conventions used for chemical and radiological contaminants (see USEPA (2016i) for more details), outlier criteria were applied to all detection records to exclude any records above or below the thresholds via the flagging process described

in Section B.4.3. These criteria were specific to DBPs and based on 100 times the MCL or 1/100 times the minimum MDL. Additional discussion about DBP outliers is included in Section B.4.4.4. Exhibit B.35 lists the specific outlier criteria for each contaminant.

It is important to note that TOC and alkalinity inventory analyses (i.e., count of samples) in Chapter 6 and this appendix do not reflect the low-level outlier thresholds. However, the low-level outliers were removed for all *occurrence* analyses presented.

Exhibit B.35: MDL, MCL and Outlier Criteria for Each Set of Contaminants

Contaminant	Minimum MDL (µg/L)	Low Outlier Criteria (µg/L)	MCL (µg/L)	High Outlier Criteria (µg/L)
THM4[1]	0.001	0.00001	80	8,000
HAA5[1]	0.012	0.00012	60	6,000
Bromate	0.12	0.0012	10	1,000
Chlorite	0.45	0.0045	1,000	100,000
TOC	36.0	100.0	N/A	100,000
Alkalinity	N/A	1000	N/A	1,500

[1] The outlier criteria used for THM4 and HAA5 were also applied to individual THM and HAA species. Note that the MCL for THM4 identifies this group as TTHM.

Step 6: Manual Removal: After applying the filter criteria, an additional five records (three in the THM dataset and two in the HAA dataset) were removed manually because they were identified as records that were duplicated during the QA/QC process. The remaining records were then used to conduct the SYR3 occurrence analyses. No other reasons to manually remove individual records were identified.

B.4.4.2 Summary of Filter Protocol Results

DBP Dataset: After applying the filter protocol to more than five million SYR3 ICR DBP records, more than 80 percent of the records remained in the final dataset that was used for conducting occurrence analyses. Most of the records were removed in either Step 1, due to QA/QC issues identified during the record collection process, or in Step 4, due to sampling point location or water facility types that did not correspond with occurrence relevant to DBP regulations. Exhibit B.36 documents the specific counts of records included and excluded in each step for each of the four contaminants.

TOC Dataset: Exhibit B.37 documents the specific counts of records included and excluded in each step for TOC and alkalinity. Over 400,000 records were run against the filter protocol, of which greater than 95 percent of the records for each analyte (TOC and alkalinity) were included for final analysis. The majority of the excluded records were removed in Step 1, due to QA/QC issues identified during the record collection process, or in Step 3, due to sampling point locations that did not correspond with the normal analyte monitoring locations.

Exhibit B.36: Results of DBP Filter Protocol, by Step and Contaminant

Step	THM		HAA		Chlorite		Bromate	
	Included	Excluded	Included	Excluded	Included	Excluded	Included	Excluded
Original Records	2,973,132		2,127,211		28,484		12,765	
Step 1: Analyze	2,905,791	67,341	2,107,389	19,822	28,017	467	11,893	872
Step 2: Units	2,905,601	190	2,107,145	244	28,016	1	11,892	1
Step 3: Sample Type Code	2,904,436	1,265	2,106,274	871	27,897	119	11,890	2
Step 4: Sampling Point Location Type & Water Facility Type	2,267,112	637,324	1,890,180	216,094	25,989	1,908	8,886	3,004
Step 5: Outlier Removal	2,267,069	43	1,890,149	31	25,989	0	8,884	2
Step 6: Manual Removal	2,267,066	3	1,890,147	2	25,989	0	8,884	0
Final Records	2,267,066		1,890,147		25,989		8,884	
Percent Included	76%		89%		91%		70%	

Exhibit B.37: Results of TOC dataset Filter Protocol, by Step and Contaminant

QA/QC Step	Alkalinity		TOC	
	Included	Excluded	Included	Excluded
Original records	215,058		240,506	
QA/QC Step 1: Analyze[1]	210,029	5,029	236,530	3,976
QA/QC Step 2: Units	209,968	61	236,526	4
QA/QC Step 3: Sample type code	209,626	342	236,445	81
QA/QC Step 4: Remove TOC records > 100 mg/L; remove alkalinity records > 1,500 mg/L	209,602	24	236,377	68
QA/QC Step 5: Results that could not be identified as raw or finished	201,682	7,920	232,567	3,810
Final Records	201,682		232,567	
Percent Included	93.8%		96.7%	

[1] Step 1 includes the following QA filters to exclude: records that were confirmed to be duplicates, records from transient water systems, records from outside the date range, records from systems with missing inventory information and records marked as non-compliance.

B.4.4.3 Systematic Errors and State-Specific Considerations

During exploratory analyses of the occurrence databases, both before and after applying the filter criteria, it became clear that in specific instances, there may have been systematic errors not captured by the QA/QC process as developed and implemented. Many, if not all of these cases, were due to unforeseen data quality concerns or specific circumstances for an individual state. While these cases are not believed to have an impact on the analytical results and conclusions,

the potential issues are highlighted in the following sections. Systematic errors and state-specific considerations were only evaluated on the DBP dataset.

B.4.4.4 DBP Outlier Analysis

Upon an exploratory analysis of the data, it became clear that both very high and very low outliers existed for both non-detection and detection records. Some of these records were several orders of magnitude larger or smaller than what would be expected based on previous DBP ICR data for DBPs, even for outliers.

The primary hypothesis for these outliers was that some records may have incorrect units due to a data entry error. For example, a THM4 record of 8 µg/L could have been incorrectly entered as 8 mg/L. Upon conversion as part of the QA/QC process, this would be converted to 8,000 µg/L, or 100 times greater than the MCL for THM4. Even if this record was flagged during the QA/QC process as a potential outlier, if there was not enough information available to reasonably exclude it, then the record would have been left in the database and not flagged for exclusion because it does not meet the outlier criteria of greater than 100 times the MCL or less than 100 times the MDL. Without additional information, it would not be possible to determine with 100 percent accuracy if this type of unit error is present or if the value is a true outlier. As such, EPA has included these potential outliers in the national-level occurrence analyses presented in this document.

A thorough analysis of the outliers within the DBP and TOC datasets was conducted to determine if there appeared to be any systematic errors leading to these suspect results, and more importantly, the potential impact of these records on the occurrence analyses results and conclusions. The details and results of this outlier analysis are presented in the following sections.

B.4.4.5 DBP Outlier Analysis: Detection Records

Detection records for THM4, HAA5, chlorite and bromate were compared to tighter thresholds than those included in Section B.4.3. Specifically, the thresholds were less than the minimum MDL or greater than 10 times the MCL. For all four contaminants, detections less than the minimum MDL had units entered as "UG/L," so no conversion or data entry error could be identified. For detections greater than 10 times the MCL, some records were indeed entered as "MG/L," while others were labeled as "UG/L." In some cases, the state had no response about these records. In other cases, the state responded and confirmed the accuracy of the outlier. Additionally, some of the states reported all records in "MG/L," even those that were not outliers and identified as a potential units error.

Since there were no clear systematic errors regarding the detection outliers, a sensitivity analysis was conducted to determine if the exclusion of these records would have any bearing on the long term average contaminant levels assessed in the Phase 2 analyses. Changing the outlier criteria from the current levels of greater than 100 times the MCL or less than 100 times the MDL did not appear to have an impact on the results of the Phase 2 analyses and the conclusions drawn from them. As part of the QA protocol implemented during the SYR3 ICR process, EPA flagged all of these records and provided the states with an opportunity to review them for accuracy and

revise if appropriate. While it is possible that some of the records may still be incorrect after this process, it would be impossible for EPA to independently determine if a flagged record is inaccurate without additional information from the states. Since an adjustment in the outlier criteria would have no impacts on the final Phase 2 analyses and resulting conclusions, EPA deemed the current protocol and dataset to be sufficient for use as part of the SYR3 occurrence analyses.

B.4.4.6 DBP Outlier Analysis: Summary

Based on the sensitivity analyses conducted, as well as the overall small number of records identified as potential remaining outliers, no further adjustments were made to any of these records despite the potential existence of some kind of data entry error.

B.4.4.7 State-Specific Considerations

This section provides additional information on DBP data and TOC data.

B.4.4.8 TOC Data

Two non-SDWIS states (California and Michigan) did not make a designation as to whether their data were for compliance. For all TOC inventory and occurrence analyses, EPA assumed that all data from these two states were for compliance.

Appendix C. Supporting Information for Treatment (Appendix to Chapter 7)

C.1 Introduction and Scope

This appendix provides additional information in support of Chapter 7. Specifically, this appendix includes support information for the analysis of the paired total organic carbon (TOC) dataset, analysis of the Information Collection Rule Treatment Study Database (ICRTSD) using granular activated carbon (GAC), as well as study-specific information related to some control approaches presented in Chapter 7 (advanced oxidation and alternative disinfectants), and documentation of the creation of the paired TOC dataset from the SYR3 ICR data. References cited within this appendix are provided at the end of Chapter 7.

C.2 Supporting Information for the Analysis of the Paired TOC Dataset from SYR3 ICR

C.2.1 Inventory Information for the Paired TOC Dataset

Documentation of the creation of the paired TOC dataset from the SYR3 ICR data is included in Section C.6. The 3x3 matrix-based TOC removal requirements are only applicable to the SW treatment plants (or facilities in the SYR ICR dataset) with raw water TOC levels greater than 2 mg/L; therefore, the paired TOC monitoring results were first separated into two groups, those with annual average raw water TOC levels greater than 2 mg/L versus those with average raw water TOC levels $\leq$ 2 mg/L. Exhibit C.1 and Exhibit C.2 show the number of facilities in each state included in the paired TOC dataset for all facilities and facilities with raw water TOC levels greater than 2 mg/L, respectively. There are 21 states and 1 region that have at least 1 pair of TOC monitoring records in at least one of the years between 2006 and 2011. Most of these states have a relatively consistent count of facilities across different years. Some states (e.g., Vermont, Nevada and Oklahoma) have few pairs of TOC data while other states (e.g., Kentucky, North Carolina, Pennsylvania and West Virginia, etc.) have many pairs. A comparison between Exhibit C.1 and Exhibit C.2 indicates that those states with relatively high counts of paired TOC records generally also have relatively high counts of paired TOC records with annual raw water TOC levels greater than 2 mg/L (along with relatively high counts of paired TOC records with annual raw water TOC levels $\leq$ 2 mg/L, which are excluded in Exhibit C.2).

Exhibit C.1: Count of Facilities with Paired TOC Data per State per Year for All Facilities in the Dataset

State	2006	2007	2008	2009	2010	2011
AK	16	14	14	14	14	15
AL	78	82	84	86	83	84
IA	20	20	20	20	15	16
IL	82	82	83	84	85	85
IN	0	0	0	41	41	40

State	2006	2007	2008	2009	2010	2011
KY	144	143	145	146	146	147
ME	2	3	5	6	6	23
MT	6	6	5	4	9	11
NC	130	134	140	140	145	148
ND	19	18	19	20	18	19
NJ	31	31	30	30	31	32
NV	2	2	2	2	2	2
NY	11	9	9	9	9	9
OK	5	4	6	5	5	5
PA	182	176	247	248	244	241
Region 08	11	12	12	11	12	10
SC	52	52	53	52	51	52
UT	25	36	32	26	24	23
VA	123	124	124	126	124	125
VT	1	1	1	1	1	1
WV	114	115	114	115	113	114
WY	16	15	15	14	17	17
All	**1,070**	**1,079**	**1,160**	**1,200**	**1,195**	**1,219**

Exhibit C.2: Count of Facilities with Paired TOC Data and with Annual Average Raw Water > 2 mg/L per State per Year

State	2006	2007	2008	2009	2010	2011
AK	11	10	10	9	11	11
AL	58	58	72	75	67	69
IA	17	17	17	17	13	14
IL	70	73	68	69	69	68
IN	0	0	0	38	36	32
KY	116	118	119	112	123	126
ME	2	3	5	6	6	19
MT	4	5	4	3	8	10

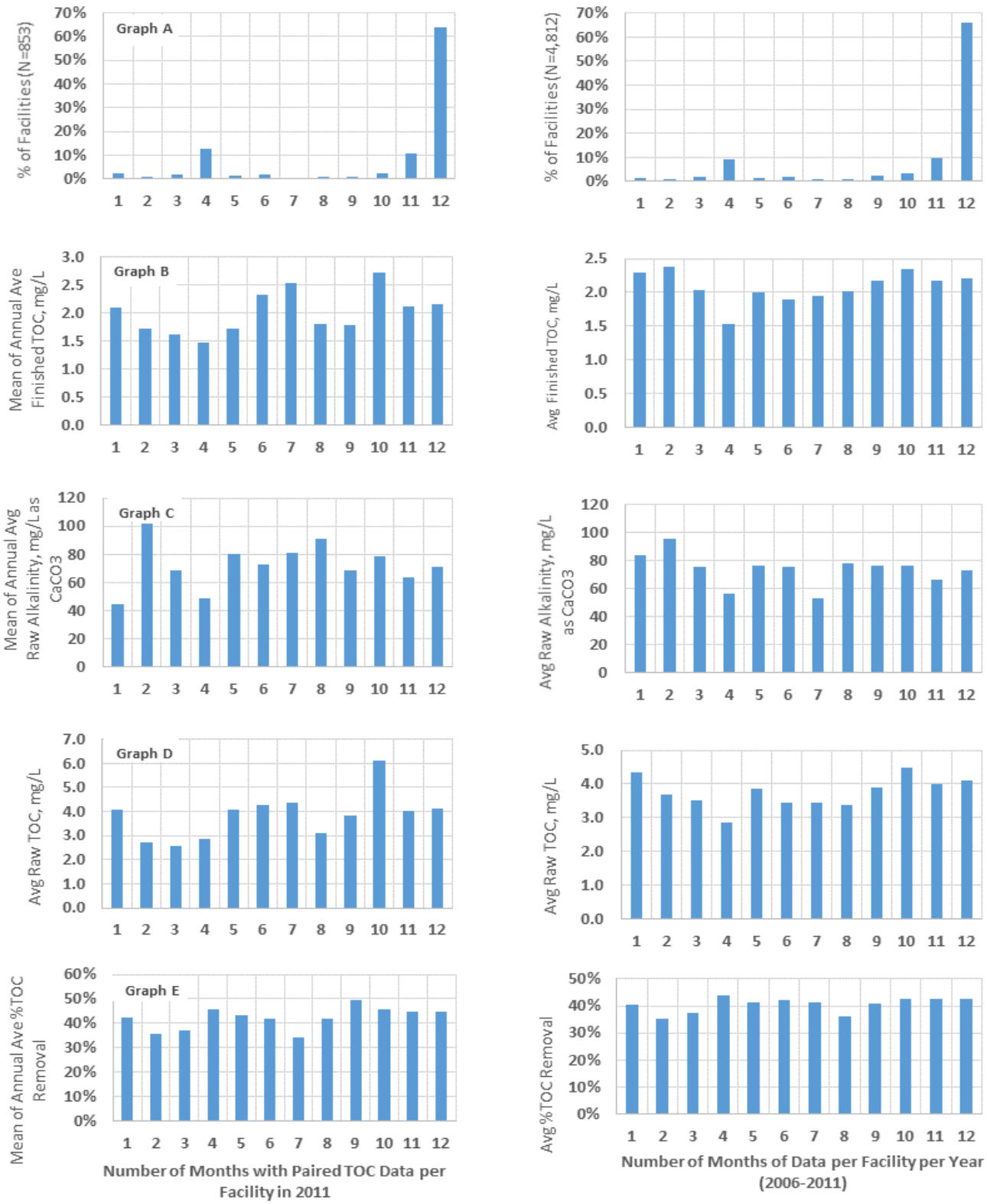
State	2006	2007	2008	2009	2010	2011
NC	78	85	95	91	95	94
ND	19	18	19	20	18	19
NJ	30	30	27	28	28	28
NV	0	0	0	0	0	0
NY	11	8	9	9	8	8
OK	5	4	5	5	5	5
PA	100	104	130	123	128	150
Region 08	8	9	10	11	11	9
SC	41	40	45	42	40	41
UT	16	18	17	13	11	14
VA	63	67	87	76	74	72
VT	1	1	1	1	1	1
WV	62	70	60	61	66	47
WY	11	11	12	12	15	14
All	**723**	**749**	**812**	**821**	**833**	**851**

Since EPA does not have the information from each state on the inventory number of facilities (or plants) with conventional treatment trains, TOC monitoring implementation, and record management programs from the individual states, it is not possible to assess the completeness of facilities with the paired TOC data records (versus the inventory facilities) from these 21 states plus 1 region. To EPA's knowledge, nevertheless, it is the largest and most comprehensive dataset since the DBP ICR dataset in 1997-1998 that allows for a national level assessment of the treatment performance among the facilities/plants (most likely using conventional treatment trains) in terms of TOC removal and TOC levels in the treated water. This dataset was further analyzed in context of the 3x3 matrix indicated in Exhibit 7.1 of Chapter 7 to provide a further characterization of the dataset and potential associated biases.

As described in Chapter 7, the construct of the existing TT requirements for TOC removal under Stage 1 D/DBPR could also lead to a different number of months of required monitoring per system during any given calendar year (e.g., plants with a treated water TOC running annual average of less than 2 mg/L for two consecutive years or less than 1 mg/L for one year may reduce monitoring for both TOC and alkalinity to one paired sample per plant per quarter). Graph A in Exhibit C.3 indicates a distribution of facilities with TOC data with different counts of months in the most recent calendar year of 2011. Of the facilities that provided data, 66 percent had 12 months of data; about 10 percent had 11 months of data. All other months of data were 1 to 2 percent of the total. A relatively high percentage of facilities with four months of data could be attributable to the reduced quarterly monitoring compliance schedule, as indicated by the lowest mean of annual averages of treated water TOC (as indicated by Graph B in Exhibit

C.3), which in turn could be related to a relatively low mean of raw water TOC (as indicated by Graph C in Exhibit C.3) and alkalinity (as indicated by Graph D in Exhibit C.3). As indicated by Graph E in Exhibit C.3, means of annual averages of TOC removal appear relatively constant across different number of months per facility. For this reason, all of the facilities (regardless of number of months) were included in the subsequent data analysis. Furthermore, Exhibit C.4 shows that the analytical results with all years of SYR3 ICR data (i.e., 2006-2011) appear very similar to the results shown in Exhibit C.3 with the data from 2011 only. Thus, all years of data were used for further statistical analysis of the 3x3 matrix to represent national occurrence, thereby maximizing the count of facility years (i.e., number of facilities x number of years).

Exhibit C.3: Count of Months (2011) (left); Exhibit C.4: Count of Months (2006-2011) (right)



C.2.2 TOC Removal at Raw Water TOC Levels ≤ 2 versus > 2 mg/L

As explained above, all years of data were collectively used for the statistical analysis presented in this appendix (unless being noted) for maximizing the count of facility years (i.e., number of facilities x number of years). Since the 3x3 matrix-based TOC removal requirements are only applicable to the facilities with raw water TOC level greater than 2 mg/L, the paired TOC monitoring results were first separated into two groups, facilities with annual average raw water TOC levels greater than 2 mg/L and facilities with annual average raw water TOC levels ≤ 2 mg/L. The summary statistics with data for all of years in Exhibit C.5 indicate that the percentages of TOC removal appear noticeably lower when the raw water TOC levels were ≤ 2 mg/L (approximately one-third of facility years), compared to the raw water TOC level greater than 2 mg/L (approximately two-thirds of facility years), except for the upper end (e.g., 90th percentiles). This observation can be expected because facilities with raw TOC water levels ≤ 2 mg/L are not required to meet any TOC removal requirements. Moreover, with relatively low influent TOC levels, there may not need to be high levels of DBP precursor removal to meet DBP MCLs. Exhibit C.6 shows a similar observation with the data from 2011. A comparison between Exhibit C.5 and Exhibit C.6 indicates that the percentages of TOC removal from the 2011 data generally appear slightly higher than those with the data from all years (e.g., 44.5 percent vs 42.5 percent mean for the annual average raw water TOC levels greater than 2 mg/L). This could be attributable to the influence of the Stage 2 D/DBPR that was promulgated in 2006, which requires the systems to calculate locational running annual averages (LRAAs) rather than RAAs of TTHM/HAA5 levels for compliance with their maximum contaminant levels (MCLs) (as further discussed in Section C.2.5 on Temporal Trends of TOC Removal).

