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The fate of two isothiazolinone biocides, 5-chloro-2-methylisothiazol-3(2H)-one (CMI) and 2-methylisothiazol-3(2H)-one (MI), in liquid air fresheners and assessment of inhalation exposure

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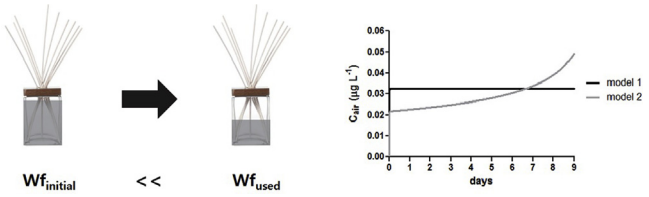
HIGHLIGHTS

- The fate of CMI and MI in liquid air fresheners was evaluated.
- Volatilization, hydrolysis, and photolysis rates were assessed.
- A new prediction model was constructed to consider the changes in weight fraction.
- The new model was compared with ConsExpo for the inhalation exposure.

GRAPHICAL ABSTRACT



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ABSTRACT

There exist public concerns regarding the two most widely used isothiazolinones (5-chloro-2-methylisothiazol-3(2H)-one (CMI) and 2-methylisothiazol-3(2H)-one (MI)) in various consumer products because they cause allergic responses in dermatitis and are potentially harmful when inhaled. Hydrolysis and photolysis tests for CMI and MI at pH 4, 7, and 9 were performed to evaluate their stability. While MI did not degrade under the test conditions, CMI slightly degraded at pH 9 via hydrolysis and at pH 4 via photolysis. To better understand human exposure to MI and CMI during the use of consumer products, the vaporization rates of MI and CMI from two commercial air fresheners were quantified in a custom-made chamber. The evaporation of MI was almost negligible over 7 d, whereas a significant amount of CMI evaporated over the same period. Because the volume of air freshener decreases over time due to evaporation of water, the MI concentration in the product increased by a factor of 1.8–2.2. The air concentration of CMI was predicted using a ConsExpo model using a fixed weight fraction (model 1) and a new model that reflects changes in the concentrations of active ingredients and the product volume over time (model 2). The concentration determined using model 1 reached a steady-state value of 0.032 μg L^{-1}, whereas that predicted using model 2 increased consistently. Inhalation exposure was also assessed using two exposure scenarios: a room and a car. Both calculated values of margin of exposure were much higher than 300, indicating a negligible inhalation risk.

1. Introduction

Biocides are added to many consumer products, and concerns have been raised regarding human exposure to such chemicals from various consumer products (e.g., Aiello et al., 2007; Gilbert and McBain, 2003; Lundov et al., 2014; Pauwels and Rogiers,

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2010). Isothiazolinones are multi-purpose biocides that are widely used in many consumer products, including personal hygiene products, air fresheners, perfume, wall paint, and deodorants (Nagorka et al., 2015; Rafoth et al., 2007; Williams, 2007). Since the 1980s, the most frequently used isothiazolinones have been 2-methyl-4-isothiazolin-3-one (MI) and 5-chloro-2-methyl-4-isothiazolin-3-one (CMI), usually in a 3:1 mixture (aka Kathon) (Nagorka et al., 2015).

Kathon is known to cause allergic responses in dermatitis via contact with air (Burnett et al., 2010; García-Gavín et al., 2010; Geier et al., 2012; Lundov et al., 2011b, 2014; Nagorka et al., 2015), and the concentration of the mixture is regulated to below 15 mg L^{-1} in both leave-on and rinse-off cosmetic products by the EU (García-Gavín et al., 2010; Lundov et al., 2011a). MI without CMI is permitted in cosmetic products at a maximum concentration of 100 mg L^{-1} (Lundov et al., 2010). The inhalation of Kathon has been shown to cause decreased weight gain and pulmonary hemorrhages in rats, showing the combined LC50 of 110 mg m^{-3} during 4 h (Burnett et al., 2010). Health Canada (2011) also performed a short-term inhalation risk assessment in rats during a 90-d period and observed rhinitis in the nasal cavity with the no observed adverse effect level (NOAEL) of 0.34 mg m^{-3}. Kathon had been used as the humidifier disinfectants that caused fatal lung disease in Korea (Lee et al., 2012; Park et al., 2015). Although most of cases were patients who used polyhexamethylene guanidine (PHMG) as the humidifier disinfectant (Kim et al., 2014), the possible link of Kathon exposure to the fatal respiratory disease has not been excluded (Korea Center for Disease Control and Prevention, 2014). Thus, potential respiratory health risks of Kathon inhalation from various consumer products must be evaluated and managed.

