Assessing Human Exposure and Odor Detection During Showering with Crude 4-(Methylcyclohexyl)methanol (MCHM) Contaminated Drinking Water

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Abstract

In 2014, crude (4-methylcyclohexyl)methanol (MCHM) spilled, contaminating the drinking water of 300,000 West Virginians and requiring “do not use” orders to protect human health. When the spill occurred, known crude MCHM physicochemical properties were insufficient to predict human inhalation and ingestion exposures. Objectives are (1) determine Henry’s Law Constants (HLCs) for 4-MCHM isomers at 7, 25, 40, and 80 °C using gas chromatography; (2) predict air concentrations of 4-MCHM and methyl-4-methylcyclohexanecarboxylate (MMCHC) during showering using an established shower model; (3) estimate human ingestion and inhalation exposure to 4-MCHM and MMCHC; and (4) determine if predicted air 4-MCHM exceeded odor threshold concentrations. Dimensionless HLCs of crude *cis*- and *trans*- 4-MCHM were measured to be $1.42 \times 10^{-4} \pm 6\%$ and $3.08 \times 10^{-4} \pm 3\%$ at 25 °C, respectively, and increase exponentially with temperature as predicted by the van’t Hoff equation. Shower air concentrations for *cis*- and *trans*-4-MCHM are predicted to be 0.089 and 0.390 ppm-v respectively after 10 min, exceeding the US EPA’s 0.01 ppm-v air screening level during initial spill conditions. Human exposure doses were predicted using measured drinking water and predicted shower air concentrations and found to greatly exceed available guidance levels in the days directly following the spill. Odors would be rapidly detected by 50% of individuals at aqueous concentrations below analytical gas chromatographic detection limits. MMCHC, a minor odorous component (0.935%) of crude MCHM, is also highly volatile and therefore is predicted to contribute to inhalation exposures and odors experienced by consumers.

1. Introduction

Worldwide, industrial chemical spills are responsible for contaminating drinking water and requiring drinking water intakes be closed or taking severe measures such as issuing “do not use” orders to protect the public health (Capel et al. 1988; Koch 2015; Manuel 2014; Zhang et al. 2011). The United States Coast Guard National Response Center (2014) reported almost 30,000 oil spills, chemical releases, or maritime security incidents in 2014. Many chemical spills that contaminate drinking water have noticeable organoleptic properties which may also produce psychological fear in consumers (Young et al. 1996; Romero et al. 1998; Boleda et al. 2007; Hrudey & Hrudy 2007; Ventura et al. 2010; Dietrich and Burlingame 2015). When contaminating industrial chemicals produce odorous volatile compounds that are readily perceived by consumers, then the affected human population will be potentially exposed through both ingestion and inhalation (Ömür-Özbek et al. 2011; Dietrich and Burlingame 2015). One such incident occurred in the early morning of January 9, 2014, when 10,000 gallons of licorice-smelling crude (4-Methylcyclohexyl)methanol (MCHM) spilled into the Elk River, which was a chilly 5 °C (Foreman et al. 2015). Some of the contaminated water passed through the drinking water treatment facility located 1.5 miles downstream, subsequently contaminating the distribution system and drinking water of over 300,000 people in Charleston, West Virginia and surrounding counties (Cooper 2014; Manuel 2014).

During the day of January 9, crude MCHM’s strong licorice-odor informed West Virginians that their drinking water and breathing air were contaminated hours before government and water utility officials made public announcements and issued “do not use” orders later that evening (Gallagher et al. 2015). The Centers for Disease Control and Prevention (CDC) established a temporary health based screening level of 1 ppm in water (ppm-aq) on January 17, 2014 after a

review of limited animal studies (CDC 2014b). Contaminant monitoring programs were quickly established for drinking water (Foreman et al. 2015; Whelton et al. 2015; WVDHSEM 2014). While crude MCHM contains at least four *cis* and *trans* substituted cyclohexane isomer pairs, plus other chemicals (Gallagher et al. 2015), only the major component, combined *cis*- and *trans*-4-MCHM, was quantitated and reported as a single value of 4-MCHM at detection limits from 2-10 ppb-aq (Foreman et al. 2015) . The only air monitoring data for crude MCHM components are odor reports by humans, as no instrumental air-sampling data were reported.