Exhibit C.5: Summary Statistics, Annual Average TOC Removal (2006-2011)

Annual Avg Raw TOC, mg/L	# Facility Years[1] (2006-2011)	Mean Avg TOC removal	Median Avg TOC removal	10%ile Avg TOC removal	90%ile Avg TOC removal
All	6,923	39.2%	39.3%	17.7%	60.8%
≤ 2	2,134	31.5%	30.5%	7.6%	60.3%
> 2	4,789	42.5%	42.3%	24.7%	60.8%

[1] Count of Facility Years (i.e., number of facilities multiplied by number of years)

Exhibit C.6: Summary Statistics, Annual Average TOC Removal in 2011

Annual Avg Raw TOC, mg/L	# Facilities (in 2011)	Mean Avg TOC removal	Median Avg TOC removal	10%ile Avg TOC removal	90%ile Avg TOC removal
All	1,219	40.9%	41.5%	18.5%	65.3%
≤ 2	368	32.4%	34.2%	5.5%	74.6%
> 2	851	44.5%	44.4%	27.0%	63.4%

To further evaluate TOC removal and TOC levels in treated water, the rest of the analytical results (except for Exhibit C.7a for a comparison) were based on the subset of data with facilities

whose annual raw water TOC levels were greater than 2 mg/L because the 3x3 matrix-based TOC removal requirements are only applicable to the facilities with raw water TOC levels greater than 2 mg/L. Cumulative distributions of raw water TOC, alkalinity and treated water TOC in each individual year are indicated in Exhibit C.7 (a and b) and Exhibit C.8 (a and b), respectively, for the annual average raw water TOC levels greater than 2 and ≤ 2 mg/L.

C.2.3 National Distributions for Individual Years

Exhibit C.7a and Exhibit C.7b show a cumulative distribution of annual average raw water TOC levels for each of the individual years, respectively, for all facilities and the facilities with annual average raw water TOC levels greater than 2 mg/L; Exhibit C.7 (a and b) and Exhibit C.8 (a and b) show this type of distribution for raw water alkalinity and treated water TOC, respectively. Overall, the year-to-year variations appear very small, which supports use of the data from all years for further statistical analysis.

Exhibit C.7a: Distribution of Annual Average Raw Water TOC Levels per Facility for Individual Years for All Facilities

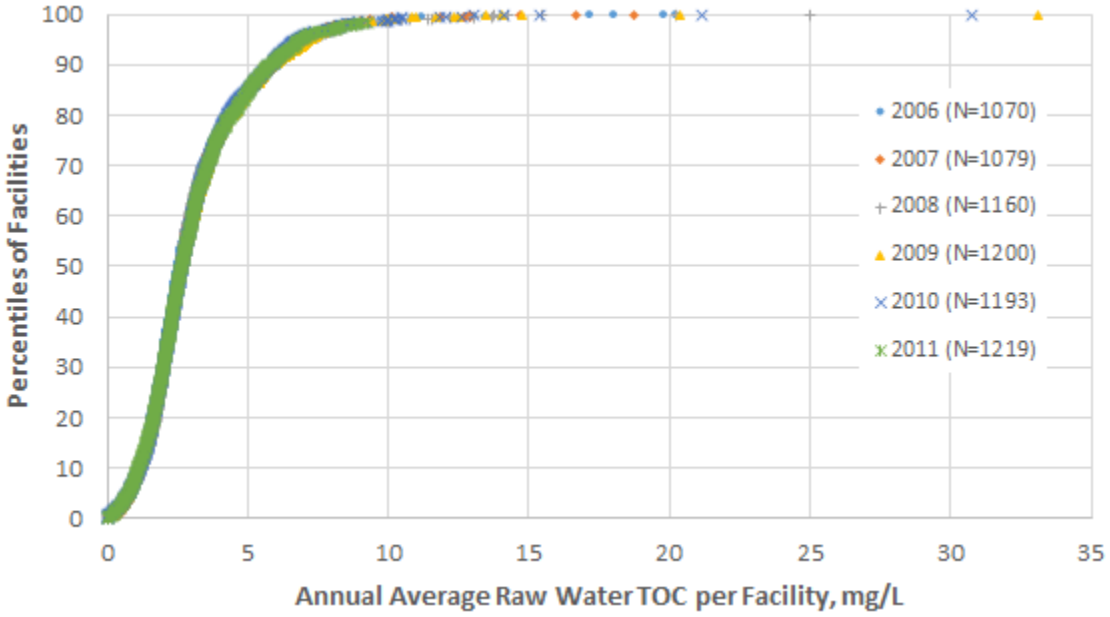


Exhibit C.7b: Distribution of Annual Average Raw Water TOC Levels per Facility for Individual Years for Facilities with Annual Average Raw Water TOC Levels > 2 mg/L

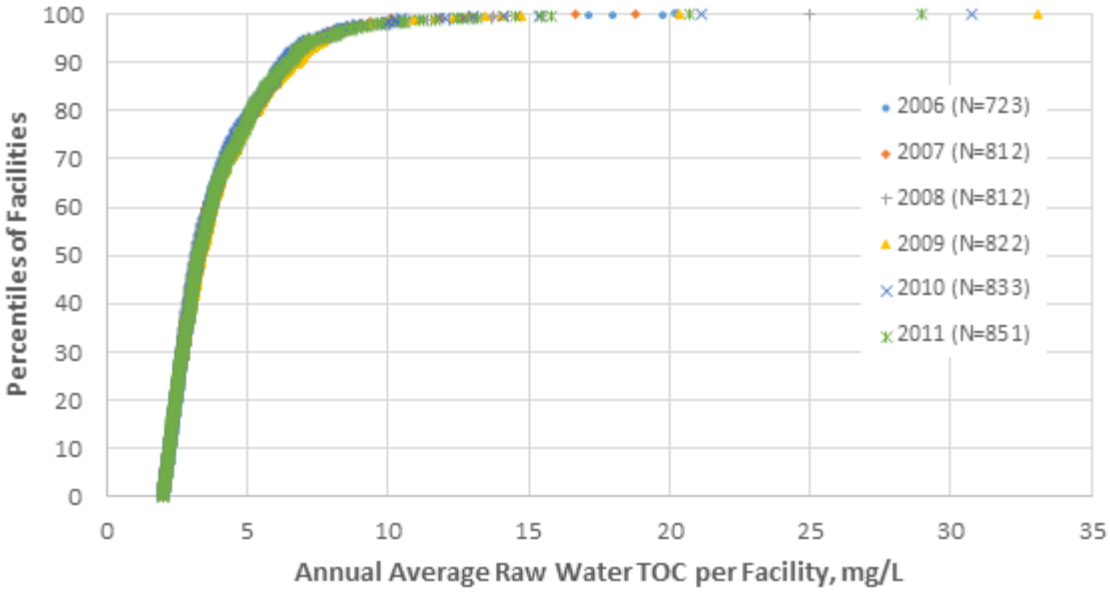


Exhibit C.8a: Distribution of Annual Average Raw Water Alkalinity Levels per Facility for Individual Years for All Facilities

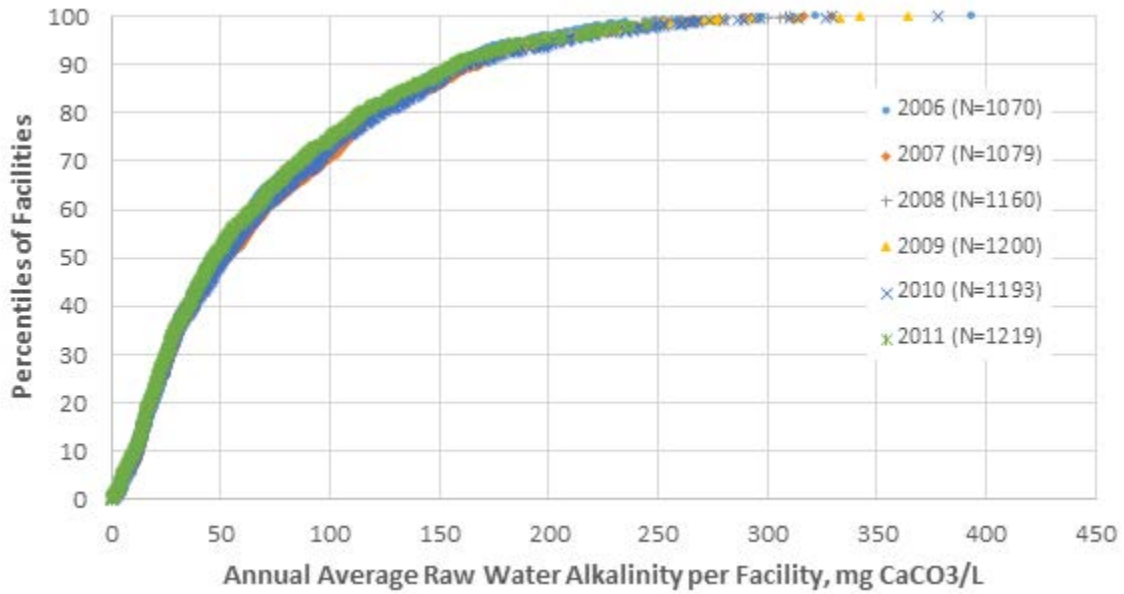


Exhibit C.8b: Distribution of Annual Average Raw Water Alkalinity Levels per Facility for Individual Years for Facilities with Annual Average Raw Water TOC Levels > 2 mg/L

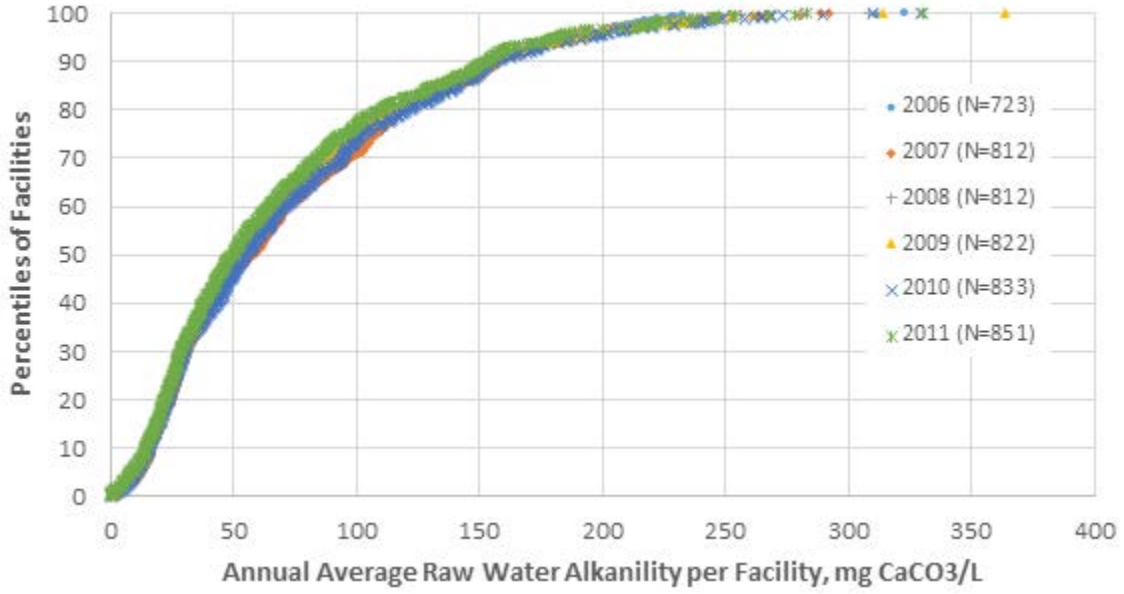


Exhibit C.9a: Distribution of Annual Average Treated Water TOC Levels per Facility for Individual Years for All Facilities

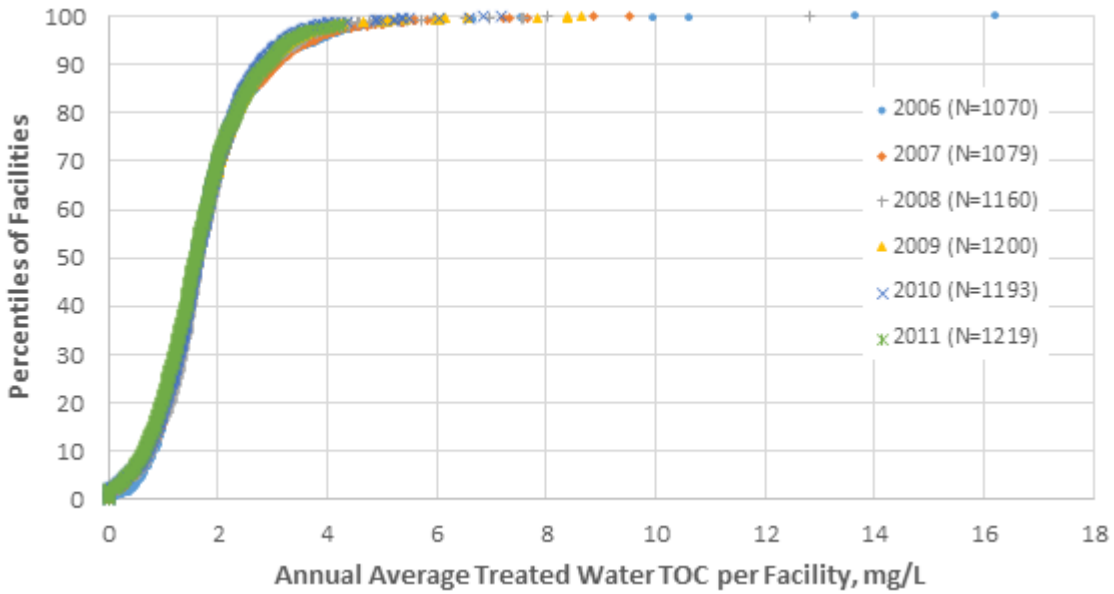
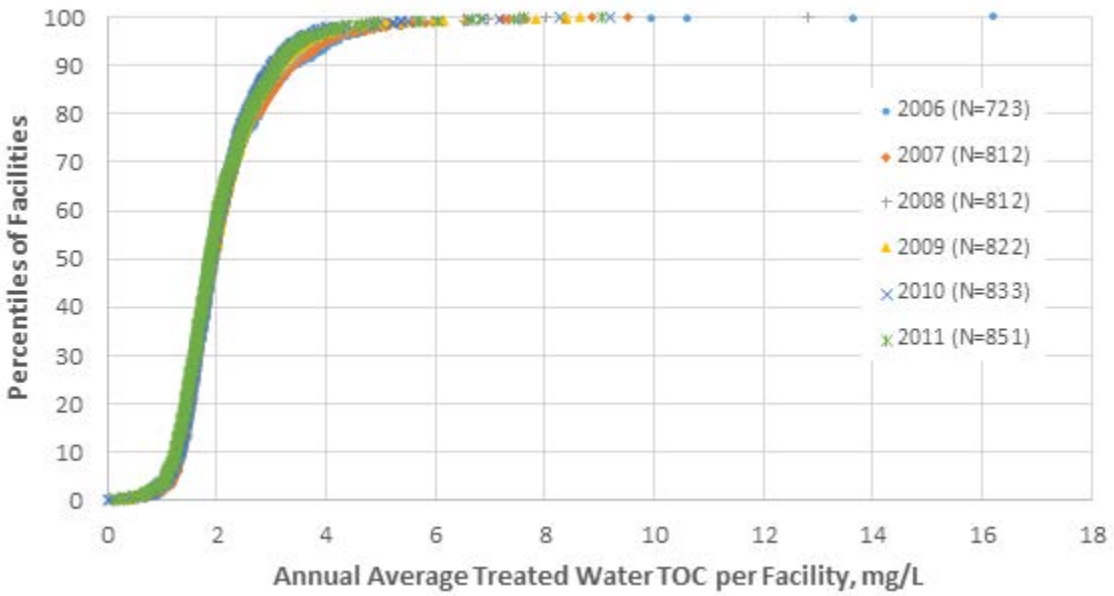


Exhibit C.9b: Distribution of Annual Average Treated Water TOC Levels per Facility for Individual Years for Facilities with Annual Average Raw Water TOC Levels > 2 mg/L



C.2.4 Treated Water TOC Levels vs Raw Water TOC and Alkalinity Levels

A higher level of raw water TOC generally led to a higher level of treated water TOC, even though the TOC removal was higher at a higher raw water TOC level (as indicated by the values of "%facility Years with Treated TOC > 2" and "Mean Treatment TOC" in Exhibit 7.4 of Chapter 7). Exhibit C.10 further displays this trend by presenting annual average raw water TOC

levels versus annual average treated water TOC levels (in a log scale). This observation could be directly attributable to the construct of existing TT requirements, which was based on the percentages of TOC removal, instead of some absolute targeted TOC levels. Exhibit C.11, however, shows that the treated water TOC levels does not appear to be affected much by the raw water alkalinity levels.

Exhibit C.10: Annual Average Raw versus Treated Water TOC Levels (in double log scales)

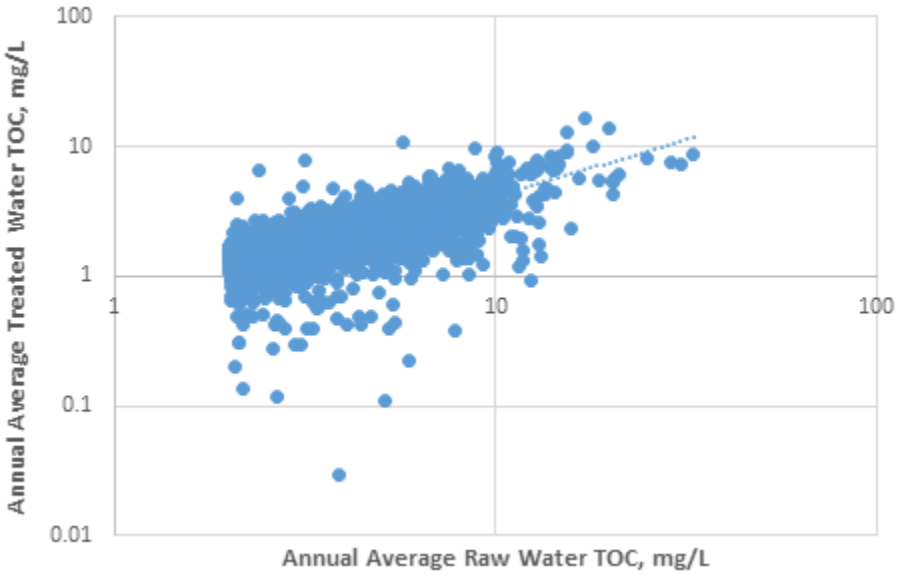
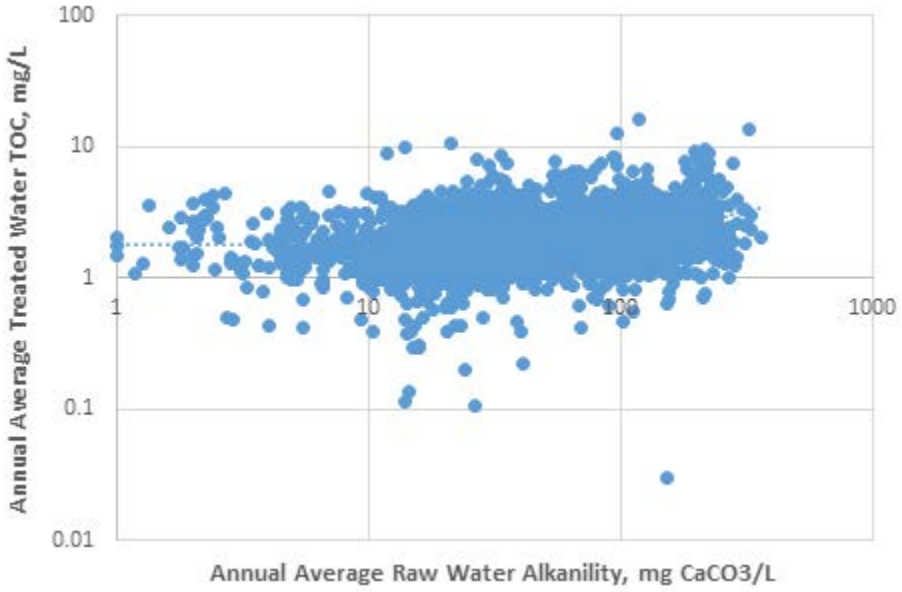


Exhibit C.11: Annual Average Raw Alkalinity Levels versus Treated Water TOC Levels (in double log scales)



C.2.5 Temporal Trends of TOC Removal

To evaluate the general temporal trend of treatment performance for TOC removal during the six-year period covered in the SYR3 ICR dataset, the facilities having paired TOC data in every year of this six-year period (with at least one month) were analyzed (and referred to as "common facilities"). Comparing the occurrence in only the common facilities eliminated any potential biases that could have been introduced by including facilities in different years. The data among the common facilities were grouped into two periods: the first three years (2006 to 2008) versus last three years (2009 to 2011). This step was taken to recognize the yearly variation of source water quality; otherwise any trends might not be discernible. The means of annual average treated water TOC levels and TOC removal over each of these two periods (i.e., means for every three years) were calculated for each of the common facilities, respectively.