Isothiazolinones are suspected to undergo chemical transformation under ambient use conditions. Previous studies regarding the stability of CMI and MI indicated that these isothiazolinones are degradable (Barman and Preston, 1992; Han et al., 2011; Kandavelu et al., 2004; Krzeminski et al., 1975; Williams, 2007). However, the results of recent kinetic studies showed that CMI and MI did not undergo hydrolysis or photolysis over a period of 30 d, except under high pH conditions (Bettero et al., 1985; US EPA, 1998; Jacobson and Williams, 2000). Thus, the potential transformations of these isothiazolinones in consumer products must be determined to better evaluate the potential health risks of CMI and MI in consumer products.

A tiered approach is often used for the risk assessment of chemicals in consumer products (Park et al., 2006). ConsExpo, which was developed by the National Institute for Public Health and the Environment of the Netherlands (RIVM), is one of the most frequently used modeling softwares for tier 1 and tier 2 evaluations. In tier 1 evaluation, the weight fraction of active ingredients is assumed to remain constant, although these ingredients may undergo chemical transformations and evaporation. For higher tier assessments, specific information is needed to predict exposure concentrations.

In this study, the hydrolysis and photolysis rates of two of the most widely used isothiazolinones—CMI and MI—were measured in batch experiments to evaluate their stability in consumer products. Based on the measured hydrolysis and photolysis rates, the evaporation rates of CMI and MI were quantified using two commercial liquid air fresheners as model consumer products. The concentrations of CMI and MI remaining in the selected air fresheners were measured in a lab-scale chamber with constant relative humidity and air change rate. A new mass balance model was developed to reflect the time-course changes in the concentrations of CMI and MI in consumer products and the consequent changes in air concentration. Finally, inhalation exposure assessments were conducted for the use of the selected liquid air fresheners in two use scenarios using both ConsExpo 4.1 and the new model, and the results were compared.

2. Materials and methods

2.1. Chemicals and materials

Analytical-grade 5-chloro-2-methyl-4-isothiazolin-3-one (CMI, 99%) and 2-methyl-4-isothiazolin-3-one (MI, 98%) were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany) and Sigma–Aldrich (St Louis, MO, USA), respectively. Concentrated hydrochloric acid (37%, Sigma–Aldrich), citric acid (97%, Sigma–Aldrich), sodium citrate (99%, Daejung, Siheung, Korea), potassium hydrogen phosphate (99%, Daejung), potassium dihydrogen phosphate (99%, Sigma–Aldrich), and sodium tetraborate (98%, Junsei, Tokyo, Japan) were used to maintain the pH values of the aqueous solutions at 4, 7, and 9. HPLC solvent-grade methanol (99.99%, Burdick & Jackson, Muskegon, MI, USA) and acetone (99.8%, Daejung) were used for the preparation of analytical standards and instrumental analyses. Anhydrous sodium sulfate (99%) and alumina oxide (98%) used for matrix solid-phase dispersion (MSPD) were purchased from Sigma–Aldrich. Sodium sulfate was baked at 400 °C for 5 h, and alumina oxide was activated at 190 °C for 12 h before use.

Two commercial liquid-type passive air fresheners using water as the solvent were purchased from local stores and stored at 4 °C until use. According to the manufacturers, only MI was added to one air freshener (AF1) as a preservative, whereas both CMI and MI were added to the other (AF2). The initial concentrations of MI in AF1 and AF2 were measured at 17.5 and 48.4 mg L^{-1}, respectively. In the subsequent tests, CMI was spiked into AF1 to an initial concentration of 50 mg L^{-1}. Although both isothiazolinones are included in AF2, CMI and MI were added at 100 mg L^{-1} because the CMI concentration was found to be only 4.4 mg L^{-1}.