The maximum 4-MCHM concentration measured in distributed drinking water was 3773 ppb-aq, measured on January 13 (WVDHSEM 2014). Human exposure to crude MCHM in drinking water occurred for weeks following the spill as indicated by consumer complaints of licorice odors in air and when using water (Maunz 2014) and also monitoring data that reported concentrations as high as 43 ppb-aq 4-MCHM in April, 2014 (Foreman et al. 2015; Whelton et al. 2015). On February 6, 2014, three schools in Charleston, WV were closed due to licorice odors and eleven additional schools entered complaints to the health department on the same day although aqueous 4-MCHM was below detection. The complaints were associated with hot water usage in bathroom taps, classrooms, and kitchen taps and dishwashers (Maunz 2014). Residents complained of adverse health effects including skin and eye irritation, nausea, vomiting, and diarrhea resulting in 369 visits to the emergency room in the 14 days following the spill (WVBPH and ATSDR 2014). These health effects are consistent with the material safety data sheet for crude MCHM which cautions that it is “harmful if swallowed”, “causes skin and eye irritation”, and “at elevated temperatures, vapor may cause irritation of eyes and respiratory tract” and recommends medical attention be sought following inhalation, contact, or ingestion exposures (Eastman Chemical Company 2011). Recent studies indicate 4-MCHM is moderately

toxic in human and yeast cells; 4-MCHM metabolites are more toxic than 4-MCHM and both 4-MCHM and its metabolites should be considered potential carcinogens (Lan et al. 2015).

Additional studies are underway to characterize the toxicity of crude MCHM and its components, including minor component methyl 4-methylcyclohexanecarboxylate (MMCHC), across a spectrum of biological processes (NTP 2014).

Consumers were not only alarmed by the health implications of the spill; there were also significant aesthetic and psychological impacts associated with drinking the water and breathing air with licorice odors. Odors in drinking water are a recognized indicator of drinking water quality and consumer confidence and as such their presence and removal are a concern for utilities (Romero et al. 1998; Knappe and Viswakumar, 2011). Odors are therefore regulated as a secondary maximum contaminant level by the US EPA (Dietrich and Burlingame 2015; U.S. EPA 1979). A population odor threshold for aqueous crude MCHM in 19-21⁰C distilled water was determined to be 0.55ppb-aq (McGuire et al. 2014). Gallagher et al. (2015) determined that *cis*-4-MCHM and *trans*-4-MCHM have overall population odor threshold concentrations (OTC), in air, of 120 ppb-v and 0.060 ppb-v respectively. Only the *trans*-isomer was predominantly described as having a strong, sweet licorice odor. Individuals previously exposed to MCHM odors have a 5.6-fold lower odor threshold concentration ($OTC_{\text{exposed,trans}} = 0.018$ ppb-v) than naïve, or unexposed, individuals ($OTC_{\text{naïve,trans}} = 0.102$ ppb-v) (Gallagher et al. 2015). In July 2014, a 30-day air short-term screening level for 4-MCHM was issued at 0.01 ppm by volume in air (ppm-v), equivalent to 10 ppb-v, which was designed to be protective of children, assuming body weight = 10 kg and inhalation rate of 17.3 m³/day (U.S. EPA 2014). Foreman et al. (2015) indicated minor crude MCHM components *cis*- and *trans*- MMCHC have high volatility and also possess a licorice-odor; no human health or odor threshold data available for MMCHC.

At the time of the spill there were few data about the physicochemical, odor-threshold, or toxicological properties of crude MCHM. Air exposure concentrations can be calculated from water concentrations if the Henry's Law Constant (HLC) and temperature are available, which they were not for *cis*- or *trans*-4-MCHM or MMCHC at the time of the spill (Eastman Chemical Company 2011; TCI America 2006). Drinking water is used at varying temperatures including chilled to 4-7 °C for drinking, typically at 40 °C for showering, and up to 80 °C for washing dishes (Virginia Department of Agriculture and Consumer Services 2010; Zhou et al. 2007). During the “do not use” order, 37.4% of affected households reported using the contaminated water. Of these households, activities included showering or bathing (80.1%), washing clothing (37.7%), and dishwashing (32.2%), all of which may use heated drinking water (CDC 2014b). After the “do not use” order was lifted, but prior to February 1, 66.8% of households reported using the water for showering or bathing (91.8%), washing clothing (93.8%), and dishwashing (67.6%) (CDC 2014b).

Henry's Law (1) defines the ratio of the gas phase concentration (C_{gas}) of a substance to the aqueous phase concentration ($C_{aqueous}$) at equilibrium:

$$C_{gas} = HLC * C_{aqueous} \quad (1)$$

where HLC is the dimensionless Henry's Law Constant for a given chemical and temperature.

The HLC temperature dependency can be modeled with the van't Hoff equation (2):

$$\ln \left(\frac{HLC_1}{HLC_2} \right) = \left(\frac{\Delta H_{soln}}{R} \right) \left[\frac{1}{T_2} - \frac{1}{T_1} \right] \quad (2)$$

where HLC_1 = the dimensionless HLC at temperature = T_1 in Kelvin, R is the universal gas constant as 8.314 J/(mol*K), and ΔH_{soln} is the enthalpy of vaporization from aqueous solution

(J/mol) for the specific chemical. Estimates for a chemical's HLC may be obtained using the EPI SuiteTM software, but the estimates do not account for isomeric differences and are provided for a limited temperature range 0-50 °C (US EPA 2012).