Exhibit C.12 shows a distribution of means of annual average treated water TOC levels per facility for the first three years compared to the last three years. A comparison of these two cumulative distribution curves indicates that there is not much difference at the lower part of the curves (i.e., less than 50th percentiles in the Y axis or less than 2 mg/L in the X axis). In the upper part of the curves, however, treated water TOC levels in the period between 2009 and 2011 consistently appear lower than the period between 2006 and 2008 (e.g., 3.3 mg/L versus 3.6 mg/L at 90th percentiles), which may be attributable to higher TOC removal in the period of 2009 and 2011, as indicated in

Exhibit C.13.

Exhibit C.12: Distributions of Treated Water TOC levels for First Three Years vs Last Three Years

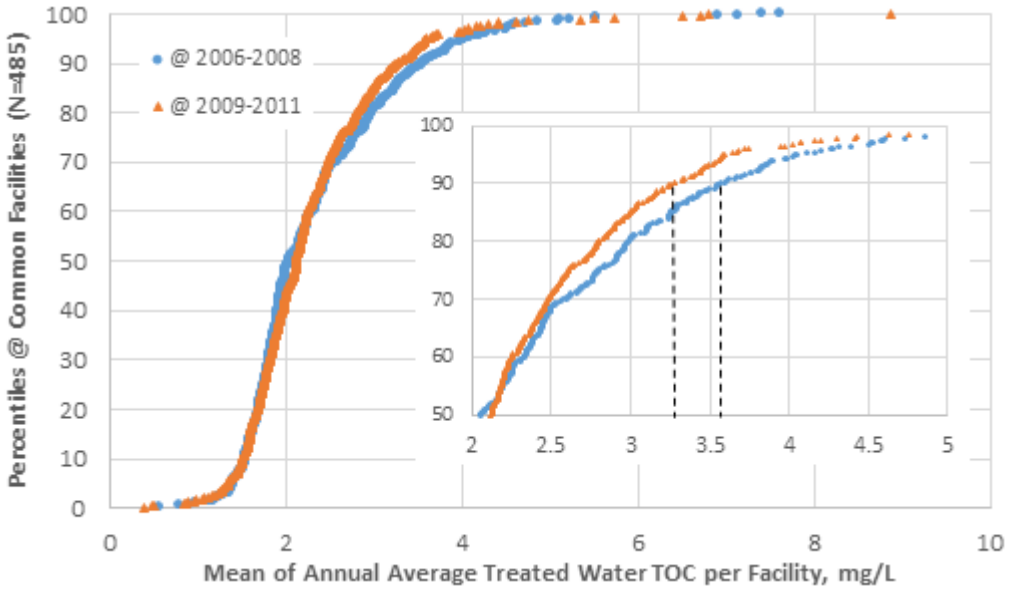
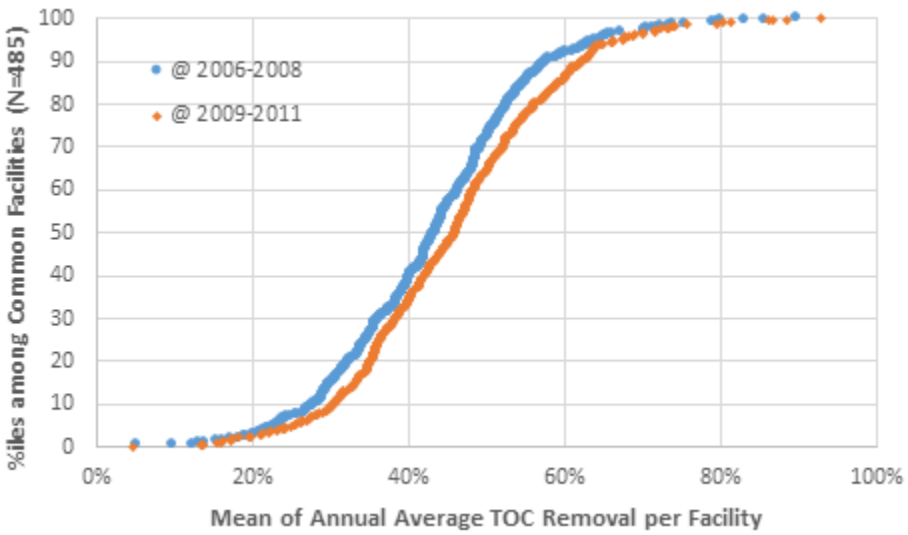


Exhibit C.13: Distribution of TOC Removal for First Three Years vs Last Three Years



To further assess the potential differences in these two periods, the percentages of change from the first period to second [i.e., (values in first period – values in second period)/(values in first period)] were calculated for the individual common facilities. To compare the changes from one period to the next, EPA examined the number of facilities that had either a 5% increase or 5% decrease in treated water TOC. As indicated in Exhibit C.14, for 2006 – 2008 treated water TOC levels ≥ 2 mg/L, there are considerably more facilities with a greater than 5 percent decrease in treated water TOC levels from the first 3 years compared to last 3 years (i.e., 117) than facilities with a greater than 5 percent increase (i.e., 53), implying that the treated water TOC levels in the period between 2009 and 2011 were generally lower than the period between 2006 and 2008 when the treated water TOC levels were greater than or equal to 2 mg/L in the period between 2006 and 2008. The opposite effect occurred for the facilities with treated water TOC levels less than 2 mg/L (i.e., 85 with treated water TOC increased by ≥ 5 percent versus 65 with treated water TOC decreased by ≥ 5 percent). This may be partially due to there being less incentive to further remove TOC when treated water TOC levels had been less than 2 mg/L (reflected by the alternative compliance criterion of the treated water TOC level less than 2 mg/L). Overall, the common facilities achieved more TOC removal during the last 3 years, as indicated by the number of facilities with indicated percent change from first 3 to last 3 years on mean annual average TOC removal in Exhibit C.14 (i.e., 120 with % removal increased by ≥ 5 percent versus 45 with %removal decreased by ≥ 5 percent when treated water TOC levels greater than or equal to 2 mg/L).

Exhibit C.14: Number of Facilities with Indicated Percent Change from First Three to Last Three Years on Mean Annual Average Treated Water TOC and TOC removal

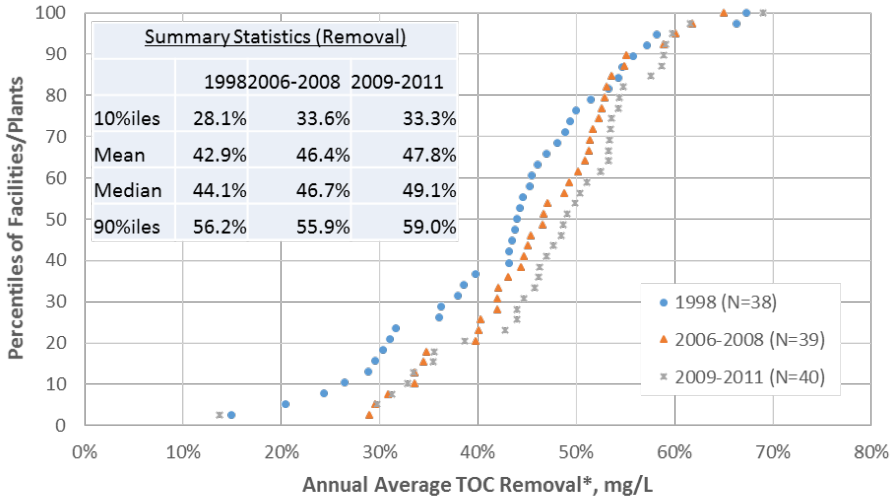
Mean of Annual Ave Treated TOC (mg/L) in 1st 3 years	Number of Facilities	Mean Annual Ave Treated TOC Increased by ≥ 5%	Mean Annual Ave Treated TOC Decreased by ≥ 5%	Mean Annual Ave Treated TOC between	Mean Annual Ave TOC %Removal Increased by ≥ 5%	Mean Annual Ave TOC %Removal Decreased by ≥ 5%	Mean Annual Ave TOC %Removal between
All	485	138	182	165	223	109	153
< 2	231	85	65	81	103	64	64
≥ 2	254	53	117	84	120	45	89

As mentioned earlier, the DBP ICR database also contains paired TOC data for all systems serving 100,000 or more. The paired TOC data were collected monthly for each of the individual treatment plants associated with these systems during the period between July 1997 and December 1998. The DBP ICR TOC data for the year 1998 were analyzed and compared to SYR3 ICR TOC data to assess the temporal trend of TOC removal from 1998 to the period between 2006 and 2011. To ensure comparability, the paired TOC data from the systems that were contained in both the DBP ICR database and the SYR3 ICR dataset (across those individual six years) were analyzed. As a result, 26 common systems (with 38 plants from the DBP ICR database and 39 facilities from the SYR3 ICR dataset, respectively) were identified. Since there were not any common fields (other than PWSID) in these two datasets to be linked to each other, a comparison was not possible for the individual plants/facilities. Instead, the cumulative distributions of TOC removal for pooled data of the plants or facilities associated with the common systems were developed and compared. As shown in Of additional note is the fact that the 1998 dataset indicated that about 15 percent of the plants (6 of 38) had less than 30 percent TOC removal, whereas only 5 percent (2 of 38) of the facilities of the SYR3 ICR dataset (of common systems) had less than 30 percent TOC reduction. In addition to the implication that considerable improvement is minimal TOC removal as a result of Stage 1 D/DBPR, it does appear that the tail on the 1998 dataset for low TOC removal might have some effect on the offset of 1998 cumulative distribution curve from the 2006 – 2011 data for the lower part of the curves.

Exhibit C.15, the TOC removal increased considerably from 1998 compared to the period of 2006 to 2011. For instance, the mean increased from 42.9 percent in 1998 to 47.8 percent between 2009 and 2011 (representing an increase of 11.4 percent); the 10th percentiles were increased from 28.1 percent in 1998 to 33.6 percent between 2009 and 2011 (representing an increase of 18.5 percent). Since the data from the DBP ICR and the SYR3 ICR were collected, respectively, before and after the Stage 1 D/DBPR, such an increment of TOC removal could be directly attributable to the effect of the TOC removal TT requirements under the Stage 1 D/DBPR for the systems serving 100,000 or more people. Of additional note is the fact that the 1998 dataset indicated that about 15 percent of the plants (6 of 38) had less than 30 percent TOC removal, whereas only 5 percent (2 of 38) of the facilities of the SYR3 ICR dataset (of common systems) had less than 30 percent TOC reduction. In addition to the implication that considerable improvement is minimal TOC removal as a result of Stage 1 D/DBPR, it does appear that the tail

on the 1998 dataset for low TOC removal might have some effect on the offset of 1998 cumulative distribution curve from the 2006 – 2011 data for the lower part of the curves.

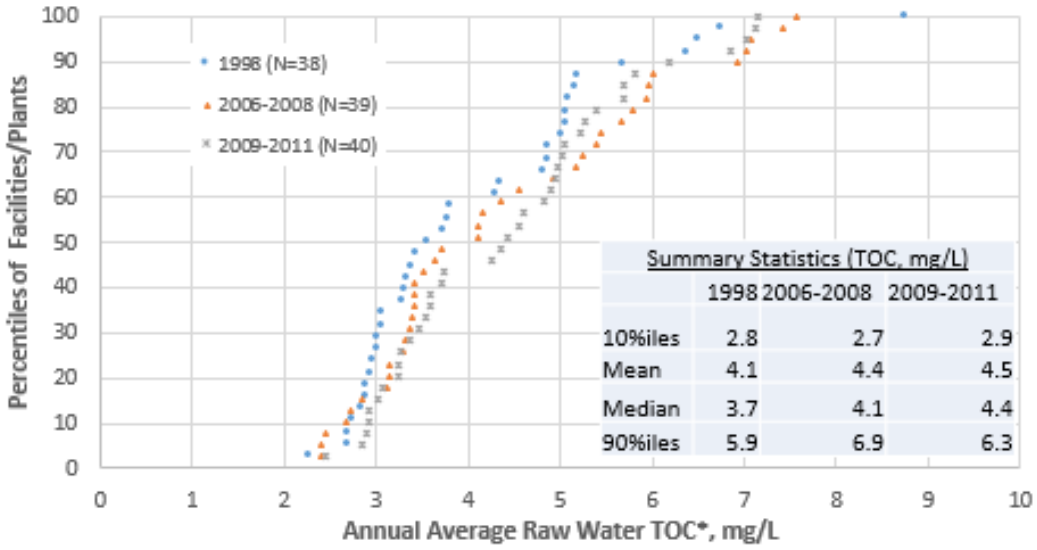
Exhibit C.15: TOC Removal among Common Systems in 1998 versus 2006-2008 and 2009-2011



* Mean over three years for periods of 2006-2008 and 2009-2011.

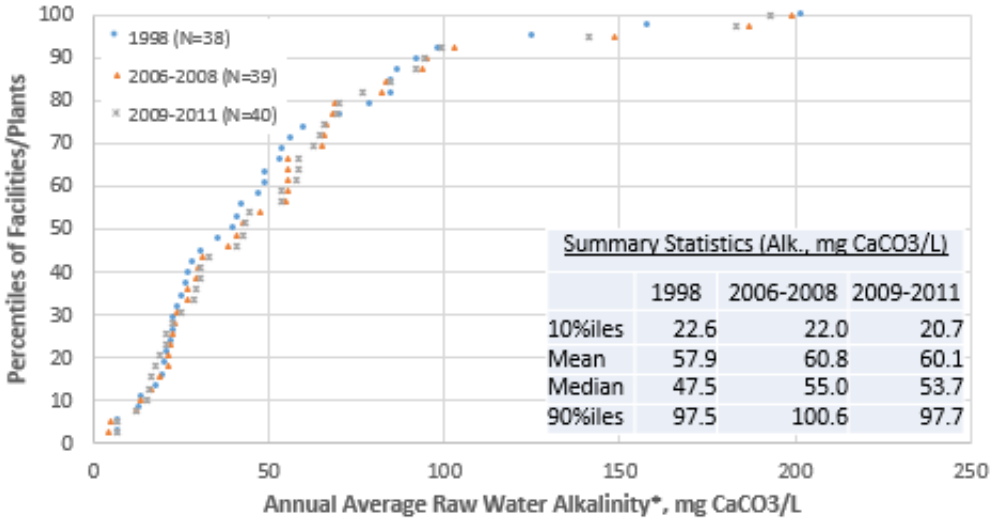
Exhibit C.16 – Exhibit C.18 show the distributions of raw water TOC, raw water alkalinity and treated water TOC among common systems in 1998 versus the periods of 2006-2008 and 2009-2011, respectively. Despite an increase of TOC removal from 1998 to the period of 2006-2011 (See Exhibit C.15), the distributions of the treated water TOC appear not much difference (see Exhibit C.18).

Exhibit C.16: Raw Water TOC among Common Systems in 1998 versus in Periods of 2006-2008 and 2009-2011



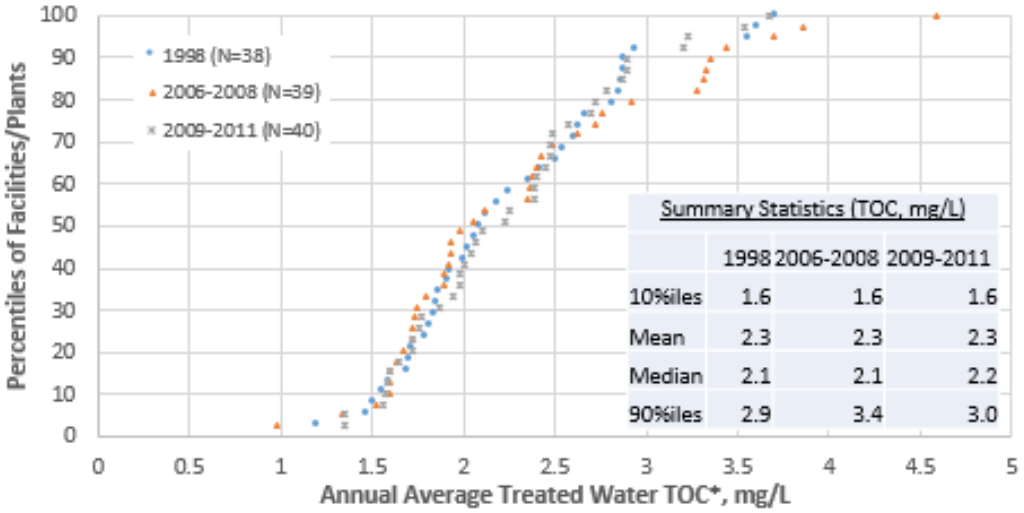
* Mean over three years for periods of 2006-2008 and 2009-2011.

Exhibit C.17: Raw Water Alkalinity among Common Systems in 1998 versus in Periods of 2006-2008 and 2009-2011



* Mean over three years for periods of 2006-2008 and 2009-2011.

Exhibit C.18: Treated Water TOC among Common Systems in 1998 versus in Periods of 2006-2008 and 2009-2011



* Mean over three years for periods of 2006-2008 and 2009-2011.

C.2.6 Distributions of Raw Water TOC and Alkalinity by System Size

Chapter 7 presents TOC removal and treated TOC levels by system size; Exhibit C.19 and Exhibit C.20 show the distributions of raw water TOC and raw water alkalinity by system size, respectively.

Exhibit C.19: Raw Water TOC Levels by Different System Sizes with SYR3 ICR Data (2006-2011)

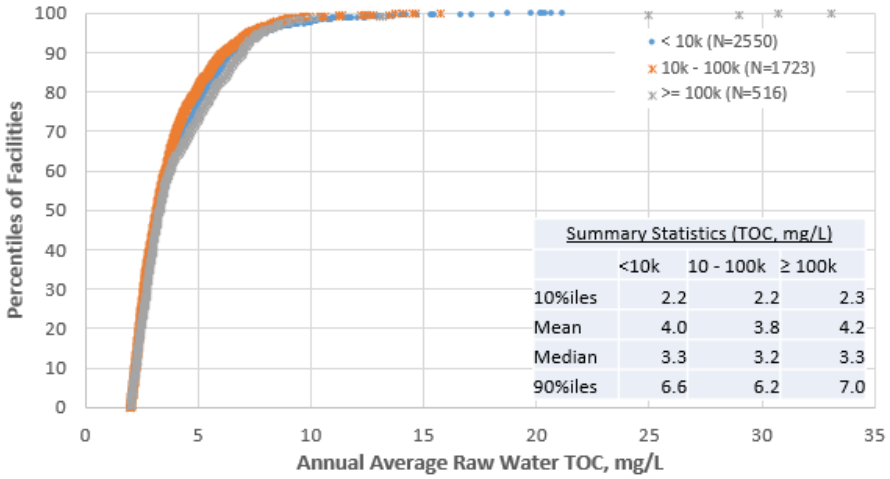
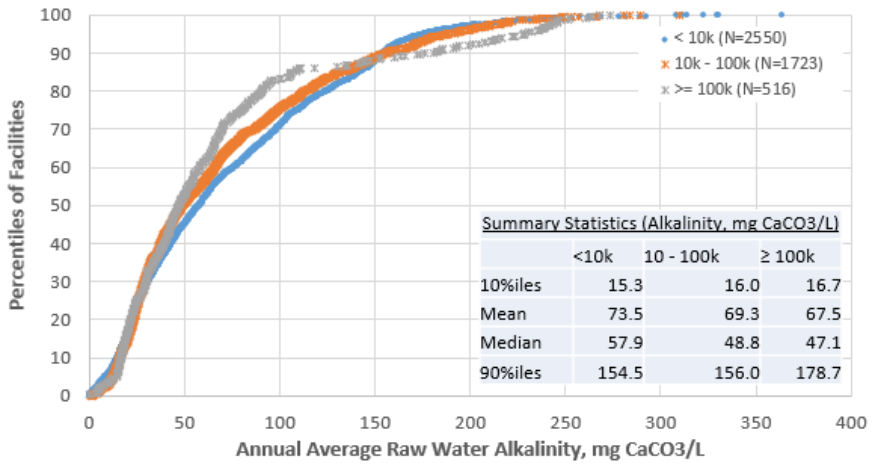


Exhibit C.20: Raw Water Alkalinity Levels by Different System Sizes with SYR3 ICR Data (2006-2011)



C.3 Supporting Information for Analysis of GAC from the Information Collection Rule Treatment Study Database (ICRTSD)

GAC can remove organic precursors to limit DBP formation but it may also cause a shift in the relative THM speciation to the more brominated species when bromide is present in source water (Summers et al., 1993; Sohn et al., 2006). One of the key concerns with GAC is how effectively it can control the formation of the potentially more harmful brominated DBPs in treated water. The purpose of this analysis is to evaluate to what extent brominated DBPs will be formed after TOC is removed to 1 and 2-mg/L by GAC under realistic drinking water treatment conditions. The bench- and pilot-scale GAC data were extracted from the EPA ICRTSD. This section presents preliminary results of the total and brominated THM (BrTHM) and HAA formation and the changes of bromine incorporation into THMs and HAAs before and after the GAC treatment for waters with varying levels of bromide.