Individual stock solutions of CMI and MI were prepared in methanol and stored at −20 °C. The stock solutions were diluted with acetone to prepare external standards for GC–MS analysis and with methanol for HPLC analysis.

2.2. MSPD elution

Matrix solid-phase dispersion (MSPD) method was chosen for extracting MI and CMI from liquid air freshener samples because it showed better performance and recoveries than liquid–liquid extraction using dichloromethane and solid-phase extraction using alumina or florisil column in the preliminary test. A schematic of the MSPD elution is presented in Fig. 1. A mixture of 2 g of baked sodium sulfate and 0.02 mL of liquid air freshener was blended by shaking gently by hand until the mixture was homogeneous. After all water from air freshener samples was absorbed by sodium sulfate, 2 g of alumina oxide was added, and the mixture was transferred into a syringe with a frit. A second frit was placed on top of the solid mixture and gently pressed with a pestle to pack the solid phase. Ten milliliters of acetone was flowed through the syringe by gravity, and the eluant was collected for GC–MS analysis. The volume of the extract was measured for quantification and was approximately 7 mL.

2.3. Hydrolysis and photolysis of isothiazolinones

2.3.1. Hydrolysis

The hydrolysis rates of CMI and MI were measured according to the OECD test guidelines at pH 4, 7, and 9 and 25 °C (OECD, 2004). Hydrolysis experiments were conducted in 1 mL of pH-buffered solution containing initial concentrations of approximately

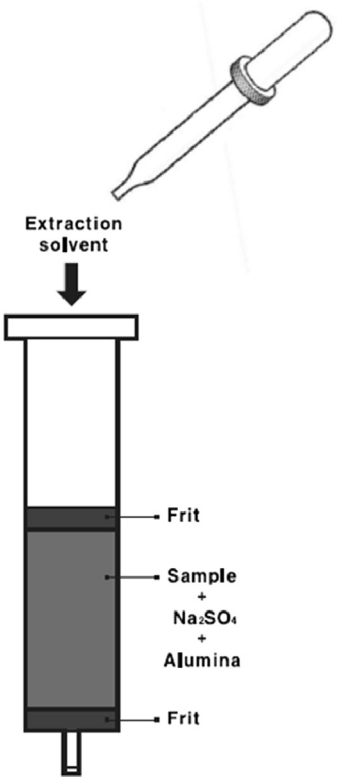

Fig. 1. The schematic description of matrix solid-phase dispersion (MSPD) for extracting CMI and MI from liquid air fresheners.

8.2 mg L^{-1} CMI and 86 mg L^{-1} MI. Citric acid and sodium citrate were used for the pH 4 buffer, potassium phosphate dibasic and potassium phosphate monobasic were used for the pH 7 buffer, and sodium tetraborate and hydrochloric acid were used for the pH 9 buffer. Changes in the aqueous concentration of CMI were monitored for 30 d because a substantial decrease in concentration was observed in a pretest at 50 °C. In contrast, for MI, the test was conducted for 14 d because the aqueous concentration of MI did not change during the pretest (Fig. S1, Supplementary Data). Hydrolysis pretests of CMI and MI were conducted for 5 d according to the OECD test guidelines at pH 4, 7 and 9 and 50 °C (OECD, 2004). The initial and final concentrations were determined by HPLC. Without significant decrease in the concentration during the pretest, the chemical was regarded as not hydrolyzable.

2.3.2. Photolysis

The experimental conditions for the photolysis experiment were the same as those described above for the hydrolysis experiment, except for the exposure to visible light (OECD, 2008). The photolysis experiments were conducted in an incubator containing a custom-made photolysis set-up consisting of a light source and a sample rack (Fig. S2, Supplementary Data). Because liquid air fresheners are mostly used in indoor environments, a 50-W three-wavelength compact fluorescent lamp (430, 545, and 610 nm; Osram, Munich, Germany) was chosen as the light source to mimic sunlight penetrating through glass windows. The light intensity was measured to be 8300 lux using an illuminometer (LX1020BS, Bestone Industrial Ltd., Guangdong, China). The sample rack consisted of 60 holes for vials. The distance between the light source and the vial surface was 15 cm, and the phototransformation experiments were conducted for 14 d.

