Roadmap for Interdisciplinary Research on Drinking Water Disinfection By-Products

Susan D. Richardson

U.S. Environmental Protection Agency, National Exposure Research Laboratory, Athens, GA
What I will cover...

• Provide an overview
• Summarize important issues with drinking water DBPs
• Focus on emerging, unregulated DBPs
• Identify gaps and where we need to go next to solve this important problem

Drinking Water DBPs—What are the Issues?

Concern over possible human health risk:

• Epidemiologic studies: risk of bladder cancer; some cause cancer in laboratory animals

• Recent concerns about possible reproductive & developmental effects (from epi studies)

Goal: Comprehensively identify DBPs formed from different disinfectants, test for toxicity, understand their formation, minimize or eliminate in drinking water
Drinking Water DBPs: How are they formed?
Fig. 12.7 Chemical network structure of humic acids according to Schulten and Schnitzer. Reproduced by permission of Springer-Verlag.
DBPs discovered in 1974

FORMATION OF HALOFORMS DURING CHLORINATION OF NATURAL WATERS

By J.J. ROOK

Waterloo, Iowa

Investigations have shown that haloforms are produced during chlorination of humic substances in natural waters. In view of possible physiological effects it is suggested that some caution might be needed in applying chlorination in such waters.

1. INTRODUCTION

Gas chromatographic headspace gas analysis, described earlier by the author, has been applied to different types of surface waters for routine quality control of water treatment at the Beremonn plant. Treatment comprises storage, superchlorination, combined activated carbon addition and coagulation, filtration, cascade aeration and postchlorination.

This analytical method, which detects low polar volatiles, such as the lower alkanes, freons, chlorinated solvents and substituted benzenes and toluenes, has shown effective removal of such micropolllutants during the 3-weeks storage of the river water, the reduction varying from 40% in winter to over 90% in summer.

Interpretation of the results has been confused by the appearance of additional peaks in the chromatograms of chlorinated water. These have been identified as being due to the formation of various halo-forms by chloro-bromination of naturally occurring humic substances.

Headspace gas chromatography of a given surface water produces a "fingerprint" of peaks on the chromatogram that does not usually change very much over long periods. Identification of the peaks requires the use of a mass spectrometer, chromatographic retention times alone not being sufficiently characteristic. Mass spectrometry has confirmed, at least for river Rhine water, that the variety of volatile micropolllutants does not vary much from year to year, but there are seasonal changes.

Comparison of headspace fingerprints of water before and after breakpoint chlorination indicated that the volatile micropolllutants passed this treatment step in diminished concentrations. A less noticeable, and initially puzzling, observation was the appearance of four new peaks, which were clearly produced by chlorination (Fig. 1). Fortunately the concentrations of the four new micropolllutants in the water were significantly reduced in subsequent purification by adsorption on to powdered activated carbon. Their concentrations were further reduced by volatilization while flowing through open channels, by filtration and finally by cascade aeration, the overall removal amounting to 60-70%.

This investigation sought to identify these by-products of chlorination and the cause of their formation. This means tracing their origin in either impurities in chlorine or in the chlorination of precursor substances present in the water.

The Occurrence of Organohalides in Chlorinated Drinking Waters

T.A. Bellar, J.J. Lichtenberg, and R.C. Krone

The national media have reported that the chlorination of water during treatment is responsible for the formation of potentially harmful chlorinated organic materials—innocuous chlorines—in the nation's water supplies. The following report by the research scientists from the National Center for Environmental Research and the EPA describes the problem and provides guidance for those concerned.

In recent years there has been great speculation and concern about the effect of chlorination on organic materials contained in natural waters and wastewaters. Considering the widespread use of chlorine in water and sewage treatment processes, household and commercial laundering, paper-pulp bleaching, and related processes, it is not surprising that the potential treatment of organic compounds by chlorination processes is a cause for concern. This concern has been heightened by the discovery of chlorinated organic substances that may react with chlorine. The effect of these reactions is not well understood, and the use of chlorination may be restricted because of their potential to form these substances. This paper describes the occurrence of organohalides in chlorinated drinking waters and provides guidance for their control.