C.3.1 Overview of ICRTSD

The ICR required surface water systems serving greater than 100,000 people with raw water TOC levels greater than 4.0 mg/L and ground water systems serving greater than 50,000 people with finished water TOC levels greater than 2 mg/L to conduct bench or pilot studies of GAC or nanofiltration for the control of DBP precursors (USEPA, 1996b). As a result, a total of 99 treatment studies, including 63 with GAC (Exhibit C.21) and 36 with nanofiltration, were conducted and results were submitted to EPA (USEPA, 1996c). EPA reviewed raw data to produce a standard set of data consistent across all studies in the ICRTSD (USEPA, 2000g). The ICRTSD represents the most extensive evaluation of GAC for control of DBPs under real-world conditions, with a wide range of source water quality and distribution system characteristics (Hooper and Allgeier, 2002). EPA used the ICRTSD to guide the selection of best available technologies (BATs) in developing the Stage 2 D/DBPR (Hooper and Allgeier, 2002; Bond and Digiano, 2004). At that time, the brominated DBP data in ICRTSD were not examined comprehensively.

In the ICR GAC treatment studies, utilities conducted bench-scale rapid small-scale column tests (RSSCT) or pilot tests. Effluent from the GAC columns was sampled over time to determine the breakthrough curves of DBP formation, TOC, UV_{254} absorbance and total organic halogens (TOX). The DBP formation was assessed under simulated distribution system (SDS) conditions with a free chorine residual. A subset of samples was also analyzed for HAA9. Each GAC breakthrough curve was fitted with a logistic function to facilitate analysis of GAC performance (USEPA 2000g). This mathematical model enables the user of the database to reconstruct breakthrough curves to find the service time for any specific value of a breakthrough parameters.

Exhibit C.21: Summary of GAC Study Types in the ICRTSD

Source Water Type	RSSCT	Pilot-Scale	Full-Scale	Sum
Surface Water	36	15	1	52
Ground Water	8	3	0	11

RSSCT = rapid small-scale column test, conducted quarterly at an empty bed contact time (EBCT) of 10 and 20 minutes. Pilot-scale tests conducted twice at an EBCT of 10 and 20 minutes.

C.3.2 Approach

The objectives of this analysis are to: 1) evaluate the formation of BrTHMs and HAAs in a SDS scenario when the influent TOC concentration is reduced to 1 or 2 mg/L by GAC prior to chlorination; and 2) evaluate the removal of BrTHM formation by GAC as a function of the bromide level.

Data were extracted from the ICRTSD based on the GAC-effluent TOC concentrations of 1 and 2 mg/L, respectively, for surface water systems. Only surface water systems were evaluated because: 1) GAC has traditionally been applied to surface water sources (Hooper and Allgeier, 2002); and 2) 52 of the 63 GAC studies, or 83 percent, used surface water sources. One full-scale study was excluded. Data were binned into plants with either low- or high-bromide source water groups. For the 1-mg/L (GAC-effluent) TOC dataset, the median bromide concentration of 64 μg/L was used as the cut-off for the low- and high-bromide bins. For the 2-mg/L TOC dataset, the median bromide concentration of 75 μg/L was used as the cut-off.

Bromine incorporation into DBP groups (THMs and HAAs) was evaluated using a bromine incorporation factor (BIF) and percentage of bromide incorporation (PBI). The equations on how to calculate the BIF and PBI are provided below:

Equations

1) Calculate the bromine incorporation factor (BIF) using molar concentrations of the DBP species:

THM BIF = THM-Br/THM4s

$$= (0 \times CHCl_3 + 1 \times CHCl_2Br + 2 \times CHClBr_2 + 3 \times CHBr_3)/(CHCl_3 + CHCl_2Br + CHClBr_2 + CHBr_3)$$

HAA BIF = HAA-Br/HAA9

= (0 x ClAA + 0 x Cl_2AA + 0 x Cl_3AA + 1 x BrAA+ 1 x BrClAA + 2 x Br_2AA + 1 x $BrCl_2AA$ + 2 x Br_2ClAA + 3 x Br_3AA) / (ClAA + Cl_2AA + Cl_3AA + BrAA + BrClAA + Br_2AA + + $BrCl_2AA$+ Br_2ClAA + Br_3AA)

The values of *n* can vary between 0 and 3, depending on the degree of bromine substitution. For example, if all THM4 is chloroform, *n* = 0, and if all THM4 is bromoform, *n* = 3.

2) Calculate the Percent Bromide Incorporation (PBI) using mass-based concentrations of Br^- and DBP species:

THM4 PBI (%) = [79.9 x (($CHCl_2Br$/163.8) + 2 x ($CHClBr_2$/208.25) + 3 x ($CHBr_3$/252.7)) /initial Br] x 100%

HAA9 PBI (%) = [79.9 x ((BrAA/138.9) + (BrClAA/173.4) + 2 x (Br_2AA/217.8) + ($BrCl_2AA$/207.8) + 2 x (Br_2ClAA/252.3) + 3 x (Br_3AA/296.7))/initial Br] x 100%

C.3.3 Results

Exhibit C.22 presents a summary of SDS conditions for the 1- and 2- mg/L TOC datasets. Exhibit C.23 presents a summary of the GAC influent and effluent water quality when GAC reduced the influent TOC to 1 or 2 mg/L. Data for both THMs and HAAs are shown whereas subsequent analysis focused on THMs because of the greater available data for brominated species. (Note: HAA6 represents regulated HAA5 plus BCAA.) Exhibit C.24 presents a summary of the GAC effluent SDS THM species categorized into low- and high-bromide groups (influent bromide concentration less than 64 µg/L and 75 µg/L as cutoffs for the 1 mg/L TOC and 2 mg/L TOC datasets, respectively). All three exhibits provide descriptive statistics, including mean, 10^{th} and 90^{th} percentile and count.

Exhibit C.25 shows the THM3 and THM4 concentrations versus bromide concentration for all bromide levels.

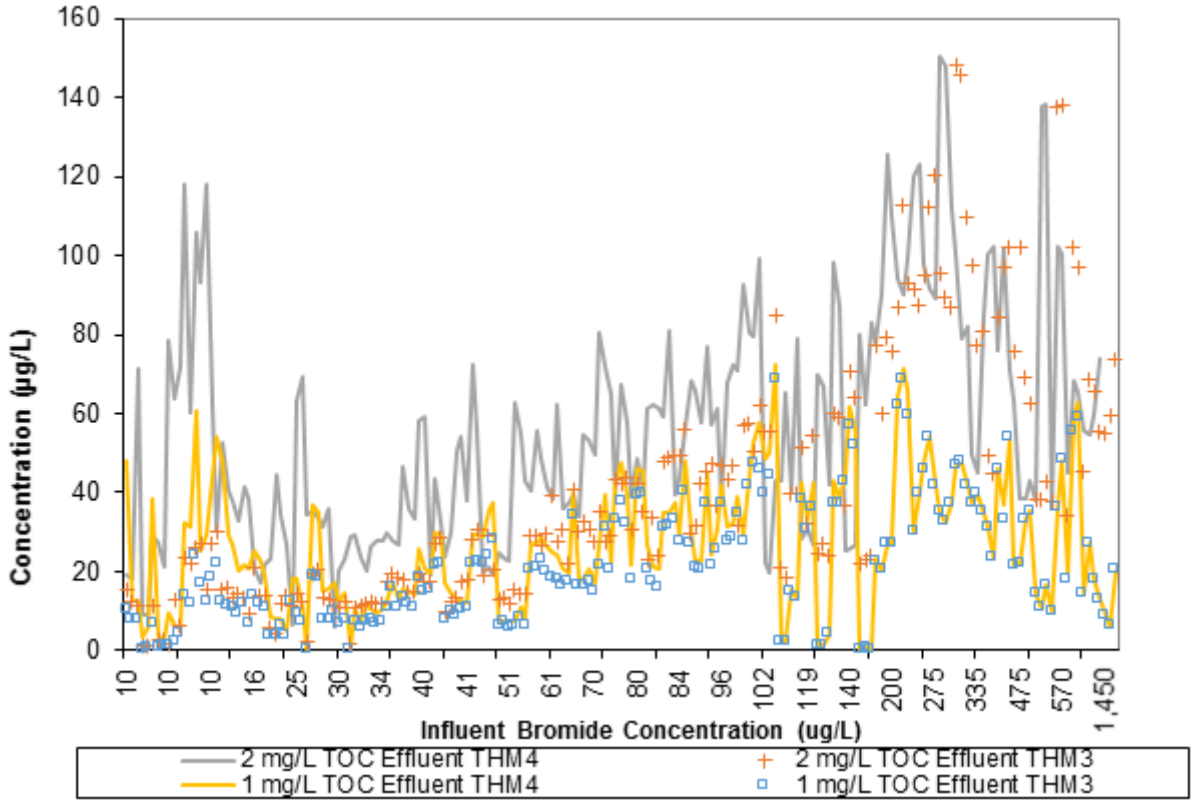


Exhibit C.26 and Exhibit C.27 show the SDS THM4 data when TOC is reduced to 1 or 2 mg/L for the high-bromide and low-bromide groups, respectively. Exhibit C.28 shows the reductions in SDS THM4 and SDS THM3 after GAC treatment for both 1- and 2-mg/L TOC datasets. Exhibit C.29 displays the median PBI for THM4s and HAA9 for the influent and effluent side-by-side for the 1- and 2-mg/L TOC datasets. Exhibit C.30 displays the median BIF for THM4s and HAA9 for the influent and effluent side-by-side for the 1- and 2-mg/L TOC datasets.

Exhibit C.22: Summary of SDS Conditions for the 1- and 2- mg/L TOC Datasets

Parameters	1-mg/L TOC Dataset			2-mg/L TOC Dataset		
	Mean	10^{th} - 90^{th} Percentile	Count	Mean	10^{th} - 90^{th} Percentile	Count
SDS Time (hours)	24	7-72	259	24	6-72	191
SDS Temp. (°C)	20	8-27	259	20	8-27	191
SDS pH	8.1	7.3-9.2	259	8.2	7.4-9.1	191
SDS Cl_2 Residual (mg/L)	0.9	0.6-1.3	259	0.9	0.6-1.2	191

SDS = simulated distribution system.

Exhibit C.23: GAC Influent and Effluent Water Quality for 1- and 2-mg/L TOC Datasets

Parameters	Influent			Effluent at TOC = 1 mg/L			Effluent at TOC = 2 mg/L		
	Mean	10^{th} - 90^{th} Percentile	Count	Mean	10^{th} - 90^{th} Percentile	Count	Mean	10^{th} - 90^{th} Percentile	Count
TOC (mg/L)	3.2	2.1-4.7	259	1.0	1.0-1.0	259	2.0	1.9-2.0	191
Br^- (µg/L)	64	10-335	259	Assuming unchanged.			Assuming unchanged.		
SDS THM4s (µg/L)	78	33-186	259	23	7-49	259	49	23-99	191
SDS THM3 (µg/L)	29	9-134	259	17	4-46	259	30	12-87	191
SDS HAA5 (µg/L)	34	16-69	251	7	2-14	251	16	7-33	184
SDS HAA6 (µg/L)	41	19-81	251	9	3-19	251	20	10-37	184
SDS HAA9 (µg/L)	54	25-93	137	13	6-26	129	28	16-45	94
SDS Br-HAAs (µg/L)	16	4-54	130	7	1-17	130	13	5-32	94
THM3/THM4s (%)	39	14-86	259	83	39-100	258	69	30-100	191
THM BIF	0.4	0.1-1.4	259	1.3	0.4-2.5	259	0.9	0.3-2.5	191
THM PBI (%)	31	13-52	259	20	2-44	259	28	11-55	191
Br-HAAs/HAA9 (%)	41	10-71	127	65	22-99	127	57	18-94	94
HAA BIF	0.4	0.1-0.9	127	0.8	0.2-1.7	127	0.6	0.1-1.6	94
HAA PBI (%)	12	6-28	127	6	2-16	127	10	5-21	94

Exhibit C.24: GAC Effluent Formation of THM Species for the 1- and 2-mg/L TOC Datasets

Parameters	1-mg/L TOC Dataset					
	Mean	10^{th} - 90^{th} Percentile	Count	Mean	10^{th} - 90^{th} Percentile	Count
	Low-Bromide Group (Br≤64 µg/L)			High-Bromide Group (Br>64 µg/L)		
SDS THM4s (µg/L)	16	7-33	129	33	13-62	129
SDS THM3 (µg/L)	10	2-21	129	31	13-59	130
SDS $CHCl_3$ (µg/L)	6	2-17	129	2	0-7	130
SDS BDCM (µg/L)	5	1-9	129	7	0-18	130
SDS DBCM (µg/L)	5	1-9	129	10	1-19	130
SDS $CHBr_3$ (µg/L)	0	0-3	129	11	3-31	130
	2-mg/L TOC Dataset					
	Low-Bromide Group (Br≤75 µg/L)			High-Bromide Group (Br>75 µg/L)		

Parameters	1-mg/L TOC Dataset					
	Mean	10th - 90th Percentile	Count	Mean	10th - 90th Percentile	Count
SDS THM4s (µg/L)	36	20-71	95	66	33-104	96
SDS THM3 (µg/L)	15	7-30	95	55	26-102	96
SDS $CHCl_3$ (µg/L)	19	8-45	95	3	0-23	96
SDS BDCM (µg/L)	10	2-18	95	13	1-32	96
SDS DBCM (µg/L)	6	2-15	95	19	8-38	96
SDS $CHBr_3$ (µg/L)	0	0-2	95	19	4-61	96

Exhibit C.25: Comparison of THM4 and THM3 Formations for 1- and 2-mg/L TOC Datasets

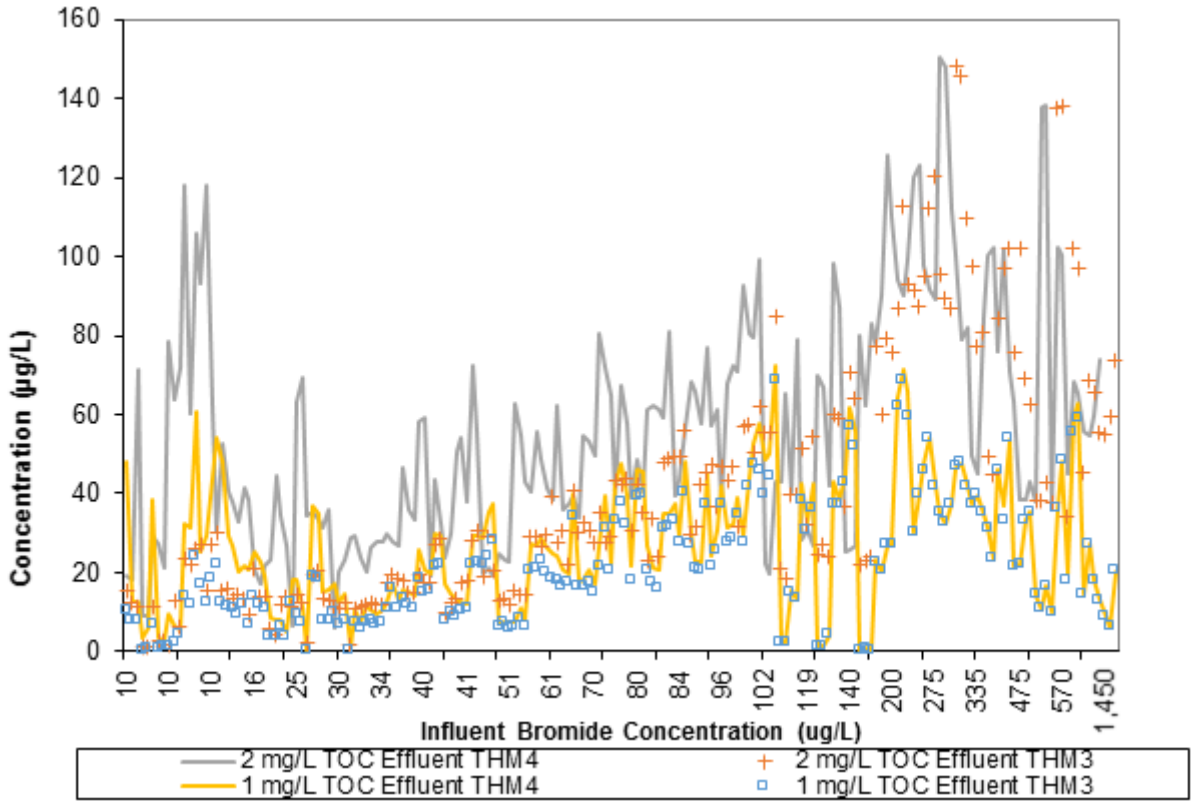


Exhibit C.26: Formation of THM4s when TOC is reduced to 1 or 2 mg/L – High Bromide Group

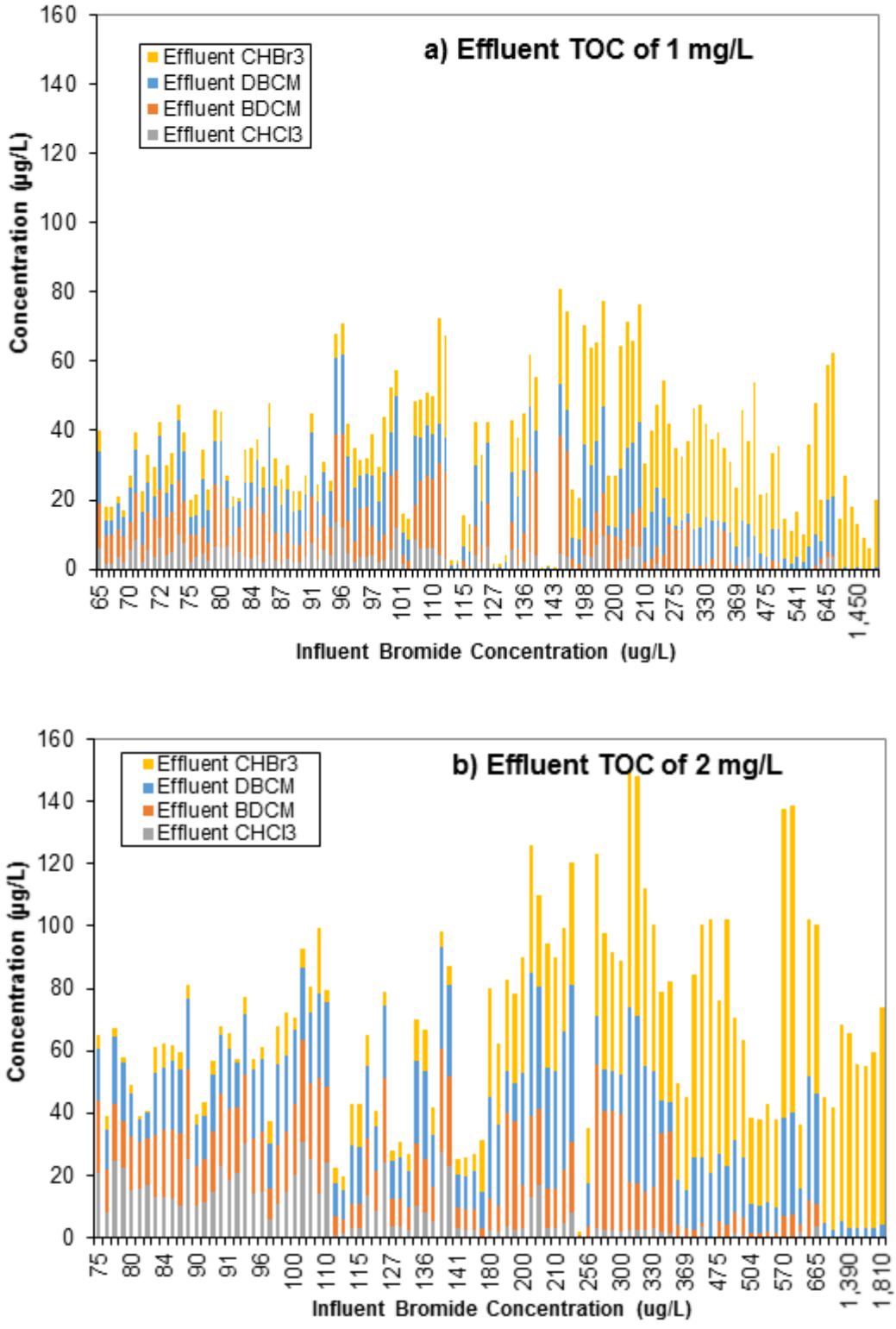


Exhibit C.27: Formation of THM4s when TOC is reduced to 1 or 2 mg/L - Low Bromide Group