2.4. Chamber tests

A custom-made, lab-scale glass chamber was used to evaluate the vaporization of water and isothiazolinones (CMI and MI) from the air freshener samples (Fig. 2). Twenty-one open glass vials containing 1 mL of air freshener were placed in the test chamber to simulate accelerated evaporation of air freshener. The air-contacting area (Ar) of each glass vial was 0.79 cm^2. The total volume of the chamber was 1.7 L and contained an air volume of 1.2 L. The air temperature was controlled with a water jacket and monitored at 25 ± 2 °C. To compensate for the evaporation of water from the air freshener samples in the chamber, the flow rate of dry air was set at 90 mL min^{-1} to achieve 50% relative humidity. The air change rate was 4.5 h^{-1}. The relative humidity was monitored using a self-recording thermo-hygrometer (Lutron Electronic, Coopersburg, PA, USA) and found to be between 45 and 55% during all experiments.

2.5. HPLC and GC–MS conditions and QA/QC

The hydrolysis and photolysis rates of CMI and MI were obtained by measuring the changes in the aqueous concentrations of CMI and MI using an HPLC equipped with a Waters 151 pump (Waters, Milford, MA, USA), a Waters 717 + auto sampler, and a Waters 2998 photodiode array detector. CMI and MI were separated using a Fortis C18 (150 mm × 4.6 mm; particle size of 5 μm) column under isocratic conditions (30% methanol and 70% water) at a flow rate of 1.0 mL min^{-1}. The injection volume was 10 μL. Both CMI and MI were monitored at 280 nm.

The CMI and MI concentrations in the MSPD extracts of air freshener samples were quantified using a GC–MS equipped with an Agilent 7890A gas chromatograph (Agilent Technologies, Santa Clara, CA, USA) and 5975C mass spectrometry detector (MSD) (Agilent). Separation was achieved using an Agilent DB-5 MS capillary column (30 m × 0.25 mm; film thickness of 0.25 μm). Nitrogen was used as the carrier gas at a constant flow rate of 1 mL min^{-1}. The GC oven temperature was programmed to

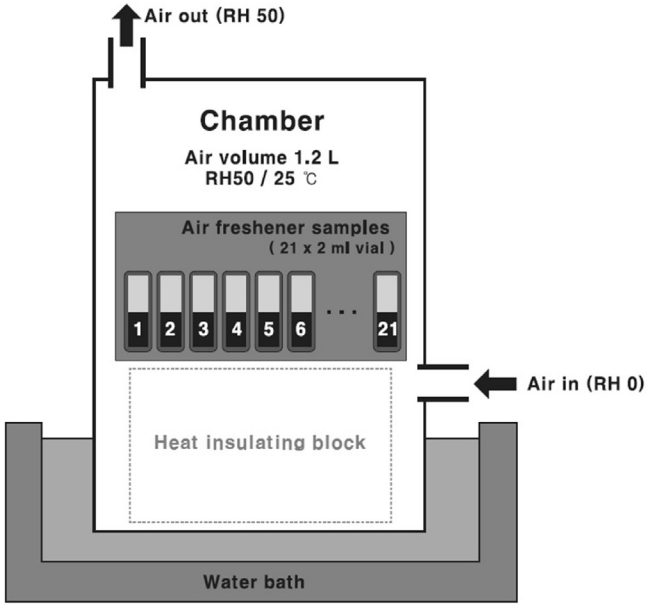

Fig. 2. A schematic diagram of the air chamber used to evaluate the evaporation and transformation of isothiazolinones in two commercial air fresheners.

increase from 60 °C (held for 1 min) to 150 °C (held for 4 min) at 10 °C min^{-1} and then to increase to 280 °C (held for 2 min) at 20 °C min^{-1}. The injection volume was 2 μL, and the injection was performed in splitless mode. The MSD was operated in the electron ionization (EI) mode (70 eV). The injection port temperature was 250 °C. The MSD was run in scan and selective ion monitoring modes. The selected mass-to-charge ratios (m/z) were 115 and 87 for MI and 149 and 85 for CMI.