Showers present an ideal scenario for human inhalation exposure to MCHM due to the elevated water temperature, extended time for exposure, increased air-water interfacial area due to water droplet formation, and small, enclosed space. A model for the transfer of contaminants from drinking water into shower air was previously developed and refined for estimation of air concentrations and detection of odorous contaminants (Little 1992; Ömür-Özbek et al. 2011). The model produced results consistent with human odor threshold concentrations and drinking water utility consumer complaint data for the common earthy-musty odorants geosmin and 2-methylisoborneol (2-MIB) (Ömür-Özbek et al. 2011).

The objectives of this research are to: 1) determine HLCs for 4-MCHM isomers at 7, 25, 40, and 80 °C and compare to US EPA EPI SuiteTM estimated values; 2) predict air concentrations of 4-MCHM and MMCHC that would occur during showering; 3) estimate human ingestion and inhalation exposure to 4-MCHM and MMCHC and compare to CDC and US EPA guidance levels where available; 4) determine if predicted air 4-MCHM concentrations exceeded odor threshold concentrations.

2. Methods

2.1. Reagents

Pure 4-MCHM was acquired from TCI Chemical (CAS 34885-03-5) and determined to be *cis*- and *trans*-(4-methylcyclohexyl)methanol in a ratio of 100:48 *cis*- to *trans*- (Dietrich et al. 2015). Crude MCHM was donated by Eastman Chemical (Product No. P18717ET, Batch TP14003010)

and was determined in our laboratory to be 31.4% *cis*- and 55.1% *trans*- (4-methylcyclohexyl)methanol (MCHM) in a ratio of 57:100 *cis*- to *trans*-, 0.935% *cis*- and *trans*-methyl-4-methylcyclohexanecarboxylate (MMCHC), and 0.1-4% of other constituents including *cis*- and *trans*-4-(methoxymethyl)cyclohexanemethanol; *cis*- and *trans* -1,4-cyclohexanedimethanol; dimethyl 1,4-cyclohexanedicarboxylate, methanol, and water (Dietrich et al. 2015). In this paper, crude MCHM refers to the crude chemical mixture, and 4-MCHM refers to *cis*- and *trans*- isomers of 4-MCHM. A mix of *cis*- and *trans*- MMCHC was obtained from Sigma-Aldrich (CAS# 51181-40-9).

2.2. Experimental design

Estimation of HLCs from 0-50 °C was performed using the HENRYWIN™ v3.20 program within EPI Suite™ v4.11 software (US EPA 2012). EPI Suite™'s HENRYWIN™ v3.20 program is based on the methodology of Hine and Mookerjee (1975) which was further developed by Meylan and Howard (1991) and is limited to providing bond method estimates of HLCs from 0-50 °C and group method estimate at 25 °C. The dimensionless HLCs for 4-MCHM were also experimentally determined for each isomer by modifying the approach in Ömür-Özbek and Dietrich (2005). Pure 4-MCHM and crude MCHM were dissolved in reagent water in silanized glassware to achieve final concentrations of 92.5 ± 3.6 ppm-aq pure 4-MCHM and 103.1 ± 1.7 ppm-aq crude 4-MCHM. In addition to pure and crude 4-MCHM, a mixture of 50% *cis*- and 50% *trans*- was created by mixing the pure and crude 4-MCHM in a proportion of 100:89 respectively. The inclusion of this mixture provided additional confirmation of *cis* and *trans*-4-MCHM measurements. Pure, crude, and 50:50 4-MCHM aqueous mixtures were stored at 7°C and stirred for 30 min prior to partitioning analysis. For partitioning analysis, 10 mL of solution was placed into a silanized, 20 mL amber glass headspace vial (Agilent, 5190-2239) and

sealed with PTFE lined septa (Restek, 21761). After equilibration, three replicates of each mixture were analyzed by gas chromatography (GC) at 7, 25, 40, and 80 °C. Total vial volume for each sample was measured to obtain accurate headspace volumes for mass balance calculations. Samples were equilibrated by submerging vials in a water bath at the desired temperature for ≥ 12 hours prior to triplicate measurements. Standard solutions of pure 4-MCHM dissolved in a 1:9 ratio nanopure water:methanol were used to establish a standard curve based on the mass of *cis*- and *trans*-4-MCHM directly injected in to the GC.