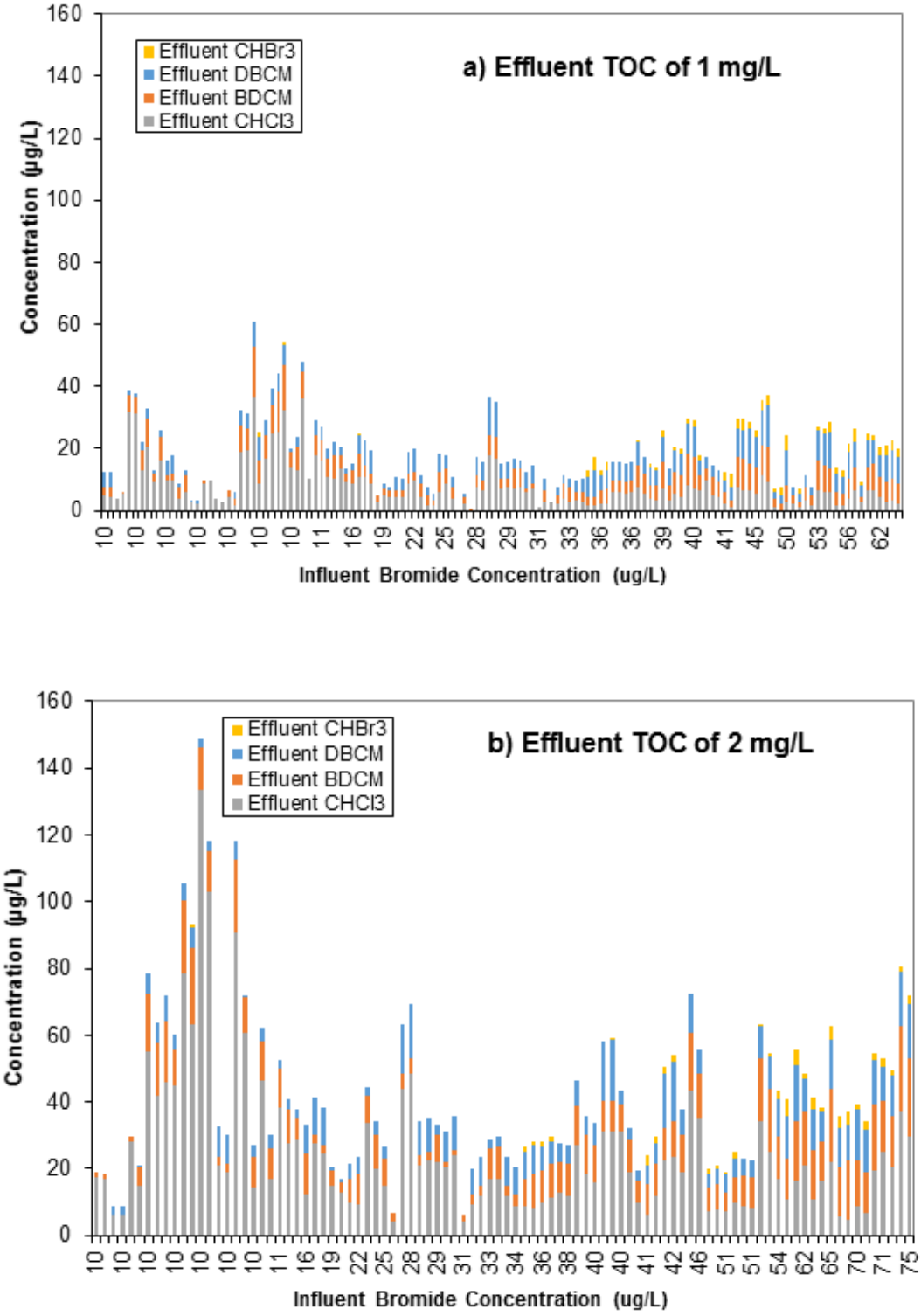
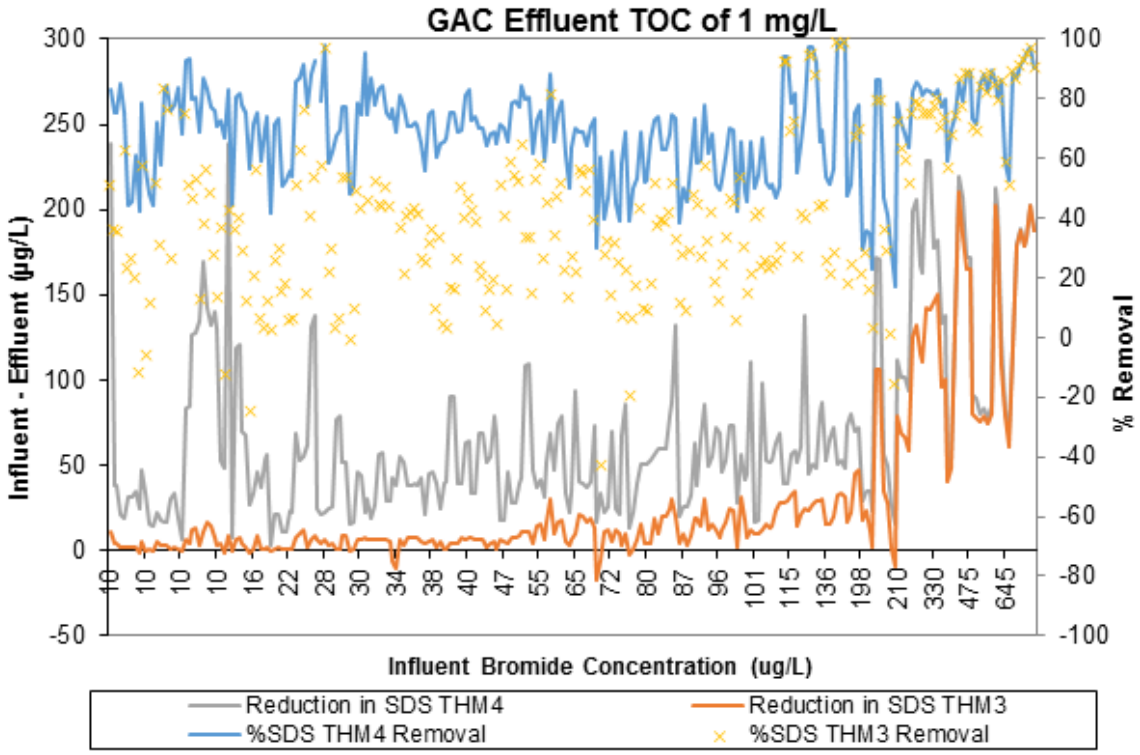


Exhibit C.28: Reductions in THM4s and THM3 Formation after GAC Treatment



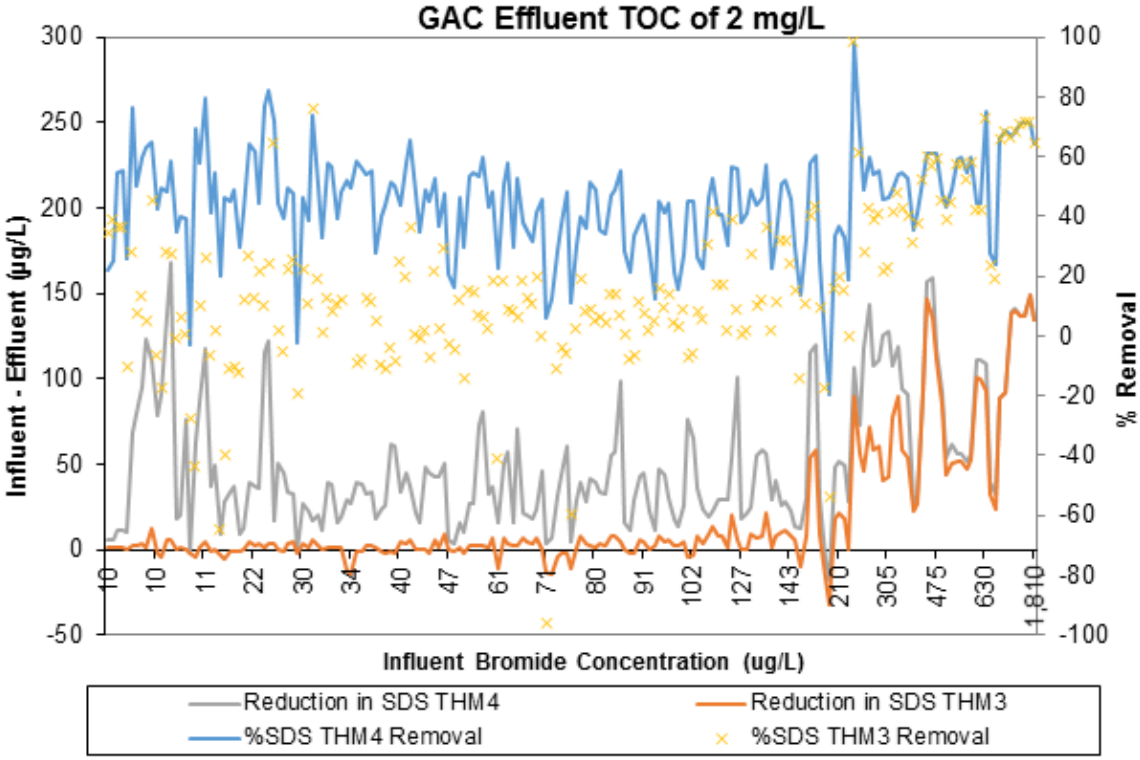


Exhibit C.29: Median Percentage of Bromine Incorporation in THM4s and HAA9

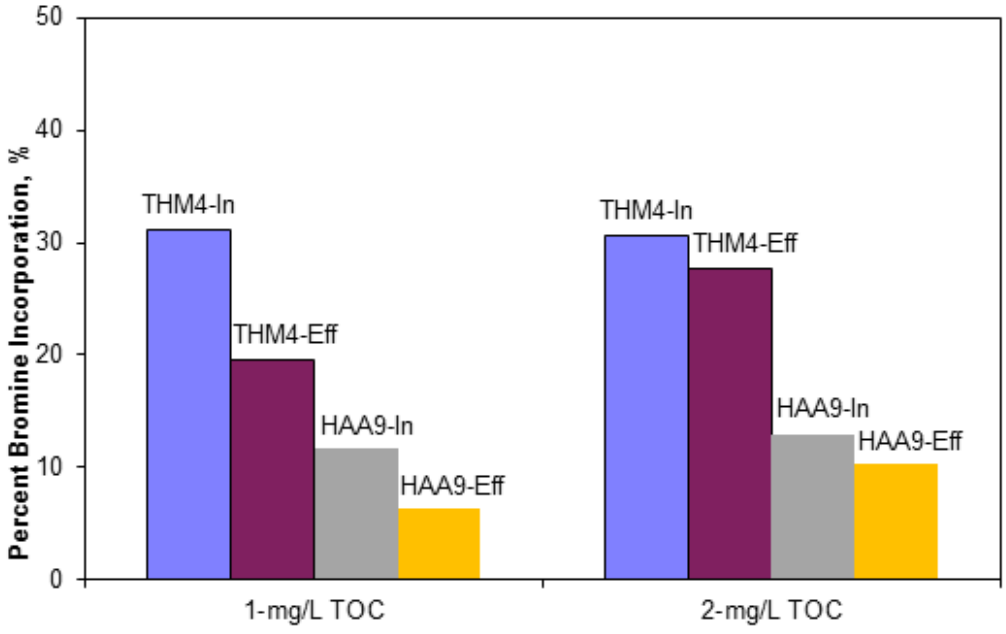
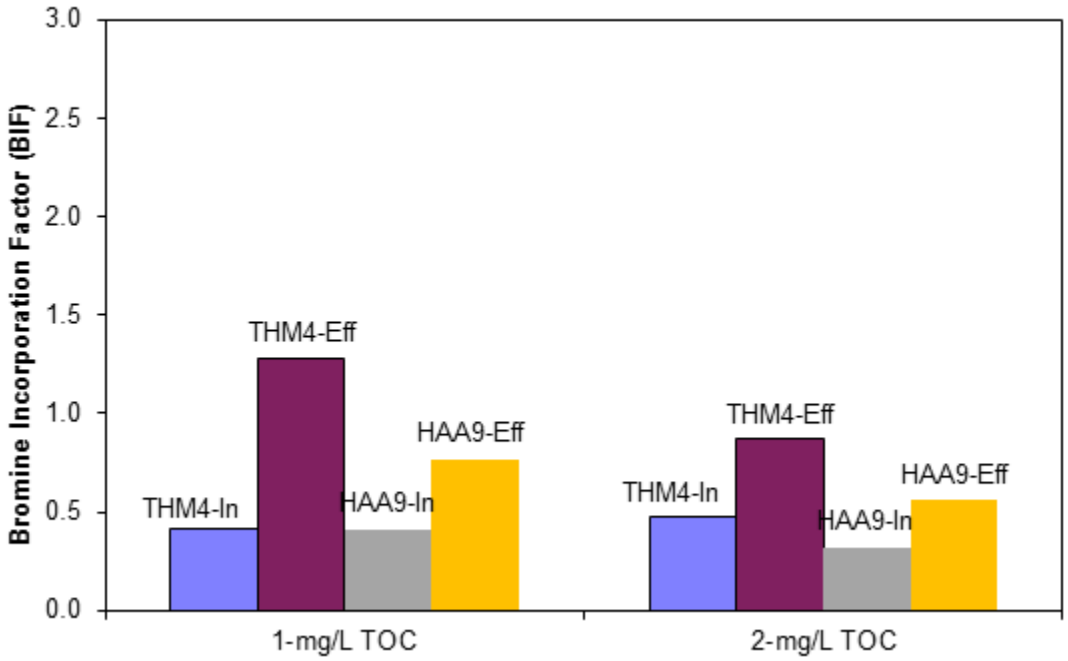


Exhibit C.30: Median Bromine Incorporation Factor in THM4s and HAA9



C.3.4 Observations

- For both 1-mg/L and 2-mg/L TOC datasets, the SDS THM data indicates a general shift in the relative THM speciation from chloroform-dominating to bromoform-dominating as the source water bromide level increases over a wide range of TOC characteristics and SDS conditions (Exhibit C.25).
- As the bromide concentration increases, formation of bromoform increases and becomes the dominating species when the source water bromide concentration exceeds 200 µg/L.
- When TOC is reduced to 1 mg/L, THM4 and HAA5 formation (at 90th percentile) is substantially below the MCLs of 80/60 µg/L. When reduced to only 2 mg/L, both THM4 and THM3 formation (at 90th percentile) exceeds 80 µg/L, but HAA5, HAA6, and HAA9 formation (at 90th percentile) is below 60 µg/L.
- Formation of both THM4 and THM3 is reduced by GAC in the 1- and 2-mg/L TOC datasets, except for a few data points where effluent THM3 formation is higher than influent (Exhibit C.26). Additional information would be needed to further evaluate the reasons why these data points showed an increase.
- As the TOC removal increases from a target effluent level of 2 to 1 mg/L, the percent reduction of BrTHMs generally also increases, especially for source waters with high bromide concentrations.
- The GAC process will result in a smaller PBI in treated water for both THMs and HAAs, similar to the effect of a coagulation process where a smaller PBI was observed for coagulated water (Sohn et al., 2006).

C.4 Advanced Oxidation Processes

Advanced Oxidation Processes (AOPs), including UV and ozone, have been used to remove NOM and organic micro-pollutants from surface water sources.

C.4.1 UV-based Applications

A combination of high UV doses and high hydrogen peroxide (H_2O_2) concentrations are needed to generate enough hydroxyl radicals to significantly reduce natural organic matter (NOM) when using UV/H_2O_2 applications (Matilainen and Sillanpaa, 2010). Excess H_2O_2 can act as a hydroxyl radical scavenger and reduce the effectiveness of the process.

Lamsal et al. (2011) and Jo et al. (2011) showed significant THM4 and HAA5 reductions but at higher UV doses (approximately 1200 mJ/cm^2) than typically used for drinking water treatment.

Chen et al. (2011) also found that high UV/H_2O_2 doses are required for removal of nitrogenous organic compounds. A recent study by Li et al. (2015) showed that high UV doses (1,400 to 4,200) by itself can increase production of monochloroacetic acid (MCAA), dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA) by forming a reactive intermediate. Matilainen and Sillanpää (2010) note that a potential drawback of UV applications is the formation of undesired byproducts, namely nitrite.

Chu et al. (2015) examined a novel UV/persulfate advanced oxidation method to control haloacetamide DBP precursors. Experiments were performed on filtered water samples with

DOC between 2.3 and 2.7 mg/L and a range of specific ultraviolet absorbance (SUVA) and dissolved organic nitrogen (DON). UV treatment was at 585 mJ/cm^2 using a low pressure UV lamp. Samples were then chlorinated for 24 hours with 1 mg/L chlorine residual. UV alone did not reduce haloacetamides, and persulfate alone broke down dissolved organic matter into smaller molecules but did not appreciably change DBP concentrations. However, 0.5 mM persulfate combined with UV treatment reduced acetamide concentrations between 79 percent and 91 percent. The treatment did not appreciably affect DOC concentrations, so the process did not result in mineralization of the organics. Nitrogenous DBPs such as dichloroacetonitrile (DCAN), trichloroacetonitrile (TCAN), trichloronitromethane and dichloronitromethane were also reduced between 60 and 100 percent. Bromate and sulfate concentrations, however, increased after treatment.

Matilainen and Sillanpää (2010) report that photocatalysis has great potential for degradation of DBP precursors due to the multiple ways it can oxidize organic compounds and remove them by adsorption. Kent et al. (2011) compared performance of UV/TiO_2 treatment using a nanostructure thin film coated with TiO_2 to using TiO_2 suspension. Results showed that the fixed film was less effective than using the TiO_2 suspension. Daugherty et al. (2011) found DBP formation increased at the UV dose of 5 kWh/m^3 but decreased at a UV doses of 80 and 160 kWh/m^3. Source water quality and organic content and characterization had a significant effect on treatment efficacy.

McCurry et al. (2015) considered the effectiveness of UV types (and other oxidants) on reducing nitrosamine formation. They examined low and medium pressure UV (and free chlorine and ozone). Experiments were performed at 10 plants representing a variety of DOC concentrations, wastewater impact and polymer use. Two of the waters selected had no *N*-nitrosodimethylamine (NDMA) formation potential by themselves but had doses of 1 or 6 mg/L polyDADMAC added. Medium-pressure (MP) UV reduced NDMA formation by 54 percent; LP UV was the least effective, lowering NDMA formation by 29 percent. MP UV showed lower effectiveness in waters treated with polyamine. At the lower doses, MP UV increased NDMA by a factor of 3.5 with the polyDADMAC. At higher doses MP UV saw continued increases.

Wang et al. (2015b) examined advanced oxidation using UV/chlorine with chlorine doses between 5 and 10 mg/L and high UV dose of 1800 mJ/cm^2. They found low THM and HAA formation from this process due to the low chlorine contact time, but they did find significant increases in DCAN and BCAN. The process also formed significant amounts of chlorate and bromate. The impact of this process on DBP formation resulting from subsequent chlorination (e.g., for distribution system residual) was not evaluated.