The instrumental detection limits determined by the error distribution method (Glaser et al., 1981) were 0.6 and 0.8 mg L^{-1} for MI and CMI in HPLC analysis and 1.3 μg L^{-1} for both MI and CMI in GC/MS analysis. The precision of the extraction method was calculated based on extraction replicates (n = 7) of AF1 spiked with CMI and was expressed as relative standard deviation (RSD): 9.5 and 15.0% for CMI and MI, respectively. Recovery was calculated using the fortification method (US FDA, 2014). The recovery of CMI was 77.9%, and that of MI was 71.8%. The coefficient of linear regression (r^2) of the external standard was at least 0.99. A known standard sample was injected in every 10 runs for quality control.

2.6. Models for predicting the air concentration

Because the air concentrations of isothiazolinones are not easy to directly measure, they were estimated according to the decreases in the CMI and MI concentrations in the products, assuming negligible degradation rates in the products based on the hydrolysis and photolysis rates.

Inhalation exposure was assessed using two models: (1) a lower tier vapor model included in ConsExpo 4.0 (Delmaar et al., 2005) and (2) a new model reflecting the mass transfer rates of the active ingredients from the air fresheners.

The lower tier ConsExpo model (model 1) predicts the air concentration (C_{air}) based on the constant weight fraction of the active ingredient (W_f) as follows:

$$C_{air} = \frac{A_0 W_f}{q V_{room} t_R} \times \left(1 - e^{-qt}\right) \quad \text{exposure } t < t_R \tag{1}$$

where A_0 is the initial amount of product used [μg], q is the ventilation rate of the room (number of air changes per day) [d^{-1}], V_{room} is the volume of the room [L], and t_R is the release time [d]. However, Equation (1) does not consider the potential changes in W_f over time.

To include the effect of changing W_f over time, a new model equation was proposed. This model includes the evaporation of the solvent and the active ingredient from the product to the ambient air of the room. The detailed derivation of the model is presented in the Supplementary Data. The time derivative of C_{air} is written:

$$\frac{dC_{air}}{dt} = -qC_{air} + \frac{k_{evap,i} A r C_{0,i}}{V_{room}} \exp\left(\left(\frac{k_{evap,i} - k_{evap,p}}{k_{evap,p}}\right) \ln\left(1 - \frac{k_{evap,p} A r}{V_0} t\right)\right) \tag{2}$$

where $C_{0,i}$ is the initial concentration of the active ingredient in the product [mg L^{-1}], $k_{evap,i}$ is the mass transfer coefficient of the chemical [cm d^{-1}], $k_{evap,p}$ is the evaporation rate constant of the product [cm d^{-1}], and Ar is the interface area of the liquid surface [cm^2]. Equation (2) was solved numerically using the forth-order Runge-Kutta method to relate C_{air} to exposure time.

2.7. Methods and scenarios used for inhalation risk assessment

Estimated human exposure (EHE) [mg kg^{-1} d^{-1}] through inhalation was estimated using the following equation:

$$EHE = C_{air} \times IR \times ET \times (1\ d/24\ h)/BW \tag{3}$$

where IR is the inhalation rate [m^3 d^{-1}], ET is the exposure time [h d^{-1}], and BW is the body weight [kg]. C_{air} was predicted with models 1 and 2. All exposure parameters used are listed in Table 1. Because air fresheners can be used in a room, car, or office, realistic worst-case exposure scenarios were constructed for a person who spends all day in the house and for a person who spends part of the day in a car (Guo et al., 2004). As the worst-case scenario, the volume of the room and the air-change rate were assumed to be 17.4 m^3 and 0.5 h^{-1}, respectively (Nielsen et al., 1994; Wolkoff and Nielsen, 1996). Continuous emission during the use of the liquid air freshener was assumed. The volume of the car and the air-change rate were assumed to be 2.7 m^3 and 1.6 h^{-1}, respectively, as measured for a typical compact car by Ott et al. (2008). The average time spent in a motor vehicle by Koreans (44.8 min) (Jang et al., 2007) was used. The CMI content in the air freshener was assumed 15 mg L^{-1}, which is the maximum allowable concentration according to EU regulations, to reflect the worst case possible although measured concentrations of CMI and MI in AF1 and AF2 were lower. The volume of the air freshener was assumed to be 30 mL.