1974 V. 23, Part 2 June

Discovery of DBPs

Jon Rook

Tom Bellar
>600 DBPs Identified

Halogenated DBPs
- Halomethanes
- Haloacids
- Haloaldehydes
- Haloketones
- Halonitriles
- Haloamides
- Haloformethanes
- Halofuranones (e.g., MX)
- Oxyhalides (e.g., bromate)
- Many others

Non-halogenated DBPs
- Nitrosamines
- Aldehydes
- Ketones
- Carboxylic acids
- Others
>600 DBPs Identified

Halogenated DBPs
- Halomethanes
- Haloacids
- Haloaldehydes
- Haloketones
- Halonitriles
- Haloamides
- Halonitromethanes
  - Halofuranones (e.g., MX)
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  - Many others

Non-halogenated DBPs
- Nitrosamines
- Aldehydes
- Ketones
- Carboxylic acids
- Others

N-DBPs
But, more than 50% still not known....

Unknown 69.9%

- THMs 13.5%
- HAAs 11.8%
- HANs 0.8%
- HALDs 1.8%
- HKs 0.9%
- HACEs 0.5%
- IodoTHMs 0.2%
- Halofuranones 0.1%
- HNM 0.5%


~50% of TOX >1000 Da: Khiari, et al., Proc. 1996 AWWA Water Quality Technology Conference
Only 11 DBPs Regulated in U.S.

<table>
<thead>
<tr>
<th>DBP</th>
<th>MCL (µg/L)</th>
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<tr>
<td>Total THMs</td>
<td>80</td>
</tr>
<tr>
<td>5 Haloacetic acids</td>
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</tr>
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Little known about occurrence, toxicity of unregulated DBPs
Regulated DBPs do not cause bladder cancer in animals!
Only 11 DBPs Regulated in U.S.

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And, you will hear some odd things next from David DeMarini, such as…
- One regulated DBP **never** tested for cancer
- Two unregulated DBPs are carcinogens
- Many unregulated DBPs more genotoxic than regulated ones
Only 11 DBPs Regulated in U.S.

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There are still many gaps to fill!!
Bladder cancer and drinking water: Pooled analysis

OR adjusted by (sex), study, age, smoking status, ever worked in high-risk occupations, heavy coffee consumption and total fluid intake

Villanueva et al., Epidemiology 2004, 15, 357-367.
Exposure routes

Inhalation  
(shower, swimming pool, etc.)
Volatile DBP  
e.g. THMs

Ingestion  
(water, coffee, tea, water-based food and beverages)
All disinfection by-products

Dermal absorption  
(swimming pool, bath, etc.)
Permeable DBPs  
e.g. THMs, haloketones, ...

TOTAL INTERNAL DOSE

Slide courtesy of Manolis Kogevinas, Centre for Research in Environmental Epidemiology/IMIM, Barcelona
Route of exposure is important….

- Can get 2X exposure from 10 min shower compared to drinking 2L of tap water (inhalation)
- Some DBPs dermally absorbed
Route of exposure is important....

- Can get 2X exposure from 10 min shower compared to drinking 2L of tap water (inhalation)
- Some DBPs dermally absorbed

Does this mean that bladder cancer is caused by volatile or dermally absorbed DBPs??

Does this mean we shouldn’t worry about high MW DBPs?

Should we study rats taking showers?
Unlike other contaminants that may or may not be present in drinking water…

DBPs are ubiquitous
But…

On the new proposed U.S. EPA Contaminant Candidate List (CCL-3) for drinking water (104 chemicals)

Only 10 of 104 chemicals are DBPs:
5 nitrosamines, formaldehyde, acetaldehyde, benzyl chloride, chlorate, bromochloromethane

And, 4 of these chosen for other reasons (industrial contaminants, etc.)

Many other DBPs far more prevalent than these, but they are not listed as priorities
Emerging DBPs

- **Halonitromethanes** (up to 3 ppb; highly genotoxic); new *in vivo* effects; increased with preozonation

- **Iodo-THMs and Iodo-Acids** (iodo-THMs up to 15 ppb; iodo-acids up to 1.7 ppb; both classes highly cytotoxic or genotoxic); increased with chloramination
  Richardson et al., *ES&T* 2008, 42, 8330.

- **Haloamides** (up to 14 ppb; highly genotoxic) may be increased with chloramination

- **Halofuranones** (up to 2.4 ppb for total MX analogues; genotoxic, carcinogenic); chloramination can also form

- **Haloacetonitriles** (up to 41 ppb; ~10% of THM4; genotoxic, cytotoxic); may be increased with chloramination

- **Nitrosamines** (up to 180 ppt; probable human carcinogens) increased with chloramination
Emerging DBPs

- EPA Method 521 for nitrosamines (GC/MS/MS); sub-ng/L detection
- NDMA on draft CCL-3 and UCMR-2
Nationwide DBP Occurrence Study