C.4.2 Ozone-based Applications

Chen et al. (2011) performed a bench scale analysis of a catalytic ozonation process whereby a catalyst, in this case TiO_2 coated aluminum, is injected into an ozonation-fluidized bed reactor. They evaluated the process with and without subsequent biofiltration for effects of ozone and catalyst dose as well as temperature and found that DBP formation decreased with increasing ozone and catalyst dose but was independent of water temperature. Results also showed that an ozone dose of 2.5 mg/L was required to reduce HAA5 to below 60 µg/L. Biofiltration effectively removed byproducts of ozonation (formaldehyde and acetaldehyde).

Bench-scale testing results from Lamsal et al. (2011) show that ozone/UV achieves mineralization of DOC and reduction in DBP formation potential, showing 77 percent reduction in THM4 formation potential and 52 percent reduction in HAA5 formation potential for ozone/UV (30 min ozone contact time, UV dose of 1140 mJ/cm2) and 70 percent reduction in THM4 formation potential and 31 percent reduction in HAA5 formation potential for H_2O_2/ozone (H_2O_2 concentration of 23 mg/L, 30 min ozone contact time).

Bose and Reckhow (2007) evaluated the effects of pre-and post-ozonation on the removal of various NOM fractions by enhanced coagulation. Results showed that while pre-ozonation increased the affinity of adsorption onto aluminum oxide surfaces for some NOM fractions, it decreased the affinity for adsorption for other fractions. For maximum NOM reduction, the authors proposed staged coagulation with an intermediate ozonation step for waters containing both humic and non-humic NOM.

Lin et al. (2015) found that 1 mg/L ozone removed 36 percent of DOC. The water treated had a DOC of 15.5 mg/L, a color of 79 hazen units, UV_{254} of 0.506 and a high humic content with most being in the 1,000 Dalton or higher molecular weight fraction.

Zhu et al. (2015) examined the effect of ozone on DBP formation from algal organic matter using ozone doses of 1.5 or 3.0 mg/L. TOC removal varied from 3.6 to 20 percent and SUVA removal was 60 percent. THM formation from the chlorination of extracellular algal matter increased; however, and for intracellular organic matter, THM increase was even greater. Increases were also seen in HAAs, mostly in the form of DCAA. Ozone did decrease haloacetonitriles (HAN) formation from extracellular organic matter, but increased it for intracellular organic matter. When chloramines were used, ozone reduced THMs by 43.6 percent for extracellular organic matter and 56 to 67 percent for intracellular organic matter. Ozone also decreased HAN formation with chloramines by 48.6 to 55 percent.

Plourde-Lescelleur et al. (2015) tested ozone doses of 0.5 or 1.0 mg/L and found that use of intermediate ozone had little effect on DOC or UV_{254} removal. Ozone reduced THM concentrations in all waters but had varying effectiveness with HAA concentrations, ranging from a 61 percent reduction to a 40 percent increase in HAA concentrations depending on the water quality. Ozone performed well in reducing the aromatic content of DOC.

Treatment for nitrosamine precursors in a river source in China was considered by Liao et al. (2014) using a pilot plant with conventional and advanced treatment with ozone and GAC. While ozone treated precursors effectively (e.g., median removal of 45 percent for NDMA and 22 percent for NDEA), GAC performed much better (e.g., median of 88 percent for NDMA and 83 percent for NDEA).

McCurry et al. (2015) studied the effect of pre-oxidation on nitrosamine formation, performing laboratory experiments using 14 water samples taken from 10 treatment plants. Plants were selected to represent a variety of DOC concentrations, wastewater impacts and polymer use. Two of the waters selected had no NDMA formation potential by themselves but had doses of 1 or 6 mg/L polyDADMAC added. NDMA formation potential was determined by exposing the treated samples to 2.5 mg/L chloramine at a 4.7:1 $Cl:NH_3$ ratio for three days. Ozone doses ranged from 0.2 to 2.0 mg/L. Ozone reduced NDMA formation by 78 percent. Ozone and MP UV showed

lower effectiveness in waters treated with polyamine. In the waters with polyDADMAC added, the NDMA formation without pre-oxidation was between 5.6 and 11 ng/L. At the lower doses, ozone increased NDMA by a factor of 6 with the polyDADMAC. At higher doses, chlorine caused a slight decrease in NDMA formation but ozone and MP UV saw continued increases. The mechanism for NDMA formation did not appear to be related to hydroxyl radicals, since scavengers had no effect.

Sohn et al. (2007) examined DOC removal after individual treatment processes in a plant with coagulation, sand filter, ozone and a biological filter. Coagulation removed the most DOC and SUVA. Removal in the filters increased in the summer months, likely due to biological activity. SUVA removal was greater than DOC removal, indicating the hydrophobic portion of DOC was removed better. Coagulation and ozonation were more effective at removing aromatic compounds, while filtration was more effective at removing aliphatic compounds. Ozonation caused the water to become more hydrophilic and other processes removed hydrophobic and hydrophilic portions evenly. Coagulation removed large molecular weight organic compounds better than smaller ones, as did ozonation. Biological filtration removed small molecular weight NOM better than larger molecular weight NOM. Total trihalomethane (THM4) formation was reduced the most through ozonation; HAAs formation was reduced the most by coagulation and ozonation. The filtration step did not effectively remove DBP precursors.

Fan et al. (2015) examined a novel pilot plant process combining coagulation, ozone, ceramic ultrafiltration and biologically activated carbon filtration. The membranes had a 60-nm pore size and 1.5 mg/L of hypochlorite was added for disinfection. The units were tested by themselves and in combination. Ozone addition significantly improved DOC removal, increasing removal by UF from 5 to 16 percent and removal by biological filtration from 45 to 65 percent. The entire process removed 73 percent of DOC. The process as a whole removed 50 percent of all THMs, 83 percent chloral hydrate, 77 percent DCAN, 51 percent TCAN, 96 percent trichloropropane and 63 percent trichloronitromethane. Ozone converted hydrophobic organic matter into hydrophilic organic matter and reduced organic matter from the 1,000 to 3,000 Dalton molecular weight range to the 200 to 500 Dalton range.

Xiao et al. (2015) examined the use of UV and hydrogen peroxide for the treatment of iodinated DBPs. Experiments were performed using deionized water, a model water and a natural water. Peroxide doses of 2, 6 and 15 mg/L were tested. The contaminant concentrations were set to 0.5 μM; the model water contained 1 mg/L DOC and 2 mmol HCO_3. The UV dose was 140 mJ/cm^2. The authors found a 4.65 percent removal of dichloroiodomethane and 25.8 percent removal of dibromoiodomethane. Higher peroxide rates increased the rate of reaction. The rate also increased slightly at lower pH. Humic substances and bicarbonate were found to interfere with the reaction. The reaction mechanism varied depending on the THM. Dichloroiodomethane degraded primarily by direct reaction with UV light while iodoform degraded mostly from reaction with formed hydroxyl radicals. The process does produce some iodate, about 2 percent of the total iodine reacted.

Shuai et al. (2012) evaluated palladium-based catalytic reduction using hydrogen gas as a clean reductant is a potential technology for removing DBPs from drinking water. Using synthesized palladium nanoparticles, the authors evaluated the activity of NDMA. Results suggested that

palladium catalysts can be tailored for optimal performance to treat a variety of contaminants in drinking water.

Radjenović et al. (2012) demonstrated use of reductive electrochemical treatment for removing low concentrations of halogenated DBPs in water. Electrochemical reduction was accomplished using a resin-impregnated graphite cathode at cathode potentials of -700, -800 and -900 mV vs. Standard Hydrogen Electrode over a 24-hour period. At the lowest potential applied (-900 mV vs. SHE), the reduction of 14 types of DBPs was greater than70 percent and 3 DBPs (chloral hydrate, chloroform, 1,1-dichloropropanone) were reduced by 31-48 percent. Other removal mechanisms (e.g., adsorption, volatilization and hydrolysis) may have partially contributed to these removal rates.

C.5 Alternative Disinfectants

C.5.1 Chloramines for Secondary Disinfection

Chen et al. (2014) evaluated chloraminated samples that had been in contact with tobacco for 24 hours to determine the precursors and reaction pathways of tobacco-specific nitrosamines formation. They confirmed that 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are byproducts from chloramine disinfection of raw water containing nicotine.

Hua and Reckhow (2007) compared DBP formation for chlorine, chloramines, chlorine with pre-ozonation, chloramine with preozonation and chlorine dioxide. They conducted experiments using seven geographically diverse surface water sources and measured both regulated and nonregulated DBPs. The results showed that while chloramines and chlorine dioxide generally form less THMs and HAAs than chlorine, they form more iodinated DBPS when iodide is present in source water.

Krasner et al. (2015) sought to develop improved strategies for controlling nitrosamine formation and develop a decision document for control alternatives. A wide range of bench-, pilot- and full-scale studies were conducted. Researchers found that polyDADMAC and polyamine are important nitrosamine precursors. Pre-oxidation is often effective at removing precursors, with ozone being most effective and permanganate being least effective. Powdered activated carbon (PAC) and GAC were also able to remove watershed-based precursors.

Lee and Westerhoff (2009) evaluated the formation of organic chloramines during chlorination and chloramination of 16 NOM solutions and 16 surface waters containing dissolved organic nitrogen. When the chlorine contact time was 10 minutes prior to ammonia addition, researchers found that organic chloramines made up 11 to 13 percent of the total combined residual measures. The proportion of organic chloramines was negligible, however, when preformed monochloramines were applied. The amount of organic chloramines formed increased as the proportion of DOC/DON decreased.

Luh and Mariñas (2014) studied the kinetics of bromochloramine formation from monochloramine and bromide ion and developed a model to predict concentrations of bromochloramine and other brominated DBPs under distribution system conditions. They determined reaction rate constants based on 11 datasets and used them to predict

monochloramine and bromochloramine concentrations for experimental conditions. The modeled values agreed with experimental data under most conditions tested.

McGuire et al. (2009) presented information on the use of chlorite ion to prevent nitrification during full-scale testing in isolated portions of the distribution system in Glendale, CA. The study consisted of 3 phases over 15 months and used a target chlorite concentration of 0.6 mg/L. Once the nitrification event was controlled by adding chlorine, the chlorite ion appeared effective at preventing additional events. Researchers concluded that chlorite application is effective at preventing nitrification, but ineffective at controlling nitrification once it is fully underway.

Nagisetty et al. (2014) conducted accelerated degradation tests in the laboratory on natural rubber, styrene butadiene rubber and sulfur-cured ethylene propylene diene monomer, three of the commonly used elastomers in water distribution systems. Chloroform was found to be a reaction by-product and other organic compounds (e.g., benzene, 1,2-benzisothiazole, styrene, toluene) leached from the elastomers. The researchers predicted that these compounds would continue to leach from elastomeric compounds over the long-term as the materials degraded in the presence of chloramines.

Park et al. (2015) examined NDMA formation from polymers added to treat water disinfected with chloramines. Their experiments were performed at pH 7.5 with 10 mg/L chloramine dose and 10 mg/L polymer. Both polyamine and polyDADMAC polymers were tested. More NDMA formed when ammonia was added before chlorine due to local dichloramine formation. Increasing the free chlorine contact time decreased NDMA formation, although it did increase free dimethylnitrosamine (DMA) when polyamine was used. The extra free DMA may not have resulted in NDMA formation because it may have become chlorinated, preventing it from reacting with chloramine. The highest NDMA concentrations were produced near the breakpoint for chlorination. With polyamine polymer, chloramine produced the most NDMA followed by chlorine, with ozone and chlorine dioxide forming the least. With polyDADMAC, ozone and chloramine formed approximately the same amount of NDMA; chlorine dioxide formed less NDMA, and chlorine formed the least.

Speitel et al. (2011) examined the role of THM4 in nitrification, to identify key factors that determine the risk of nitrification and to develop a practical framework for assessing the risk that can be used by water utilities. The study cites previous research by Wahman et al. (2006) showing that ammonia oxidizing bacteria (AOB) can biodegrade THM4 and that the byproducts of these reactions can actually be toxic to the AOB. Results from controlled laboratory experiments showed that THM4 can inhibit nitrification but at high THM4 concentrations (110 to 1,000 µg/L depending on the AOB species in the reactor biofilm).

Tian et al. (2013) studied DBP formation during chloramination of highly polluted source water that contained high levels of bromide and NOM. Ammonia was observed to inhibit the formation of DBPs.

Wert and Benotti (2010) conducted bench scale experiments on Lake Mead water to evaluate the reactions behind chloramine-based approaches to controlling bromate formation following ozonation. Researchers found that chloramines were more effective than ammonia alone in reducing bromate when ozone is used and that the order of addition of free chlorine and

ammonia did not matter. They found a chloramine dose of 1.5 mg/L was able to keep bromate under the MCL when ozone was used at a dose of 2 mg/L and with source waters containing bromide at concentrations up to 300 μg/L.

Wu et al. (2013) identified tobacco-specific nitrosamines as byproducts of chloramination in wastewater-impacted water treatment plants. Results suggested that tobacco-specific nitrosamines are a minor component of total nitrosamines in water.

Zhai et al. (2013) studied the formation of brominated DBPs during chloramination of simulated drinking waters. Chloramination favored the formation of aromatic and nitrogenous polar brominated DBPs. Bromochloramine and monobromamine were the major species formed, accounting for 54-58 percent and 42-46 percent, respectively, of the brominated DBPs formed.

C.5.2 Ozone

Bond et al. (2014) conducted laboratory experiments to determine why the combination of ozonation followed by chlorination enhanced the formation of chloropicrin. Experiments were conducted at pH 7 with an ozone dose of 5 mg/L. NOM precursors were dosed at 15 μmol and chlorine was added at a mole ratio of 15:1. Compared to chlorination alone, ozonation-chlorination increased the formation of chloropicrin from 138 to 3,740 percent for five individual NOM surrogates. NOM surrogates with amine groups were the most effective at producing chloropicrin.

Guo et al. (2007) constructed a pilot plant to study bromate formation using ozonation and biological activated carbon (BAC) filtration to treat reservoir water containing 15 to 38 μg/L of bromide. The pilot plant also included pre-ozonation, coagulation-sedimentation and sand filtration prior to ozonation. The total reaction time of the post-ozonation process was 16 minutes. Based on six months of continuous operation data, the authors found that an ozone dose of 2.0 mg/L (0.5 mg/L and 1.5 mg/L for pre- and post-ozonation, respectively) optimized the removal of organics (65 percent removal of trihalomethane formation potential (THMFP)) and limited bromate formation to less than 5 μg/L. The authors found that adding a post-ozonation step after sand filtration increased removal of THMFP to 65 percent compared to 13 percent removal with conventional treatment and 57 percent removal with pre-ozonation.

Kimbrough et al. (2010) used electrolysis prior to ozone to oxidize bromide to bromine which volatilizes. They performed bench top experiments using California State Project water with a bromide concentration of 250 μg/L. Applied current for the electrolysis ranged from 0 to 6 amps. Ozone doses were up to 4.3 mg/L. They obtained bromide removals of 27 to 50 percent depending on the current applied in electrolysis with higher current producing greater reductions.

Mao et al. (2014) studied DBP speciation with ozone dosage rates of 0 to 6 mg/L and subsequent chlorination. They used a synthetic water with 3.0 mg/L of humic acids at pH 8 and 300 μg/L bromide. In general, they found a shift to more brominated DBPs. At a 2 mg/L ozone dose, 55 percent of total DBPs were brominated.

Neeman et al. (2004) examined bromate mitigation techniques including pH adjustment, chlorine pre-oxidation and ammonia addition. They conducted pilot-scale testing with a water that

produced 20 to 25 μg/L of bromate with ozone doses sufficient to achieve 2-log *Cryptosporidium* inactivation. Chlorine pre-oxidation alone did not reduce bromate below the MCL. pH adjustment and ammonia addition were found to be effective but required large chemical doses. They found the most effective treatment was pre-chlorination with 0.5 mg/L of chlorine followed by addition of 0.1 mg/L ammonia. This treatment achieved a bromate concentration of 5 μg/L without requiring excessive chlorine doses to remove residual ammonia.

Shah et al. (2012) evaluated four primary disinfectants (ozone, chlorine, chlorine dioxide, UV) for their effects on NDMA formation using six water sources impacted by treated wastewater and four other treated water streams impacted by polyDADMAC polymer or ion exchange resin. Disinfectant doses were sufficient to achieve at least a 3-log reduction of *Giardia*. To test NDMA formation potential the samples were dosed with 2.5 mg/L chloramine after the oxidation treatment. Ozone reduced NDMA formation by 50 percent at exposures as lows as 0.4 mg-min/L whereas a similar reduction with chlorine required about 60 mg-min/L. In some cases pre-oxidation with chlorine led to increased NDMA formation at low chlorine doses. Chlorine dioxide showed little reduction in NDMA formation to increased formation with some waters. UV reduced NDMA formation by 30 percent at a UV dose of 500 mJ/cm^2. None of the oxidants caused regulated DBPs to increase above the MCL.

Wang et al. (2014) conducted bench-scale experiments to study DBP formation following ozonation for primary disinfection and either chlorination or chloramination for secondary disinfection. Natural lake water was treated with 0.6 to 1.0 mg/L ozone and either chlorine or chloramine. Compared to chlorination, ozonation at a dose of 0.6-1.0 mg O_3/mg DOC reduced levels of THAAs by 62 to 63 percent for chlorination, dihaloacetonitriles by 53-55 percent for chlorination and 14-26 percent for chloramination and THMs by 19 percent for chloramination. The formation of several other DBPs, however, increased significantly. Halonitromethanes increased by a factor of 4.7 to 5.6 for chlorination and 2.1 to 2.7 for chloramination. Haloketones increased 4.8 to 7.1 times with chlorination and 2.5 to 2.9 times with chloramination. Dihaloacetic acids increased 1.5 to 2.4 times with chlorination and 0.3 to 0.6 times with chloramination. Bromine substitution factors were higher when chlorine was used as the residual disinfectant than with chloramine.

Zhang et al. (2008) examined the effect of adding metal oxides to ozonated waters to reduce bromate formation. They examined bromide concentrations of 0.5 to 2.0 mg/L and ozone was 4.5 mg/L. They found that cerium oxide was the most effective, reducing bromate formation by 20 to 84 percent depending on bromide concentration and pH. FeOOH was also found to reduce bromate formation, but not as much as cerium oxide.

C.5.3 UV

Dotson et al. (2012) compared THM4 formation at three full-scale water treatment plants with and without UV disinfection. Of 27 water treatment plants responding to an online survey on implementing UV disinfection, the majority reported no effect on DBP formation. Two of the plants use chloramines for secondary disinfection and one uses free chlorine. UV dosage rates varied from 28 to 140 mJ/cm^2. THM4 concentrations varied by +/- 3 μg/L with and without UV treatment, with no discernable trend.

Liu et al. (2012) evaluated changes in NOM in four waters due to UV irradiation using low or medium pressure UV lamps followed by free chlorine or chloramine disinfection. Samples were dosed with 30 mg/L of chloramine or chlorine and then irradiated in laboratory apparatus for 300 seconds. The test waters were synthetic waters containing no bromide. UV disinfection at normal disinfection doses significantly increased the specific DBP formation potential (total amount of chloroform, dichloroacetic acid and TCAA formation potential normalized by dissolved organic carbon), with increases ranging from 8 to 48 percent. Increases were higher when chlorine was used than when chloramine was used.

Lyon et al. (2012) observed the formation of chloropicrin, bromopicrin, chloral hydrate and cyanogen chloride in three drinking water source samples treated with UV followed by either chlorination or chloramination. Chlorine was dosed at 1 mg/L. Chloropicrin formation doubled in nitrate-spiked samples (1-10 mg/L N/L) with 40 mJ/cm^2 medium pressure UV treatment followed by chloramination and increased three- to six-fold after UV treatment and chlorination. Bromopicrin formation increased in samples containing bromide (0.5-1 mg/L) and nitrate (1-10 mg N/L) when pretreated with either low-pressure or medium-pressure UV at 40 mJ/cm^2 followed by chlorination. Regulated THMs and HAAs were not affected by UV pretreatment at dosage rates of 40-186 mJ/cm^2 but THMs did increase by 30 to 40 percent at doses of 1000 mJ/cm^2.

Qian et al. (2012) conducted bench-scale testing to demonstrate how UV disinfection could remove or change halobenzoquinones (HBQs) in drinking water. Water samples spiked with 50 nmol HBQs at pH 7.5 were irradiated with low power UV lamps. At UV dosage rates of 50 and 200 mJ/cm^2 in tap water samples, removal rates of HBQs were 80 and greater than 90 percent, respectively.