The no observed adverse effect level (NOAEL) was 0.34 mg m^{-3} in air obtained by Health Canada (2011) in rats during a 90-d period was used. The estimated reference dose (RfD) was 0.06 mg kg_{bw}^{-1} d^{-1}. Including uncertainty factors of short-term to long-term test (3-fold), interspecies extrapolation (10-fold), and intraspecies extrapolation (10-fold), the target MOE of 300 was used for long-term inhalation (Health Canada, 2011).

3. Results and discussion

3.1. Chemical transformation of CMI and MI in water

Slight decreases in the CMI concentration (7–35%) were observed in the hydrolysis test at pH 9 and the phototransformation test at pH 4 and 9 (Figs. S3 and S4, Supplementary Data), whereas no noticeable decrease of MI was observed under any test conditions. At pH 9, the phototransformation rate constant was not significantly different from the hydrolysis rate constant at the same pH (0.038 d^{-1}), indicating that the photolysis rate is much slower than the hydrolysis rate (Fig. S5, Supplementary Data). The first-order photolysis rate constant was determined to be 0.019 d^{-1} for CMI at pH 4.

The standard illuminance specified by Korean Industrial Standards (KS) for an office is 500 lux (Korean Agency for Technology and Standard, 1998), whereas the measured intensity in the incubator was 8300 lux, which exceeded the standard value by a factor of 16.6. Because observable phototransformation occurred only at

Table 1
Exposure parameters used in the risk assessment for two exposure scenarios: in a room and in a car.

	Room	Car
Inhalation rate (m^3 d^{-1})	14.2	
Body weight (kg)	62.8	
Volume (m^3)	17.4	2.7
Air change rate (h^{-1})	0.5	1.6
Exposure time (h)	24	0.53

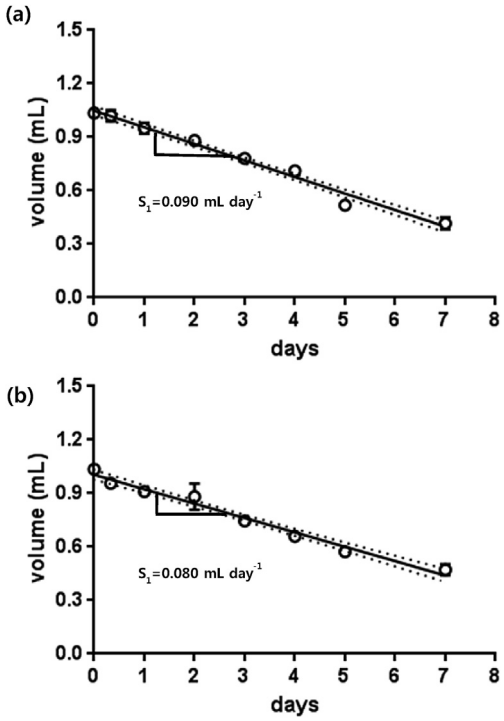

Fig. 3. Decreases in the volumes of (a) AF1 and (b) AF2 with time in chamber tests. The dashed lines indicate 95% confidence intervals. The slopes of the regression represent the evaporation rate constant of the solvent, and error bars denote the standard deviations of triplicate measurements.

pH 4 under strong exposure to visible light and no significant changes were observed in UV/vis spectra, it is unlikely that CMI and MI undergo measurable photodegradation under typical use conditions. Biological transformation was assumed to be negligible because CMI and MI are biocides. Thus, the only possible transformation of isothiazolinones in air fresheners likely occurs via hydrolysis at basic pH. However, the solution pH values of the AF1 and AF2 were measured to be 7.04 and 5.53, respectively. Therefore, only evaporative loss from the liquid air fresheners was considered in the following exposure assessments.

3.2. Chamber tests and mass transfer modeling

As shown in Fig. 3, significant solvent evaporation occurred during the chamber tests. The evaporation rate constants for AF1 and AF2 were 0.090 and 0.080 mL d^{-1}, respectively. Reducing the volume of liquid air fresheners may enrich the added biocide active ingredients in the product when the rate of biocide evaporation is lower than that of the solvent.