2.2.1. Headspace GC Analysis

Headspace was analyzed using gas chromatograph with a flame ionization detector (GC-FID) (Thermo Scientific, Finnigan TraceGC Ultra) in conjunction with Thermo HS2000 autosampler and 30 m, 0.25 mmID Restek Rxi®-5sil MS column. For standard and sample analysis the GC-FID temperature program initiates at 35 °C for 3 min, increases to 140 °C at the rate of 5 °C/min where it is held for 3 min for a total of 25 min. The GC inlet is 250 °C and injection is splitless. N₂ carrier gas flow is 2.0 ml/min, H₂ flow is 35 ml/min, and air flow is 350 ml/min. The FID is 275 °C during testing. For standards analysis, 1 µL of each standard was manually injected using a SGE 10 µL syringe. For sample analysis, 200 µL of gas phase was injected at a rate of 5 ml/min by the HS 2000 autosampler. The 40 °C and 80 °C samples are incubated at 40 °C and 80 °C, respectively, for 30 min prior to analysis. Each sample vial was measured three times. The *cis*- and *trans*-4-MCHM retention times are 21.2 and 20.5 min respectively. *cis*- and *trans*-4-MCHM mass measurements were converted to gas phase concentrations by dividing mass by volume injected (200 µL).

2.2.2. Aqueous Phase GC Analysis

After aqueous chemical analysis, 200 μL aqueous samples were taken from each vial and diluted 1:9 with methanol to a final volume of 2 mL. Samples were analyzed using GC-FID (Hewlett Packard 5890) with Hewlett Packard 7673 autosampler. Each sample was measured three times. The *cis*- and *trans*-4-MCHM retention times are 6.67 and 6.20 min respectively. For sample analysis the GC-FID temperature program initiates at 100 $^{\circ}\text{C}$ and holds for 3 min, increases to 140 $^{\circ}\text{C}$ at a rate of 20 $^{\circ}\text{C}/\text{min}$, and held for 2.5 min for a total of 7.5 min. The GC injector is set at 250 $^{\circ}\text{C}$ and injection is splitless. N_2 carrier gas flow is 2.0 ml/min, H_2 flow is 35 ml/min, and air flow is 350 ml/min. The FID is 275 $^{\circ}\text{C}$ during testing. For standard and sample analysis, 1 μL of liquid is injected by the HP 7673.

2.2.3. HLC determination

Both pure and crude MCHM were tested to account for influence of minor crude components on 4-MCHM chemical properties. For each isomer, the mean of the gas phase concentrations ($n=3$) was divided by the mean of the aqueous phase concentrations ($n=3$). To determine the composite 4-MCHM HLC, the concentrations of *cis*-4-MCHM and *trans*-4-MCHM were added for the headspace and divided by the sum of the aqueous phase concentrations. Mass balance recovery was calculated by dividing the total mass of 4-MCHM in the sample vial post equilibration by the total mass of 4-MCHM_{aqueous} prior to equilibration as measured by GC.

2.2.4 Quality Assurance and Control

To ensure appropriate QA/QC, GC calibration curves in the concentration range of interest were generated using pure MCHM standards. R-squared values for both *cis*- and *trans*-4-MCHM isomers ranged from 0.9995-0.9997 during the project. Blank and check standards were analyzed with each batch of samples. Check samples ensured < 10% deviation from expected concentration. Blank samples ensured no contamination or residual MCHM was present. All

experiments were performed in triplicate and each sample was measured in triplicate to ensure accuracy of results.

2.3. Shower Model

The HLCs used in the shower model were calculated according to the van't Hoff equation (2).

We assumed a constant enthalpy over the temperature range of interest (7-80 °C). Enthalpies were calculated by nonlinear regression of the measured HLCs (R Development Core Team 2011). Diffusion of 4-MCHM isomers and MMCHC at the air-water interface in a shower was determined using a previously developed model (Little 1992; Ömür-Özbek et al. 2011).

Figure 1. Schematics of shower model. C_{in} and C_{out} are the aqueous concentrations entering and leaving the shower; Q_L is the water flow rate; Q_b and Q_s are the air exchange rate between house-bathroom and bathroom-shower; V_b and V_s are the bathroom and shower volumes; and y_a , y_b , and y_s are the air concentrations in the house, bathroom, and shower.

The shower model (Figure 1) assumes the shower head water flow rate and shower stall and bathroom air flow rates are constant, the water flowing through the shower stall follows a plug flow model system, and the shower stall and bathroom air each follow a completely mixed flow model. The transient mass balance on shower stall air yields:

$$\left(\frac{dy_s}{dt} \right) V_s = Q_L (C_{in} - C_{out}) - Q_s (y_s - y_b) \quad (4)$$