- Prioritized >500 unregulated DBPs reported in literature (likely to cause cancer)
- Measured these in waters across U.S.
- Important findings:
  - New emerging DBPs identified (e.g., iodo-acids)
  - Alternative disinfectants increased formation of many priority DBPs
  - Many priority, unregulated DBPs found at significant levels

Halonitromethane Genotoxicity

Water Disinfection By-Product (mM)

Average Median SCGE Tail Moment

Acute Cytotoxicity

% Viable Cells

Dibromonitromethane
Bromonitromethane
Tribromonitromethane
MX (EMX)
Bromoacetic Acid
Dibromoacetic Acid
Tribromoacetic Acid
Ethylmethanesulfonate
Chloroacetic Acid
Dichloroacetic Acid
Trichloroacetic Acid
Bromate

Plewa et al., ES&T 2004, 38, 4713-4722.
Halonitromethanes also genotoxic to Salmonella (DeMarini et al.)
**DBNM produces DNA adducts in the livers of rats after only 30 days of exposure** (in vivo, male and female rats)

Tony also now seeing effects in normal human colon cells

Data courtesy of Tony DeAngelo & Leon King, U.S. EPA, NHEERL, RTP, NC
Iodo-THMs

New Iodo-Acids

Iodoacetic acid

Bromoiodoacetic acid

(Z)-3-Bromo-3-iodopropenoic acid

(E)-3-Bromo-3-iodopropenoic acid

(E)-2-Iodo-3-methylbutenedioic acid

Initially discovered using GC/MS
Highly genotoxic
Increase in formation with NH₂Cl vs. Cl₂
Occurrence Study now completed (23 cities in U.S. & Canada)

Chlorine:

\[
I^- + HOCl \xrightarrow{\text{fast}} HOI \xrightarrow{\text{fast}} IO_2^- \xrightarrow{\text{fast}} IO_3^- 
\]

Sink for iodide

HOCl also competes for rxn with NOM, so much lower iodo-DBPs with chlorine

Chloramines:

\[
I^- + NH_2Cl \xrightarrow{\text{fast}} HOI \xrightarrow{\text{slow}} IO_2^- \xrightarrow{\text{fast}} IO_3^- 
\]

HOI also has longer half-life in chloraminated waters

Adapted from Bichsel and von Gunten, 1999 and 2000
Genotoxicity of Iodoacetic acid


IA also caused developmental effects in mouse embryos (Hunter et al., 1995)
Haloamides

- New class of DBP recently identified
- Nationwide DBP Occurrence Study: up to 14 ug/L; NH$_2$Cl may increase their formation
- Highly genotoxic, cytotoxic
- New iodoamide DBP: Bromoiodoacetamide
  - Found in drinking water from 6 states

Haloamides--Cytotoxicity

Data courtesy of Michael Plewa, University of Illinois
Haloamides--Genotoxicity

Data courtesy of Michael Plewa, University of Illinois
Genotoxicity of Other DBPs

DBP Chemical Class

- Haloacetic Acids
- Haloacetamides
- Haloacetonitriles
- Bromo/iodo acetonitriles
- Bromo/iodo nitromethanes
- Halo nitromethanes

Single Cell Gel Electrophoresis Genotoxicity Potency
Log Molar Concentration (4 h Exposure)

Not Genotoxic: DCAA, TCAA, BDCAA, Dichloroacetamide, Chloroform
Chlorodibromomethane, 3,3-Dibromopropenoic Acid,
3-Iodo-3-bromopropenoic Acid, 2,3,3-Tribromopropenoic Acid

Data courtesy of Michael Plewa, University of Illinois
But, all of this toxicity testing is for separate, individual DBPs…

**DBPs**
are really present as **MIXTURES**

>300 DBPs probably present in glass of water
Integrated Disinfection By-products Mixtures Research: Toxicological and Chemical Evaluation of Alternative Disinfection Treatment Scenarios

A collaborative effort between:
NHEERL (National Health and Environmental Effects Research Laboratory), RTP
NERL (National Exposure Research Laboratory), Athens
NRMRL (National Risk Management Research Laboratory), Cincinnati
NCEA (National Center for Environmental Assessment), Cincinnati

Purpose:
To address concerns related to potential health effects from exposure to DBPs that cannot be addressed directly from toxicological studies of individual DBPs or simple DBP mixtures

Sid Hunter will cover this study on Tuesday
What about >50% unidentified DBPs that are believed to be high molecular weight?
Bioassay-Directed Research

Molecular size:
Ultrafiltration membrane device

Fractions collected: >5kDa  3-5kDa  1-3kDa  <1kDa  500-1kDa  <500Da

MS and Toxicity Characterization of drinking water fractions
Genomic DNA Damage Analysis of Ultrafiltration Fractions

Plant 1 (Chloramination, high Br)  
Corresponding raw waters not genotoxic

Plant 2 (Chlorination, low Br)
Genomic DNA Damage Analysis of Ultrafiltration Fractions

Does this mean that we don’t need to worry about DBPs >5000 Da?
Does this mean our focus on lower molecular weight DBPs was good?
But, what about 1000-3000 Da fraction?
DBPs can also form from pollutants...