C.5.4 Chlorine Dioxide

Linder et al. (2006) examined the use of chlorine dioxide at the Wemlinger water treatment plant in Aurora, Colorado. The plant came close to exceeding the chlorite MCL after switching from chlorine to chlorine dioxide (Linder et al. 2006). In July 2003, the plant began feeding chlorine at the same application point as the chlorine dioxide using a chlorine to chlorine dioxide feed ratio of 0.66:1. The chlorine reacts with chlorite to reform chlorine dioxide. Based on bench testing results, the feed ratio was changed to 1:1 to improve control of chlorite formation. THM4 levels were reduced from 50 μg/L to 35 μg/L when simultaneous dosing began in July 2003. Further reductions in THM4 levels from 35 μg/L to less than 20 μg/L were accomplished over the period 2004 to 2006 when chemical dosing was optimized.

Sorlini and Collivignarelli (2005) examined formation of THMs by chlorine dioxide and chlorine in batch tests in 10 natural surface water sources in Italy. The water ranged in pH from 7.6 to 8.5 with TOC between 2.4 and 6.0 mg/L and bromide between nondetect and 0.58 mg/L. Chlorine dioxide doses ranged from 0.4 to 2.9 mg/L. Chlorine dioxide resulted in reduction in THM4 formation by up to 98 percent from that formed by chlorine depending on the chlorine dose. Concentrations of THM4 never increased over 10 μg/L with chlorine dioxide even at the highest chlorine dioxide doses.

Williams and Persich (2014) investigated replacing chlorine with chlorine dioxide as a preoxidant for removing iron and manganese and reducing DBPs at a 13.5 millions of gallons per day (MGD) conventional surface water treatment plant on a Pacific island. They also investigated use of GAC and aeration. Raw water TOC levels were typically 2 to 3 mg/L. THM4 and HAA5 concentrations in the distribution system were 70 to 190 μg/L and 40 to 140 μg/L, respectively. Eliminating chlorination reduced these value to 30 to 70 μg/L and 10 to 35 μg/L respectively. Aeration reduced THMs by 50 percent initially, but the THMs reformed resulting in a final decrease in the distribution system of only 3 percent. Chlorine dioxide was the most effective preoxidant for removing iron and manganese and also reduced THMs and HAA5s by 34 and 53 percent, respectively.

Ye et al. (2013) investigated the formation of iodinated DBPs following chlorine dioxide addition under laboratory treatment conditions in China. They found that only about 1 μg/L of iodinated THMs were formed at 0.5 mg/L chlorine dioxide dose. Iodoform increased to 186 μg/L when chlorine dioxide dose increased to 2.5 mg/L. Further increases in chlorine dioxide dose led to less iodo-DBPs. Iodinated THMs increased with increasing iodide concentration with iodoform increasing from 12.2 μg/L at 0.6 mg/L iodide to 579.9 μg/L at 12.7 mg/L iodide. Iodoacetic acids were relatively stable with the same increase in iodide concentration. pH also had an effect on formation with both I-THMs and I-HAAs peaking at pH 8. Formation of I-THMs at pH 8 was about 10 times the formation at pH 5, while I-HAAs increased a factor of approximately 4. DOC concentrations also showed a maxima effect with iodo-DBP formation reaching a maximum between 4 and 7 mg/L DOC depending on the specific DBP. The researchers concluded that the use of chlorine dioxide in typical water treatment processes may not lead to substantial amounts of iodinated DBPs. The maximum formation of iodinated DBPs occurred at pH of 8.

C.5.5 Mixed Disinfectants/Oxidants

Compton (2007) examined a 3.5 MGD mixed oxidant plant in Kentucky. The plant had been using a chlorine dose of 3.0 mg/L. Switching to mixed oxidants allowed a dose of 1.5 mg/L while maintaining the same residual. They found a 33 percent drop in THMs at the plant after the switch to mixed oxidants.

Pisarenko et al. (2013) compared THM4 and HAA5 formation during treatment of Colorado River water with two different chlorine sources (a mixed oxidant solution and sodium hypochlorite) followed by UV light treatment. The water had a pH value of 8.1 and a TOC of 2.6 mg/L. The UV and chlorine doses used, however, were higher than typical doses used in water treatment. Comparable amounts of THMs were produced for all reactions and no differences were observed for samples treated by the mixed oxidant solution or sodium hypochlorite. Slightly more HAA5 were formed for samples treated with the sodium hypochlorite (37 μg/L) compared to samples treated with the mixed oxidant solution (34 μg/L).

Rodriguez-Mozaz et al. (2010) compared a mixed oxidant generator to traditional chlorination at pH 3.5. They found similar total DBP levels but the mixed oxidants produced more chloroform, TCAA and DCAA than chlorine.

C.6 Creation of the SYR3 ICR Paired TOC Dataset

The SYR3 ICR dataset contains TOC and alkalinity data from 2006 through 2011. A total of 43 states (34 SDWIS and 9 non-SDWIS states[4]) provided data for TOC and/or alkalinity. EPA applied the same filter protocol to TOC and alkalinity as was applied to the THM, HAA, chlorite and bromate data. For details on these QA/QC steps, including specific counts of records included and excluded in each step for TOC and alkalinity, refer to Appendix B (the appendix to Chapter 6).

To evaluate the percent removal of TOC using the SYR3 data, a "paired" TOC dataset was created that included, for each treatment plant, the average monthly concentrations of TOC and alkalinity in source (raw) water paired with the corresponding average finished water concentration of TOC. (Note that the raw and finished concentrations were not necessarily from the same sampling event but were from the same sampling location and month.) Exhibit C.31 describes the fields that are included in the file.

Exhibit C.31: Fields contained in the final "paired" TOC dataset

Field Name	Description
PWSID	Public water system identification number (PWSID)
Month	Month (1 through 12)
Year	Year (2006 through 2011)
Population Served (Retail)	Retail population served by the water system
System type	Water system type according to federal requirements C = Community water system NTNC = Non-transient non-community water system
Source Water Type	Primary water source for the water system. GU = Ground water Under Direct Influence of Surface Water GUP = Purchased Ground Water Under Direct Influence of Surface Water GW = Ground Water GWP = Purchased Ground Water SW = Surface Water SWP = Purchased Surface Water
Water Facility ID	Unique identifier for each water system facility.
State Facility ID	Identifier for each water system facility that is unique within a particular state
State Assigned ID Code	A state-assigned value which identifies the water system facility.

[4] About 75% of all states currently store and manage at least portions of their compliance monitoring data in the Safe Drinking Water Information System/State Version (SDWIS/State). The majority of states using SDWIS/State that submitted data to EPA used a SDWIS Query Extract Tool, developed and provided by EPA, to extract and compile the EPA-requested compliance monitoring data. The states not using SDWIS/State submitted their compliance monitoring data "as is," resulting in a variety of formats of datasets submitted to EPA. Furthermore, not all of the requested data from the non-SDWIS states was in a format usable to EPA for the SYR3 analyses.

Field Name	Description
Avg Of Raw TOC (mg/L)	Monthly average (in mg/L) total organic carbon (TOC) concentration in raw water
Avg Of Raw Alkalinity (mg/L)	Monthly average (in mg/L) alkalinity concentration in raw water
Avg Of Finished TOC (mg/L)	Monthly average (in mg/L) total organic carbon (TOC) concentration in finished water

Upon completion of the QA/QC review (as described in Appendix B to Chapter 6), the remaining TOC and alkalinity data were used to create a "paired" TOC-alkalinity dataset. This dataset presents, for each treatment plant, the monthly average concentrations of TOC and alkalinity in source (raw) water paired with the corresponding average finished water concentration of TOC. Exhibit C.32 documents the specific counts of records, systems and facilities included in each step of the creation of the "paired" dataset for TOC and alkalinity. Below Exhibit C.32 are more detailed descriptions of the steps described in this table.

Exhibit C.32: Counts of the number of records, systems and facilities/plants in each step to create the final "paired" dataset

Data Processing (DP) Steps	Alkalinity			TOC		
	# Records	# Systems	# Facilities / Plants[1]	# Records	# Systems	# Facilities / Plants[1]
Original count of records after QA Steps	201,682	15,059	25,628	232,567	2,836	6,041
DP Step 1: When facility flow data were available, calculated raw water plant-level averages (by linking to facility-flow table) for each month/year. See description of the facility-flow table below.	77,939	2,920	4,488	65,238	1,309	1,586
DP Step 2: Calculated finished water plant-level averages for each month/year	N/A	N/A	N/A	114,007	2,404	3,148
DP Step 3: Paired raw & finished plant-level averages for each month/year for all plants with raw water TOC, raw water alkalinity and finished water TOC	49,117	837	917	49,117	837	917
DP Step 4: When facility flow data were not available, raw & finished water plant-level averages for each month/year results could be paired if the raw and finished water results were both collected at the treatment plant (raw results prior to treatment and finished results after treatment). Note: These results do not represent a subset of the results from Steps 1 thru 3.	17,078	403	446	17,078	403	446
DP Step 5: Appended two sets of paired results together from Steps 3 and 4	66,195	1,209	1,333	66,195	1,209	1,333
DP Step 6: A final plant-level average was calculated for the situations when raw water from more than one facility (intake) was flowing to a single treatment plant. This final averaging step yielded a single (finished water) treatment plant average TOC value for each month/year.	66,067	1,209	1,333	66,067	1,209	1,333

Data Processing (DP) Steps	Alkalinity			TOC		
	# Records	# Systems	# Facilities / Plants[1]	# Records	# Systems	# Facilities / Plants[1]
DP Step 7: Removed additional records: non-zero TOC values (raw and finished) less than 0.1 mg/L and non-zero (raw) alkalinity values less than 1 mg/L	65,771	1,208	1,331	65,771	1,208	1,331

[1] For Steps 1 and 2, the column represents a count of facilities. For Steps 3 through 6, this column represents a count of (finished water) treatment plants.

Data Processing Steps 1, 2 and 3 (from Exhibit C.32):

For each month and year of data, raw water TOC and alkalinity averages were calculated at the plant-level. (Plant-level information was obtained by linking to the "facility flow" information contained within the SYR3 ICR database (via the field TINWSF_IS_NUMBER).[5] All non-detections were set equal to 0 for the calculation of averages. If multiple samples were collected in a given month for a particular location, the TOC (and/or alkalinity values) were averaged. Finished water TOC averages were calculated in a similar fashion at the plant-level for each month/year. Next, the raw water TOC, alkalinity and finished water TOC averages were paired (whenever possible) for each month and year of data.

Data Processing Step 4 (from Exhibit C.32):

Facility flow data were only provided by the SDWIS/State users; thus, no non-SDWIS/State users could be included in Steps 1 through 3 of the process. However, it was possible to pair raw and finished water results for some non-SDWIS/State users (as well as some SDWIS/State users) if both the raw water and the finished water results were collected at the treatment plant (i.e., raw results prior to treatment and finished results after treatment). Average raw water concentrations for TOC and alkalinity, as well as finished water concentrations for TOC, were calculated for these situations described above.

Data Processing Step 5 (from Exhibit C.32):

Plant-level averages from Steps 3 and 4 were appended into a single dataset.

Data Processing Step 6 (from Exhibit C.32):

There were situations when raw water from more than one facility (intake) was flowing to a single treatment plant. In these cases, all raw water values collected at more than one facility that led to a single treatment plant were averaged for a given month. Then that single average was linked up with the finished water average for the treatment plant. An example of this situation is presented below in Exhibit C.33a and C.33b.

The treatment plant "TP01" from the water system (AL0001313) presented in Exhibit C.33a had raw water results that were collected both at the intake (TYPE_CODE (Raw) = "IN"), as well as

[5] The SDWIS/Fed database, as well as SDWIS/State databases, include a table of facility flow information that indicates for a given PWSID the relationship between the various facilities (i.e., which facilities' water flows to another facility).

at the treatment plant (TYPE_CODE (Raw) = "TP") before treatment. In a situation such as this, the raw TOC (and raw alkalinity) from both raw source sites (facilities) were pooled for a given month, and the monthly average calculated. Likewise, finished water TOC concentrations from that month were averaged for the single (finished water) treatment plant to establish the corresponding (i.e., paired) monthly average finished water TOC value. Exhibit C.33b presents the results of that averaging; these are the numbers that appear in the final "paired" dataset.

Exhibit C.33a: Example of two raw water facilities that link to the same treatment plant

PWSID	Month	Year	TINWSF_IS_NUMBER (Raw)	ST_ASGN_IDENT_CD (Raw)	TYPE_CODE (Raw)	SixYrWsf_ID (Finished)	TINWSF_IS_NUMBER (Finished)	ST_ASGN_IDENT_CD (Finished)	TYPE_CODE (Finished)	Raw TOC (mg/L)	Raw Alkalinity (mg/L)	Finished TOC (mg/L)
AL0001313	12	2009	5544	IN001	IN	1176	3438	TP101	TP	3.9	18	1.6
AL0001313	12	2009	3438	TP101	TP	1176	3438	TP101	TP	2.2	18	1.6

Exhibit C.33b: Example of the averaging of the raw water results for the two facilities

PWSID	Month	Year	SixYr Wsf_ID	TINWSF_IS_NUMBER	ST_ASGN_IDENT_CD	Average of Raw TOC (mg/L)	Average of Raw Alkalinity (mg/L)	Average of Finished TOC (mg/L)
AL0001313	12	2009	1176	3438	TP101	3.05	18	1.6

Data Processing Step 7 (from Exhibit C.32):

After the final paired dataset had been created, it was determined that there were some potential low outliers for both TOC and alkalinity that remained in the dataset. All remaining individual TOC values (raw and finished) that were greater than 0 but less than 0.1 mg/L and alkalinity records (raw) that were greater than 0 but less than 1 mg/L were excluded as these data were thought to be unrealistically low and likely in error. (Note that the zeroes represented non-detections. As explained earlier, all non-detections were set equal to 0 for the calculation of averages.)

The final "paired" dataset includes average monthly raw water and finished water TOC concentrations at the treatment plant-level, along with raw water alkalinity concentrations for each year from 2006 to 2011. (Note that not all plants have results for all 12 months of each year.) A total of 65,771 results are included from 1,208 water systems located in 22 states.

Appendix D. Consideration of Other Regulatory Revisions for MDBP Rules – Additional Issues (Appendix to Chapter 8)

This appendix provides additional examples of implementation issues that are related to the Microbial and Disinfectants/Disinfection Byproducts (MDBP) rules.

D.1 Compliance Options for Consecutive Systems Receiving Finished Water with DBP Levels Close to MCLs

Consecutive systems have limited tools for compliance but are required to provide water that complies with federal and state requirements for DBPs. Under §141.64(b)(2), best available technologies (BATs) address ways to limit additional DBP formation once the consecutive system receives finished water; however, treatment to remove already formed DBPs is expensive and technically complex. Since many contracts between wholesale and consecutive systems address only quantity (not quality), consecutive systems may have difficulty complying. In particular, smaller systems have fewer compliance options and also have less "buying power" than relatively larger customers to modify contracts. EPA noted that there are limited DBP compliance options available for consecutive systems receiving water at or close to the TTHM or HAA5 maximum contaminant levels (MCLs) from a wholesale system (Chapter 7 provides information about DBP treatment technologies).

D.2 Stage 1 D/DBPR MRDL Monitoring — Public Water Systems with Source Water Ammonia

In some systems, monitoring for compliance with the maximum disinfectant residual (MRDL) may not fully capture the total concentration of residual disinfectant. Under §141.72, public water systems (PWSs) must maintain a residual disinfectant in their distribution system (monitoring requirements are discussed under §141.74 (b)(6)(i) for unfiltered systems, in §141.74 (c)(3)(i) for filtered systems, and in §141.132(c)(1) for disinfectant residual). Systems with ammonia in their source water and using free chlorine as a disinfectant will form chloramines until enough free chlorine is added to react with all the ammonia; after that point, residual chlorine will exist as free chlorine (this is called "breakpoint" chlorination). Systems should measure total chlorine to account for all chlorine exposure. However, systems that use free chlorine as a residual disinfectant, have ammonia in their source water, and measure free chlorine to determine compliance with the chlorine MRDL will not capture the chloramine portion and will therefore not accurately determine exposure and compliance with the MRDL.

Similarly, systems that use chloramine as a residual disinfectant often measure combined chlorine. If those systems do not control their processes well, they may add excess free chlorine so that the combined chlorine measurement may underestimate the actual exposure.

D.3 Stage 2 D/DBPR MCL Compliance Calculations

Some systems may be masking MCL violations by incorporating results of extra samples into their compliance calculations. Under §141.621(a)(2), systems are required to conduct monitoring at a quarterly or annual frequency, with very small ground water systems allowed to reduce monitoring to as infrequently as once every three years (§141.623). Also, systems are required to

include monitoring locations, monitoring dates and compliance calculation procedures as elements of their Subpart V (Stage 2 Disinfectants and Disinfection Byproducts Rule (D/DBPR)) monitoring plans – see 40 CFR §141.622(a)(1), in particular, paragraph (iii). No system is required to monitor more frequently than quarterly at any compliance location. However, states may require or systems may elect to conduct more frequent monitoring and that additional information is used in compliance calculations. Based on anecdotal reports, some systems monitor more frequently, but only when the quarterly sample shows a high level of DBPs and the system has a concern about MCL compliance. While there are good reasons to take more samples than the required minimum, there is an increased possibility of systems mischaracterizing exposure and MCL compliance when this occurs. For example, systems may take additional samples only when and where additional monitoring can help compliance calculations (and not when there may be no advantage). In this case, the systems may not appropriately weight compliance samples in a quarter, thereby distorting the degree of public health protection provided.

D.4 Stage 1 and 2 D/DBPR THM4/HAA5 Compliance Monitoring — Flushing Lines Before Sample Collection

Sampling practices at some systems may result in DBP samples that are not representative of the water in the distribution system. Analytical methods that require flushing prior to sampling are written with the intention of flushing the premise plumbing from within the building, such that samples are truly representative of the water immediately available from the distribution system. One example is EPA Method 551.1 (GC/Electron Capture Detection) (USEPA, 1995c), which is approved for THMs (see Section 8 on Sample Collection). This is also related to requirements in §141.621 to select sample locations based on high DBP levels. There have been reports that some systems collecting compliance samples at hydrants are flushing their distribution systems (not just their premise plumbing) immediately prior to collecting THM4 and HAA5 compliance samples. This reduces water age of the collected sample and (all other parameters being equal) reduces the observed levels of these DBPs. Flushing the distribution system immediately before compliance monitoring will result in underestimates of the actual exposure to THM4 and HAA5 and thereby distort the degree of public health protection provided.

Appendix E. Additional Information Related to Chlorine Burn Analysis

E.1 Introduction

Systems that use chloramines as a residual disinfectant (generally as part of a compliance strategy to meet DBP MCLs) often temporarily switch to free chlorine as the residual disinfectant for a period (from 2-8 weeks) in order to control nitrification in the distribution system. This practice is commonly called a "chlorine burn." During the chlorine burn, higher levels of DBPs (i.e., THM4, HAA5 and other chlorination DBPs) are expected to form. Systems often conduct their compliance monitoring outside of the chlorine burn period, and therefore, potentially higher THM4 and HAA5 levels are not included in compliance calculations. Actual exposures may be significantly higher than reported exposures in such cases.

The effects of chlorine burn periods on exposure to DBPs might become increasingly important in light of the potential adverse health effects (reproductive and developmental) related to short-term exposure to DBPs in chlorinated drinking. Further, such elevated concentrations of DBPs, depending upon their levels and duration, could be important for more accurately assessing running annual average (RAA) exposures. For example, if the burn period were for a month, the theoretical contribution of that month's THM4 or HAA5 occurrence could represent one-third of the occurrence for that quarter and if considered, could substantially affect the actual average concentration for that quarter as well as that for the RAA.

Data gaps exist for several areas related to chlorine burn – e.g., the percent of the industry that uses this practice, the frequency and length of time for which the burns are performed and the levels of DBPs produced by short-term exposures during those periods. This appendix provides an estimate of the impact of a switch in disinfectant use, specifically from chloramine to chlorine, on the levels of DBPs.