where V_s is the shower stall volume, Q_s is the air flowrate in the shower stall, and y_b is the concentration of the odorant in air entering the shower stall from the bathroom. A similar transient mass balance exists for the bathroom air. The above differential equations are solved analytically using y_{si} and y_{bi} at $t = 0$ as initial conditions (see Supplemental Material); the dynamic-state equations for the odorant concentration in the shower stall and the bathroom air are obtained from Little (1992) and Kim et al. (2004). Liquid and gas diffusivities were estimated as 7.36×10^{-10} and 6.71×10^{-6} m²/s respectively for MCHM and as 6.84×10^{-10} and 6.37×10^{-6} m²/s for MMCHC (U.S. EPA 2013). The shower model was applied to two scenarios, a high exposure of 4000 ppb-aq 4-MCHM representative of highest measured concentration in the distribution system (i.e., 3773 ppb-aq (WVDHSEM 2014), and 40 ppb-aq 4-MCHM representing measured low concentrations in the weeks following flushing of the distribution system (e.g., 43 ppb-aq (Foreman et al. 2015)).

2.4. Inhalation and Ingestion Exposure

Inhalation and ingestion exposures were estimated by calculation of a daily dose (mg/kg/d). Adults were assumed to weigh 70 kg, ingest 2 L/d of water, and inhale 20 m³/d of air. Children were assumed to weigh 15 kg, ingest 1 L/d of water, and inhale 17.3 m³/d of air (U.S. EPA

2014). Inhalation exposures were calculated assuming a 4000 ppb-aq influent 4-MCHM and a 15 minute shower by integrating the area under the predicted shower concentration curves versus time data for 0-15 min (Figure 4).

2.5. 4-MCHM Odor Detection

To estimate 4-MCHM aqueous concentration resulting in odor detection, the shower air concentrations predicted by the shower model for 4-MCHM isomers are compared to logistic regression curves for human odor thresholds for detection of 4-MCHM isomers given in Gallagher et al. (2015).

3. Results

3.1. Gas Chromatography

Distinct peaks for both *cis*- and *trans*-4-MCHM were apparent in the headspace and aqueous phase chromatography for pure and crude 4-MCHM (Figure 2). Isomer identification was confirmed with nuclear magnetic resonance spectroscopy in our lab and others (Foreman et al. 2015; Gallagher et al. 2015). For the low ppm-aq concentrations analyzed with GC, no additional peaks were present in aqueous measurements for pure or crude MCHM.

Two additional quantifiable peaks were present in headspace measurements of crude MCHM at only 40 °C and 80 °C. The two peaks were confirmed to be isomers of MMCHC by comparison of retention times with a MMCHC standard (Figure 2b). Headspace analysis comparing total area of 4-MCHM isomer peaks to total area of MMCHC isomer peaks in crude MCHM at 40 °C show an average ratio of 6.5:1 4-MCHM:MMCHC indicating greater volatility of MMCHC given the aqueous ratio of 92.5:1 4-MCHM:MMCHC.

Figure 2. Pure (a) and crude (b) 4-MCHM headspace chromatograms at 40°C. *Trans*- 4-MCHM elutes first with a retention time 20.5. *cis*-4-MCHM elutes second with retention time 21.2. The crude MCHM headspace had a second set of peaks eluting at 22.1 and 22.35 min were determined to be isomers of MMCHC by retention time comparison with MMCHC standard.

3.2. Henry's Law Constant Determination

The 25 °C EPI Suite™ Bond estimation of HLC is 3.53×10^{-4} , and the Group estimate predicts slightly lower volatility with HLC estimation of 2.63×10^{-4} in dimensionless form. Isomer specific estimations are not predicted by this software.

HLCs measured experimentally at 25 °C results in a composite 4-MCHM HLC value of $2.91 \times 10^{-4} \pm 8\%$ and $2.48 \times 10^{-4} \pm 4\%$ for pure 4-MCHM and crude 4-MCHM, respectively. Mass balance recovery for 4-MCHM is $89.5\% \pm 11.6\%$. Results for 50:50 4-MCHM aqueous mixture can be found in the Supplemental Material.

Table 1. Experimentally Determined Henry's Law Constant with coefficient of variation at 7-80 °C.

		<i>trans</i> -4-MCHM	<i>cis</i> -4-MCHM	4-MCHM ^a
Source	Temperature °C	Henry's Law Constant 10^{-4} , mean $\pm$ relative standard deviation		
Pure 4-MCHM	7	$1.90 \pm 21\%$	$0.98 \pm 28\%$	$1.28 \pm 25\%$
	25	$4.85 \pm 7\%$	$2.00 \pm 8\%$	$2.91 \pm 8\%$
	40	$15.20 \pm 24\%$	$6.38 \pm 9\%$	$9.11 \pm 15\%$
	80	$30.60 \pm 3\%$	$30.50 \pm 5\%$	$30.50 \pm 4\%$
Crude 4-MCHM	7	$1.53 \pm 12\%$	$1.24 \pm 15\%$	$1.43 \pm 13\%$
	25	$3.08 \pm 3\%$	$1.42 \pm 6\%$	$2.48 \pm 4\%$
	40	$13.50 \pm 26\%$	$6.95 \pm 14\%$	$10.90 \pm 21\%$
	80	$32.10 \pm 27\%$	$34.30 \pm 17\%$	$32.90 \pm 23\%$
		Enthalpy, 10^4 joules per mole (mean $\pm$ relative standard error)		
Experimental		$2.72 \pm 9\%$	$4.06 \pm 6\%$	$3.31 \pm 6\%$

^a EPI Suite™ estimated HLC values for 4-MCHM at 25 °C are 3.53×10^{-4} and 2.63×10^{-4} by the Bond and Group methods respectively.