- Pesticides
- Pharmaceuticals
- Antibacterial agents
- Estrogens
- Textile dyes
- Pesticides
- Bisphenol A
- Parabens
- Alkylphenol ethoxylate surfactants
- Algal toxins
Formation of NDMA from a fungicide

Schmidt and Brauch, *ES&T* 2008

Urs von Gunten also has new results indicating the catalytic effect of bromide on this reaction.
Formation of iodo-DBPs from X-ray contrast media

iopamidol + NOM $\xrightarrow{\text{HOCl, NH}_2\text{Cl}}$ iodo-DBPs

Richardson, Duirk, Lindell, Cornelison, Ternes, presented at Micropol Conference, June 2009
## Iodo-DBP Occurrence Study

<table>
<thead>
<tr>
<th>Plant</th>
<th>Iodide (µg/L)</th>
<th>Sum iodo-acids (µg/L)</th>
<th>Sum iodo-THMs (µg/L)</th>
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</thead>
<tbody>
<tr>
<td>Plant 2</td>
<td>1.0</td>
<td>0.37</td>
<td>4.9</td>
</tr>
<tr>
<td>Plant 4</td>
<td>ND</td>
<td>0.10</td>
<td>1.2</td>
</tr>
<tr>
<td>Plant 11</td>
<td>1.5</td>
<td>0.21</td>
<td>2.3</td>
</tr>
<tr>
<td>Plant 15</td>
<td>ND</td>
<td>0.17</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Detection limit = 0.13 µg/L

## ICM in U.S. Drinking Water Sources (ng/L)

<table>
<thead>
<tr>
<th>Plant</th>
<th>Iopamidol</th>
<th>Iomeprol</th>
<th>Iopromide</th>
<th>Iohexol</th>
<th>Diatrizoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant 1</td>
<td>11</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Plant 2</td>
<td>510</td>
<td>ND</td>
<td>24</td>
<td>120</td>
<td>93</td>
</tr>
<tr>
<td>Plant 4</td>
<td>110</td>
<td>ND</td>
<td>6</td>
<td>49</td>
<td>ND</td>
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<tr>
<td>Plant 10</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Plant 11</td>
<td>100</td>
<td>ND</td>
<td>ND</td>
<td>85</td>
<td>ND</td>
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<tr>
<td>Plant 12</td>
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<td>120</td>
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<td>Plant 13</td>
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<tr>
<td>Plant 15</td>
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<tr>
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<td>Plant 19</td>
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 Courtesy of Thomas Ternes, Federal Institute of Hydrology, Germany  
 ICM measured using LC/ESI-MS/MS; DLs = 5-20 ng/L
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*Courtesy of Thomas Ternes, Federal Institute of Hydrology, Germany*

ICM measured using LC/ESI-MS/MS; DLs = 5-20 ng/L
• Human health effects not solved yet—need more toxicity studies

• Studies on route of exposure
  Have we been looking at the wrong route of exposure?

• DBPs are present as complex mixtures—need toxicity studies addressing this

• What is in the unidentified fraction—anything of concern?

• What about ‘pollutant’ DBPs?

• What about DBPs from alternative disinfectants—do we know everything we need to know before plants switch?

• Chloramination? UV disinfection? Membrane disinfection?

• What about other respiratory/skin effects reported for chloraminated water? Need showering and dermal exposure studies
Serious skin rash issues….

“Before”
Showering with chloraminated water

“After”
Showering with chlorinated water at the YMCA in another town
Acknowledgments

Michael Plewa

Jane Ellen Simmons

Tony DeAngelo

David DeMarini

A few fabulous toxicologists who have helped push this field forward....

Also, Mike Narotsky, Sid Hunter, Rex Pegram, ....
In closing…

For the other chemists in the audience:

Ever wonder what happens when you have to scale things up for toxicity testing?

(Especially when working with Michael Plewa)
The Land of Extraordinarily Large Lab Equipment

Toxicity?
20 L → 1 mL

Chris
Steve
Cristal