Fig. 4 shows the measured CMI and MI concentrations in AF1 and AF2 during the chamber tests. The CMI concentration increased only slightly over 7 d (Fig. 4a and b), whereas the MI concentration increased significantly (Fig. 4c and d). The dashed lines in Fig. 4 indicate the concentrations that would be expected if CMI or MI in air fresheners is not volatile; these expected concentrations were in agreement with the measured MI concentration, indicating that the volatilization of MI from air fresheners is almost negligible. The MI concentration was enriched by a factor of 1.5–2.8 after 7 d in the test chamber. The differences in the volatilization rates of CMI and MI may be explained by the greater Henry's law constant of CMI (35.61 Pa L mol^{-1}) compared with that of MI (1.96 Pa L mol^{-1}) (Alvarez-Rivera et al., 2012).

The evaporation rate constant of AF1 ($k_{evap,p}$) was calculated to be 0.12 cm d^{-1} using Equation S4 (Supplementary Data), and the mass transfer coefficient of CMI from AF1 ($k_{evap,i}$) was calculated to be 0.076 cm d^{-1} using Equation S7 (Supplementary Data). Fig. 5 shows the predicted air concentration (C_{air}) of CMI in the chamber assuming that the decreases in the CMI concentrations in the air fresheners were due to the evaporation and other potential transformations and that the losses are negligible using the two models described previously (model 1 and 2). The predicted C_{air} reached a

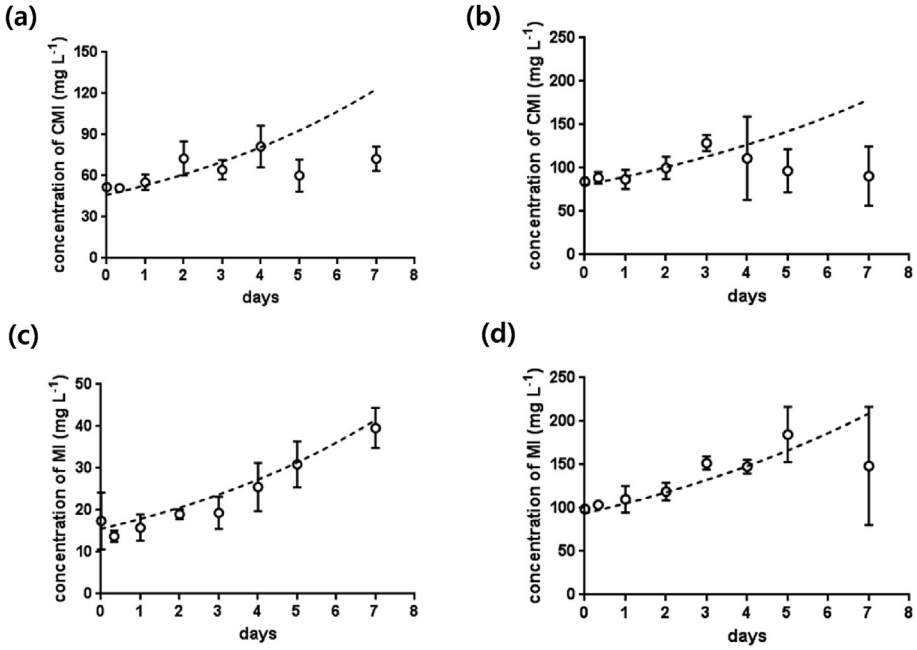

Fig. 4. Changes in the CMI concentration in (a) AF1 and (b) AF2 and the MI concentration in (c) AF1 and (d) AF2 with time. Dashed lines indicate the predicted concentrations of CMI and MI assuming that no evaporation occurred during the test. Error bars denote the standard deviations of triplicate measurements.

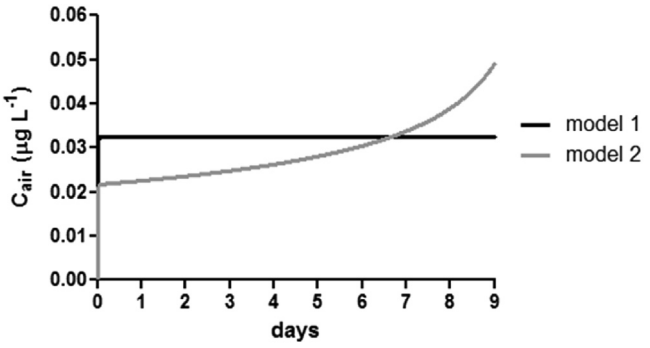

Fig. 5. Modeling the changes in the CMI air concentration using the ConsExpo program with a constant weight fraction, represented by a black line (model 1). For comparison, we applied a mass transfer coefficient (MTC) of the compound at mass balance (model 2), which is represented by a gray line.