HLCs measured at 7, 25, 40, and 80 °C demonstrate an exponential increase of volatility (Table 1). Measured HLCs show good agreement with EPI Suite™ predicted values for 0-50 °C (Figure 3) and HLC according to the van't Hoff equation (See Supplemental Material, Figure S1). A Wilcox test (R Development Core Team 2011) shows *cis*- and *trans*- HLC values are

significantly different for 7, 25, and 40 °C ($p < 0.05$). The relationship between the inverse temperature in Kelvin vs the natural log of the HLC is linear with R^2 values of 0.931 to 0.987 for *cis*- isomer, *trans*- isomer, and 4-MCHM measurements which is consistent with the relationship described in Robbins et al. (1993) (See Supplemental Material, Figure S2). Overall, these results indicate HLCs increase exponentially with temperature.

Figure 3. Comparison of Henry's Law Constant sensitivity to temperature for MMCHC and 4-MCHM based on EPI Suite™ from 0 -50 °C and measured Henry's Law Constants at 7, 25, 40, and 80 °C.

3.3. Air Concentrations during Showering

Enthalpies of volatilization from aqueous solutions for *cis*- and *trans*-4-MCHM were determined to be 4060 J/mol and 2740 J/mol, respectively (Table 1). When the regression results are applied

to the van't Hoff equation (2) over the temperature range of interest (0-80 °C), there is good agreement with measured HLC values (See Supplemental Material, Figure S1).

Assuming 4000 ppb-aq influent 4-MCHM, the shower model predicts *cis*- and *trans*- 4-MCHM of 89 and 390 ppb-v respectively after 10 min and 97 and 428 ppb-v respectively after 25 min. 4-MCHM isomers achieve air concentrations in excess of the EPA air screening level after < 1 min of showering. In the weeks following the spill the 4-MCHM persisted at low levels (<10 - 43ppb-aq (Foreman et al. 2015)) in the distribution system leading to ambient concentrations of 0.97 and 4.3 ppb-v for *cis*- and *trans*- 4-MCHM after 25 min of showering based on 40 ppb-aq 4-MCHM influent (Figure 4).

Figure 4. Volatile crude MCHM component concentrations over time in shower air. Air concentrations resulting from influent MCHM concentration at 4000 ppb-aq are represented on the left axis and 40 ppb-aq on the right axis. The curves for each compound may be read from either axis as they have the same shape at either influent concentration. Water temperature is at 40 °C.

MMCHC was also modeled using an EPI SuiteTM estimated HLC of 0.0173 at 25 °C and enthalpy of 43140 J/mol. Assuming 4000 ppb-aq influent 4-MCHM, MMCHC air concentrations reach 127 ppb-v after 10 minutes and 181 ppb-v after 25 min of showering. With 40 ppb-aq influent 4-MCHM, MMCHC air concentrations reach 1.8 ppb-v after 25 min of showering (Figure 4).

Predicted 4-MCHM inhalation doses during showering and ingestion doses from drinking water are shown in Table 2. For 4-MCHM isomers, shower inhalation generally accounts for 10% or less of exposure compared to drinking water. As expected, the doses at 40 ppb-aq influent 4-MCHM are 100 fold lower, while ratios for inhalation to ingestion remain the same.

Table 2. Doses of crude MCHM contaminants from showering and drinking for adults and children for an aqueous concentration of 4000 ppb-aq 4-MCHM.

Contaminant	Adult			Child		
	Inhalation in Shower (mg/kg/d)	Ingestion of Drinking Water (mg/kg/d)	Ratio ^a	Inhalation in Shower (mg/kg/d)	Ingestion of Drinking Water (mg/kg/d)	Ratio ^a
<i>trans</i> -4-MCHM	4.90 x 10 ⁻³	7.27 x 10 ⁻²	0.067	1.98 x 10 ⁻²	1.70 x 10 ⁻¹	0.117
<i>cis</i> -4-MCHM	1.11 x 10 ⁻³	4.16 x 10 ⁻²	0.027	4.50 x 10 ⁻³	9.70 x 10 ⁻²	0.046
MMCHC	1.68 x 10 ⁻³	1.14 x 10 ⁻³	1.471	6.79 x 10 ⁻³	2.67 x 10 ⁻³	2.545

^aInhalation dose divided by ingestion dose

MMCHC ingestion doses are always lower than those of 4-MCHM isomers, but MMCHC's inhalation doses fall between *trans*-4-MCHM and *cis*-4-MCHM. This is due to MMCHC's low aqueous concentration but much higher volatility, which also results in the shower inhalation exposure to be approximately 1.5 and 2.5 times the ingestion exposure for adults and children respectively.