E.2 Data Sources

EPA considered a variety of available data sources to understand the increased concentrations of TTHM during a chlorine burn period. Insufficient information about this topic was provided in the SYR3 ICR. EPA found that information in the following two data sources was helpful for estimating the increase in concentration of THM4 during a chlorine burn:

1) DBP ICR Database (USEPA, 2000e) – A national database containing 18 months (i.e., July 1997 – Dec. 1998) of treatment and occurrence data for MDBPs for all of water systems serving more than 100,000 people (approximately 350 systems and 550 treatment plants). The information in this database was collected under the 1996 DBP Information Collection Rule (i.e., DBP ICR).

2) ICR Treatment Study Database (USEPA, 2000f) – A national database containing bench/pilot study results of GAC/membrane performance in the context of TOC removal among approximately 70 water treatment plants selected from the DBP ICR database, with high TOC levels in the source water. The information in this database also was collected under the DBP ICR. The database also was released to the public during the final stage of development of Stage 1 DBPR.

The DBP ICR database was examined to identify plants that used chloramines as a disinfectant (this was reported by calendar quarter). For those plant quarters, EPA identified the baseline concentrations of DBPs. Such concentrations were identified to serve as a proxy for the period outside of a chlorine burn.

Estimates of the concentrations of THMs during a chlorine burn period were obtained for the same plants from the ICR Treatment Study database (ICRTD). That database consists mainly of plants using chloramines being evaluated for the effects on TTHM and HAA occurrence upon application of GAC or membranes (bench and pilot scale studies) and use of a chlorine residual. As part of this effort, utilities collected simulation distribution samples (SDS), representing post treatment and distribution system water quality conditions, before and after application of GAC using free chlorine as the residual. Alternatively, the DBP ICR database includes SDS water quality samples with measurements of THM4 and HAA5 using chloramines as the disinfectant residual.

Both datasets contain a large amount of data elements. For the purposes of this analysis, only certain elements were culled from each source. The elements used are listed in Exhibit E.1. For both databases, the sampling date was converted to a calendar month (1 – 12) and quarter (1 – 4) to link entries between the two sources.

Exhibit E.1: Data Elements from DBP ICR AUX 1 Database and ICR Treatment Study Database

Key Data Elements
ICR DBP AUX 1 Database (AUX1)
PWSID
ICR Plant ID
Sample Period (7 -18, only last 12 months. Otherwise, some plant calendar quarters could appear twice with different treatment types or disinfectant types)
Sample Quarter (3 – 6, only last 4 quarters. Otherwise, some plant calendar quarters could appear twice with different treatment types or disinfectant types)
Plant Calendar Month (1 – 12, to be created per existing Plant Month ID)
Plant Calendar Quarter (1 – 4, to be created per existing Plant Quarter)
Source Water Type
Treatment Plant Type
Treatment Plant Disinfectant Type
Distribution System Disinfectant Type (CLM only)
Source Water TOC (used as a reference for finished water TOC. TOC could be reported monthly)
Finished Water TOC (to be compared with TOC in influent to GAC or membrane in ICRTD. TOC could be reported monthly)

Key Data Elements
Residence Time in DS (to be compared with the SDS incubation time in ICRTD)
TTHM/HAA5 at SDS (If multiple values exist, average shall be used to ensure a unique value for each quarter, to be compared with SDS TTHM/HAA5 levels in ICRTD)
TTHM/HAA5 at AVG1 and AVG2 (average of AVG1 and AVG2 shall be used to ensure a unique value for each quarter, to be compared with SDS TTHM/HAA5 levels in ICRTD)
Key Data Elements from ICR Treatment Study Database (ICRTD)
ICR Plant ID
TSID
Test Run ID
Sampling Date
RunStart
Plant Calendar Month (1 – 12, to be created per Sampling Date. If the Sampling Date is missing, the RunStart date shall be used)
Plant Calendar Quarter (1 to 4, to be created per Plant Calendar Month)
Sampling location ID (i.e., A, B, or C, to be created per plant treatability study reports)
Test Type (GAC or membrane)
Time_SDS
TOC in influent (If multiple values exist, average shall be used to ensure a unique value for each quarter)
SDS TTHM/HAA5 in influent (If multiple values exist, average shall be used to ensure a unique value for each quarter)

E.3 Methods

Exhibit E.2 shows the specific data elements from AUX1 and ICRTD that were used in the simulated chlorine burn analysis. The difference between the DBPs measured in the DBP ICR database (THM4 and HAA5 SDS measurements) and the analogous plant quarters in the ICRTD were used to serve as a proxy for the potential water quality implications of a chlorine burn as practiced by chloraminating systems. The two databases were linked based on the Plant ID and plant calendar quarter. The differences between TTHM, HAA5, TOC, and Residence Time values between the two databases were calculated as well as the percent difference of TOC and Residence time. These calculated elements will be used and discussed further in the Initial Results section below. Exhibit E.3 shows the data elements calculated in the analysis.

Exhibit E.2: Data Elements from AUX1 and ICRTD Used in Simulated Chlorine Burn Analysis

Data Element
PWSID
ICR Plant ID
Plant Calendar Quarter

Data Element
Treatment Plant Disinfectant Type
Test Type (GAC or membrane)
Source Water Type
AUX1 Finished Water TOC
AUX1 TTHM
AUX1 HAA5
AUX1 Residence Time (days)
ICRTD TOC in Influent
ICRTD TTHM
ICRTD HAA5
ICRTD Residence Time (hours)

Exhibit E.3: Data Elements Calculated in the Analysis

Data Element
ΔTTHM = ICRTD – AUX1(SDS)
ΔHAA5 = ICRTD – AUX1(SDS)
ΔTOC = ICRTD – AUX1
ΔTime = ICRTD – AUX1
%TOC Difference = (AUX1 - ICRTD)/AUX1
%Time Difference = (AUX1 - ICRTD)/AUX1

E.4 Initial Results

Based on the available data, direct comparisons were performed for 85 plant quarters and 33 plants at SDS, and 83 plant quarters and 32 plants at AVG. The results were divided based on primary disinfectant type used during the plant quarter; CL2_CLM plants were also further subdivided based on plant type. Calculations for the values listed in Exhibit E.3 were performed for each of the five categories of primary disinfectant types, along with the number of corresponding plants and plant quarters. Exhibit E.4 through Exhibit E.7 show the results for THM4, HAA5, TOC, and Residence Time for the SDS values. The "delta" and percent difference columns are highlighted in purple since those are the main variables of interest. The results at AVG are not shown, but were roughly equivalent to the SDS results.

Exhibit E.4: Results of THM4 Comparison

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTTHM
CLM	7	20	28.1 (0.0 – 63.0)	152.4 (41.6 – 253.1)	124.3 (-14.0 – 243.7)
CL2_CLM	19	45	45.1 (2.5 – 102.6)	197.0 (26.6 – 966.1)	151.9 (-25.6 – 910.1)

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTTHM
O3 or CLX	7	18	27.4 (1.2 – 111.2)	89.1 (32.3 – 150.0)	61.7 (-30.5 – 120.3)
CL2_CLM_CONV	8	16	54.6 (20.0 – 102.6)	283.2 (43.1 – 966.1)	228.6 (-10.0 – 910.1)
CL2_CLM_SOFT	11	29	39.8 (2.5 – 95.7)	149.4 (26.6 – 424.2)	109.6 (-25.6 – 394.7)

Exhibit E.5: Results of HAA5 Comparison

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔHAA5
CLM	7	20	18.5 (0.0 – 31.01)	58.3 (13.9 – 112.0)	39.8 (-10.4 – 97.0)
CL2_CLM	19	45	30.9 (9.6 – 71.8)	132.9 (15.6 – 1396.2)	103.4 (-36.8 – 1356.2)
O3 or CLX	7	18	17.8 (1.8 – 52.7)	33.9 (0.0 – 79.2)	17.1 (-6.9 – 54.9)
CL2_CLM_CONV	8	16	34.2 (17.7 – 64.3)	257.6 (33.5 – 1396.2)	225.5 (-2.2 – 1356.2)
CL2_CLM_SOFT	11	29	29.2 (9.6 – 71.8)	64.2 (15.6 – 291.9)	36.0 (-36.8 – 258.7)

Exhibit E.6: Results of TOC Comparison

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTOC	%DiffTOC
CLM	7	20	4.7 (0.9 – 12.9)	5.7 (2.6 – 11.5)	1.1 (-2.9 – 3.5)	-58% (-372% – 22%)
CL2_CLM	19	45	4.2 (1.8 – 11.8)	5.4 (2.0 – 16.7)	1.2 (-2.6 – 13.1)	-34% (-364% – 37%)
O3 or CLX	7	18	3.2 (1.9 – 4.9)	3.4 (2.1 – 4.9)	0.2 (-1.4 – 0.9)	-9% (-41% – 29%)
CL2_CLM_CONV	8	16	3.9 (1.8 – 8.4)	6.1 (2.1 – 16.7)	2.3 (-2.6 – 13.1)	-74% (-364% – 31%)
CL2_CLM_SOFT	11	29	4.5 (2.0 – 11.8)	5.0 (2.0 – 13.0)	0.6 (-1.6 – 3.7)	-11% (-54% – 37%)

Exhibit E.7: Results of Residence Time Comparison

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTime	%DiffTime
CLM	7	20	21.8 (7.2 – 48.0)	18.3 (3.0 – 47.6)	-3.6 (-18.6 – 11.1)	17% (-66% – 86%)
CL2_CLM	19	45	48.7 (12.0 – 182.4)	40.8 (40.8 – 232.3)	-7.9 (-72.4 – 49.9)	-1% (-300% – 78%)
O3 or CLX	7	18	50.1 (16.8 – 192.0)	31.9 (20.2 – 96.2)	-18.2 (-144.3 – 11.3)	13% (-67% – 75%)
CL2_CLM_CONV	8	16	37.4 (12.0 – 72.0)	43.0 (18.2 – 96.0)	5.7 (-24.0 – 48.0)	-27% (-200% – 50%)
CL2_CLM_SOFT	11	29	55.0 (12.0 – 182.4)	39.6 (6.0 – 232.3)	-15.4 (-72.4 – 49.9)	12% (-300% – 78%)

Based on the preliminary results, there is a notable increase in mean THM4 concentration when comparing the baseline results from the DBP ICR database with the chlorine burn proxy data from the ICRTD for all types of disinfectant. A similar, though smaller, trend occurs for HAA5. In both cases, there is a large range of DBP concentrations and subsequent differences; the largest difference is over 900 ppb. This large range may indicate that some of the plant quarters, though correctly linked between the two databases, are not similar enough to readily compare or may have elevated DBP concentrations for some other reason, such as sampling location. TOC and residence time were measured to determine if these parameters may explain some of these results. Some very high TOC values are reported in the ICRTD, which results in percent differences in excess of 300%. A similar type of trend was observed for the residence time in some quarters. These results indicate that some of the plant quarter comparisons may not be suitable to compare for the purposes of evaluating a simulated chlorine burn, since there are other variables besides chloramine/chlorine use that could affect the DBP concentration observed.

In order to remove the potential outliers or unusable data, plant quarters were flagged for removal based on different criteria. In the most restrictive case, if either the %DiffTOC or %DifTime were greater than 25%, then that plant quarter was removed from the analysis. A threshold of 50% was also used. The number of plants flagged for each disinfectant type is listed in Exhibit E.8. The 25% threshold leaves only 25 plant quarters in the analysis, compared to 44 based on the 50% threshold. The main disinfectant type associated with the outliers is CL2_CLM. For subsequent analyses, in order to balance a desire to remove outliers with the need to more fully assess the potential impact of a chlorine burn across a broader set of plants, any plants flagged not meeting the 50% threshold criteria were removed from the dataset.

Exhibit E.8: Number of Flags Based on %DiffTOC and %DiffTime Criteria

Primary Disinfectant Type	Number of Plant Quarters	Total Number of Flags		Number of TOC Flags		Number of Time Flags	
		|% Diff| < 25%	|% Diff| < 50%	|% Diff| < 25%	|% Diff| < 50%	|% Diff| < 25%	|% Diff| < 50%
All	85	60	41	31	10	45	31
CLM	20	13	8	10	3	6	5
CL2_CLM	45	36	26	17	10	30	16
O3 or CLX	18	10	6	4	0	8	6
CL2_CLM_CONV	16	11	11	7	6	7	5
CL2_CLM_SOFT	29	25	15	10	4	23	11

E.5 Results after Outlier Removal

Exhibit E.9 through Exhibit E.12 illustrate the results from the analysis after excluding the 41 plant quarters based on either the %DiffTOC or %DiffTime criteria. The overall trend is the same as before—there is a notable increase in THM4 concentrations when comparing the ICRTD to the DBP ICR database. However, the range of concentrations is much narrower due to the removal of outliers. The same results are apparent for HAA5, TOC, and residence time. Exhibit E.13 and Exhibit E.14 depict the distribution of ΔTHM4 with ΔTOC and ΔTime.

Exhibit E.9: Results of THM4 Comparison after Outlier Removal

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTTHM
CLM	5	11	21.4 (7.9 – 45.9)	185.1 (67.7 – 253.1)	163.7 (28.0 – 243.7)
CL2_CLM	10	21	47.3 (14.4 – 88.5)	188.6 (60.3 – 424.2)	141.3 (-10.0 – 394.7)
O3 or CLX	5	11	26.7 (1.2 – 111.1)	95.6 (47.1 – 150.0)	68.8 (-30.5 – 120.3)
CL2_CLM_CONV	3	6	53.2 (26.0 – 88.5)	182.6 (78.5 – 275.7)	129.4 (-10.0 – 244.8)
CL2_CLM_SOFT	7	15	45.0 (14.1 – 75.1)	191.0 (60.3 – 424.2)	146.0 (-3.9 – 394.7)

Exhibit E.10: Results of HAA5 Comparison after Outlier Removal

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔHAA5
CLM	5	11	18.7 (7.0 – 31.0)	77.3 (33.0 – 112.0)	58.6 (14.2 – 97.0)

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔHAA5
CL2_CLM	10	21	36.7 (9.6 – 71.8)	77.4 (20.2 – 291.9)	44.2 (-36.8 – 258.7)
O3 or CLX	5	11	22.1 (8.4 – 52.7)	39.9 (15.1 – 79.2)	19.8 (-6.9 – 54.9)
CL2_CLM_CONV	3	6	29.1 (17.7 – 61.7)	51.6 (33.5 – 77.3)	27.4 (-2.2 – 54.5)
CL2_CLM_SOFT	7	15	39.4 (9.6 – 71.8)	87.6 (20.2 – 291.9)	50.9 (-36.8 – 258.7)

Exhibit E.11: Results of TOC Comparison after Outlier Removal

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTOC	%DiffTOC
CLM	5	11	6.7 (2.4 – 12.9)	7.4 (3.4 – 11.5)	0.7 (-2.9 – 2.6)	-19% (-48% – 22%)
CL2_CLM	10	21	4.9 (2.2 – 11.8)	5.4 (2.4 – 13.0)	0.5 (-1.6 – 3.7)	-9% (-45% – 37%)
O3 or CLX	5	11	3.6 (2.3 – 4.9)	3.8 (3.2 – 4.9)	0.2 (-1.4 – 0.9)	-9% (-41% – 29%)
CL2_CLM_CONV	3	6	3.7 (3.0 – 4.4)	4.0 (2.8 – 5.8)	0.4 (-0.9 – 1.5)	-10% (-34% – 23%)
CL2_CLM_SOFT	7	15	5.3 (2.2 – 11.8)	5.9 (2.4 – 13.0)	0.6 (-1.6 – 3.7)	-8% (-45% – 37%)

Exhibit E.12: Results of Residence Time Comparison after Outlier Removal

Primary Disinfectant Type	Number of Plants	Number of Plant Quarters	ICR DBP	ICRTD	ΔTime	%DiffTime
CLM	5	11	22.0 (7.2 – 48.0)	21.2 (6.0 – 47.6)	-0.8 (-2.6 – 2.4)	6% (-11% – 17%)
CL2_CLM	10	21	47.7 (12.0 – 182.4)	45.8 (6.1 – 232.3)	-1.9 (-12.0 – 49.9)	14% (-27% – 49%)
O3 or CLX	5	11	44.1 (24.0 – 192.0)	35.4 (23.0 – 96.2)	-8.7 (-95.8 – 5.4)	5% (-12% – 50%)
CL2_CLM_CONV	3	6	33.6 (26.4 – 48.0)	31.8 (23.8 – 48.0)	-1.8 (-2.6 – 0.0)	7% (0% – 10%)
CL2_CLM_SOFT	7	15	53.3 (12.0 – 182.4)	51.4 (6.1 – 232.3)	-1.9 (-12.0 – 49.9)	17% (-27% – 49%)

Exhibit E.13: Distribution of ΔTHM4 vs. ΔTOC, All Plants after Outlier Removal

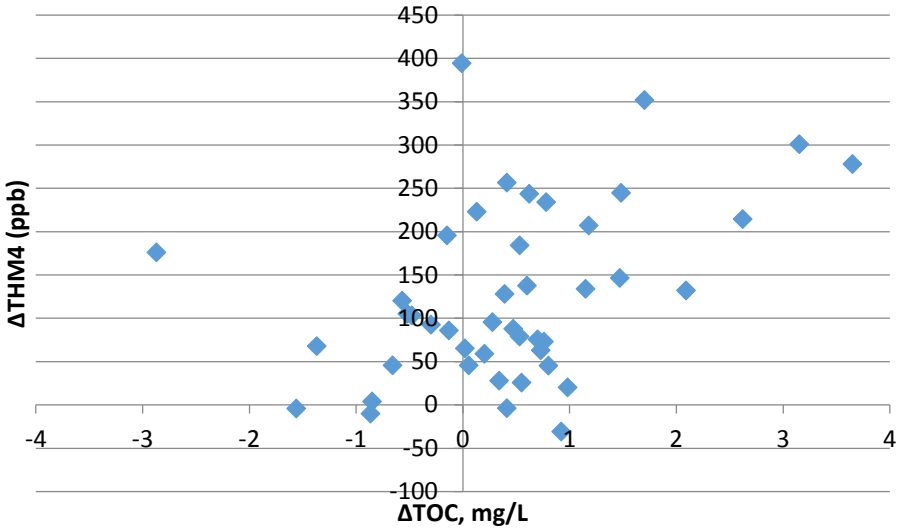
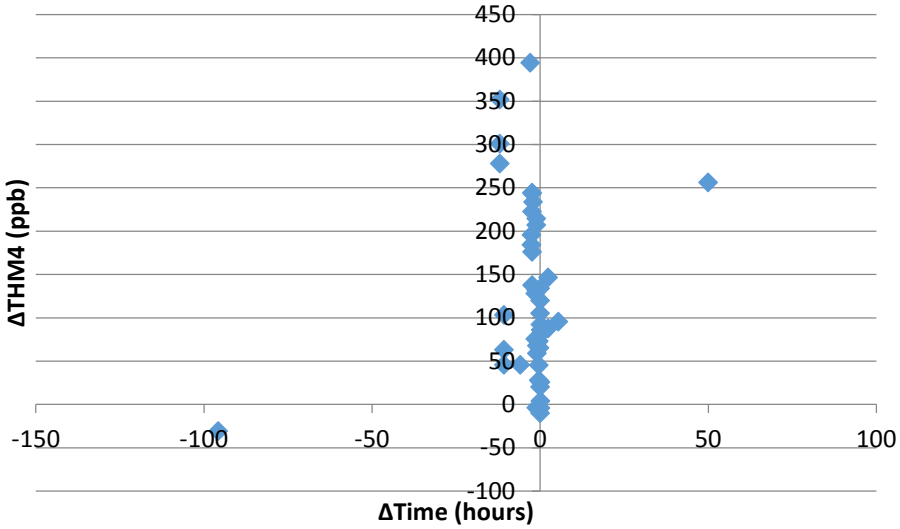


Exhibit E.14: Distribution of ΔTHM4 vs. ΔTime, All Plants after Outlier Removal



After removing the outliers via the 50% threshold, the results of the simulated chlorine burn analysis indicate that there is a likely potential for increased DBP concentrations in chloraminating plants during a chlorine burn. The difference between the DBP ICR and ICRTD THM4 levels indicate that many plants may observe a change in THM4 concentrations of at least 80 ppb. Since just the change alone is equivalent to the MCL, many plants might experience violations if samples during the chlorine burn were incorporated into the regular monitoring required under the SDWA. Exhibit E.15 depicts a distribution of all of the plants included in Exhibit E.9. As shown, approximately 60% of the plant quarters demonstrated an increase of THM4 concentrations by at least 80 ppb.

Exhibit E.15: Distribution of ΔTHM4 for All Plants Quarters Under 50% Threshold