3.4. 4-MCHM Odor Detection

When *trans*- isomer population OTCs are compared to air concentrations resulting from showering, human OTCs would have been exceeded (Figure 5). Nearly 100% of individuals, both naïve and exposed, would detect *trans*-4-MCHM odors at 1000 ppb-aq, equivalent to the 4-MCHM health based screening level. Greater than 90% of naïve and exposed individuals would detect *trans*-4-MCHM odors at 40 ppb-aq influent 4-MCHM. Additionally, there is an approximately 5.6-fold difference in the *trans*-4-MCHM concentrations 50% of naïve vs. exposed individuals would detect after 5 min of showering.

Figure 5. Estimated fraction of population detecting *trans*-4-MCHM odor during showering assuming shower volume of 1500 L, water flow of 10 L/min, water temperature of 40 °C and 63.6% of 4-MCHM as *trans*- isomer.

Ambient concentrations of less odorous *cis*-4-MCHM would be detected by less than one third of naïve individuals during steady state conditions for 4000 ppb-aq influent 4-MCHM. For exposed individuals, ambient *cis*-4-MCHM is predicted to be detected by 83.2% for 4000 ppb-aq influent 4-MCHM and by 60.5% for 40 ppb-aq influent 4-MCHM. The shower model explains the persisting odor complaints occurring weeks after the spill when 4-MCHM concentrations were measured in the distribution system up to 43 ppb-aq (Foreman et al. 2015).

4. Discussion

4.1. Henry's Law Constants

Measured HLCs at 7-40 °C are similar to EPI Suite™ v4.11 estimates (Table 1). The average composite 4-MCHM value is $2.55 \times 10^{-4} \pm 0.33 \times 10^{-4}$ which is closer to the group estimate (2.63×10^{-4}) than the bond estimate from EPI Suite™ v4.11. This indicates that EPI Suite™ v4.11 is a beneficial tool for providing estimates of the HLC values, but should not completely replace measurements as it does not account for differences in isomers, and provides two differing estimates with the bond estimation being 34% higher than the group estimation for 4-MCHM.

The higher HLCs for *trans*-4-MCHM when compared to *cis*-4-MCHM for 7, 25, and 40 °C indicate that the *trans*- isomer is more volatile than the *cis*- isomer. These data agree with other measured chemical properties of 4-MCHM isomers, including the greater solubility and solvated dipole moment of *cis*-4-MCHM when compared to *trans*-4-MCHM (Dietrich et al. 2015).

Measured HLCs show increasing volatility with increasing temperature, which indicates usage of heated drinking water would result in higher inhalation exposures and increased odor detection compared to room temperature.

4.2. Air Concentrations and Inhalation Exposures to crude MCHM

Ambient shower air concentrations for *cis*- and *trans*- 4-MCHM are predicted to be 9 to 39 times higher than the short-term air screening level (0.01 ppm-v) for 4000 ppb-aq influent 4-MCHM (U.S. EPA 2014). This indicates that the approximately 30% households still using drinking water for bathing and showering during the “do not use” order may have been exposed to high levels of inhalable 4-MCHM (CDC 2014a). As aqueous concentrations decreased in the distribution system, air concentrations also decreased below the short-term air screening level, but would not be completely eliminated until crude MCHM was no longer present in the drinking water. Predicted 4-MCHM shower inhalation doses are an order of magnitude lower than the predicted ingestion doses, but the high ambient shower air concentrations of 4-MCHM relative to the screening level during the initial days following the spill are supportive of data attributing 14.6% of 396 emergency department visits during the 14 days following the spill to “breathing mist or vapor” associated with the chemical spill (WVBPH and ATSDR 2014).

As has been previously demonstrated for trihalomethanes in drinking water, the distribution between inhalation or ingestion exposure depends on the composite interaction of the individual trihalomethane’s volatility (HLC), aqueous concentration, and human physiological parameters (Wang et al. 2007). The shower model demonstrates that, although MMCHC is only 0.935% of the aqueous crude MCHM mixture, its air concentration and inhalation exposure will exceed that of *cis*-4-MCHM during showering. Additionally, MMCHC predicted inhalation doses are 1.5-2.5 times higher than the predicted ingestion dose. This is due to the greater volatility of MMCHC when compared to 4-MCHM isomers. There are no available data on the health effects of MMCHC, but it should not be overlooked as a contributor to human inhalation exposures and odor detection. This data reinforces the importance of evaluating all components of a chemical

mixture and multiple routes of exposure. For both 4-MCHM isomers and MMCHC only showering was used to predict an inhalation dose. Other inhalation exposures, i.e., contaminated indoor and outdoor air, would have also occurred and should be assessed in future research.

4.3 Limitations

The values presented in this research represent a range of predicted inhalation exposures based on measured aqueous concentrations in the distribution system. Model predictions could not be validated because no indoor air field samples were collected during and after the crude MCHM spill. While this lack of validation remains a limitation for MCHM predictions, the shower model was previously validated for the odorous drinking water contaminants geosmin and 2-MIB exposures (Ömür-Özbek et al., 2011). In that research, air odor detection concentrations predicted by the shower model agreed with corresponding aqueous concentrations measured by utilities and known to result in consumer odor complaints.

4.4 MCHM Odor Complaints

Odor detection for crude MCHM is best represented by the *trans*-4-MCHM isomer, which has a population OTC 2000-fold lower than *cis*-4-MCHM and has the characteristic licorice odor experienced by consumers (Gallagher et al. 2015). Greater *trans*- than *cis*- isomer volatility found in this study, greater proportion of *trans*- than *cis*- in the crude, and lower odor threshold for the *trans*- isomer lends further support to *trans*-4-MCHM being the primary 4-MCHM isomer of concern for consumer inhalation exposure and associated odors (Gallagher et al. 2015).

During showering, >35% of individuals would detect *trans*-4-MCHM odors at 2 ppb-aq influent 4-MCHM which is the best available analytical detection limit used during water monitoring (Figure 5) (Foreman et al. 2015). The shower model results therefore support consumer

complaints of licorice odors in the weeks following the spill even as aqueous concentrations decreased below analytical detection limits. The use of consumer odor detections to indicate presence of a contaminant is well established for drinking water utilities which use “earthy” or “musty” odors as an indicator of the presence of geosmin or 2-MIB by drinking water utilities (Dietrich and Burlingame 2015). Detection of licorice odors should therefore be considered an indicator that crude MCHM was still present in the drinking water, and that inhalation and ingestion exposures continued for weeks even if aqueous 4-MCHM was below analytical detection.

There are no human odor threshold data for the MMCHC isomers, however, during handling by researchers in our lab and others MMCHC was noted to have a strong odor similar to that of crude MCHM (Foreman et al. 2015). Evidence from headspace analysis, high predicted volatility, and shower modeling indicate a potential for MMCHC to impact the odors detected by consumers during the days and weeks following the spill.

As expected, the odorous crude MCHM spill negatively impacted the public’s perception of their drinking water safety due to both health-fears and aesthetics. The lack of health data for inhalation and ingestion exposures, continued odors, and poor risk communication from various local and federal agencies compounded the issue (Manuel 2014). The research presented here supports the persisting consumer complaints and confirms that crude MCHM is a chemical which consumers were exposed to and able to detect at concentrations lower than established field techniques for measuring aqueous 4-MCHM in drinking water during the weeks following the spill.

5. Conclusions

The EPA's EPI Suite™ software is a useful tool for approximating chemical properties in lieu of measured chemical properties and should be considered for use in emergency situations.

However, these estimations should be treated as preliminary as they do not address differences in isomers, and predicted values vary by method.

The 4-MCHM *trans*- isomer is more volatile when compared to the *cis*- isomer for 7, 25 and 40 °C. The higher volatility of the *trans*- isomer and the 57:100 *cis*- to *trans*- isomer ratio in crude MCHM indicate a higher inhalation exposure to *trans*- than to *cis*-4-MCHM in the gas phase at 40 °C. Human inhalation exposure to both 4-MCHM isomers in initial days following the spill likely exceeded EPA's health advisory level of 0.01 ppm-v. Dose estimates predict lower inhalation exposure to 4-MCHM isomers for children and adults during showering than predicted ingestion doses, but MMCHC inhalation exposures would be 1.5 to 2.5 times higher than ingestion doses. Exposure route is important when considering chemical mixtures due to variation in chemical properties among constituents.

The odors experienced by consumers following the spill are primarily attributed to *trans*-4-MCHM due to the low OTC when compared to the *cis*- isomer. This research shows that almost 100% of exposed individuals would be able to detect an odor from the *trans*- isomer at aqueous concentrations still being exceeded in the distribution system two months following the spill. Additionally, MMCHC may have contributed to odors at water temperatures above 40 °C despite its low percentage of the crude MCHM mixture due to its high volatility and corresponding predicted air concentrations.

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