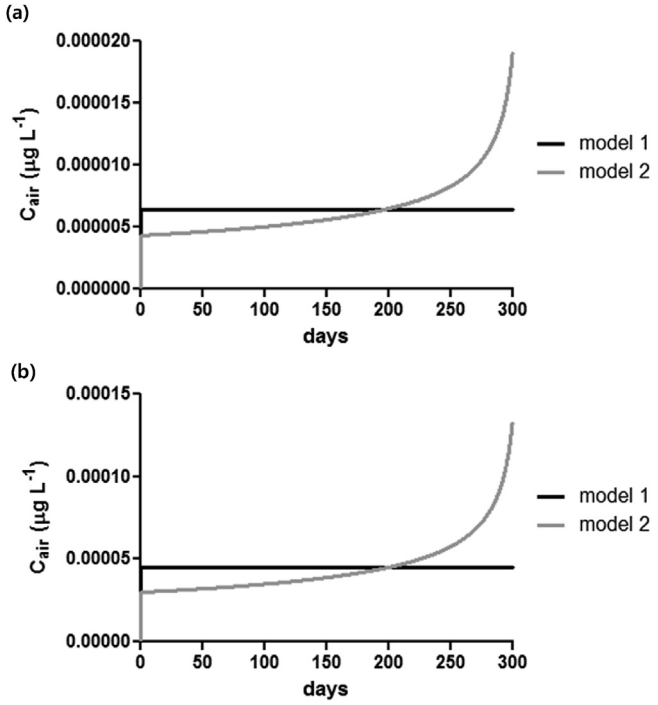

Fig. 6. Modeling the changes in the CMI air concentration using model 1 (black lines) and model 2 (gray lines) in two exposure scenarios: (a) a room and (b) a car.

steady-state value of 0.032 mg m^{-3} after a few hours using the screening model in ConsExpo (model 1). However, the numerical solution of the mass transfer model (model 2) showed a rapid increase followed by a steady increase in C_{air} because of the increase in the CMI concentration in the air fresheners. The predicted value of C_{air} using model 2 exceeded that obtained using model 1 after 6.6 d. This implies that the indoor concentration of CMI would increase as the volume of the air fresheners decreases although this should be confirmed under real use conditions.

ConsExpo adopts a tiered approach. Model 1 is a lower tier model of the inhalation route with a reasonable worst-case assumption of use conditions, which is used to provide a conservative exposure estimation in the screening stage of chemicals in consumer products before higher tier evaluation is performed. Although a constant weight fraction is assumed in Model 1, Fig. 5 shows that the chemical concentration becomes greater than the initial concentration as consumers use the products. Thus, a potential underestimation of the exposure concentration may occur when a constant weight fraction is assumed because of the differences between the solvent and solute volatilization rates.

3.3. Consumer exposure to CMI and MI from air fresheners and health risks

The steady-state C_{air} values predicted by the screening model (model 1) and the range of C_{air} values predicted by the mass transfer model (model 2) were used to assess the CMI inhalation risk using the exposure parameters listed in Table 1; the values of Ar, $k_{evap,i}$, and $k_{evap,p}$ of AF1 measured by the chamber test were used. The predicted release time (t_R) of AF1 was 306 d. Thus, two time points—1 d for the initial concentration and 270 d for the time corresponding to 90% of total release—were used. For MI, the inhalation risk was not evaluated because it exhibited negligible evaporation.

As shown in Fig. 5, which presents the changes in C_{air} predicted using models 1 and 2, the C_{air} estimated using model 1 was greater than that estimated using model 2 at early use (Fig. 6). However, the C_{air} predicted using model 2 exceeded that using model 1 after 200 d because of the increase in the CMI concentration in the liquid air freshener. The estimated C_{air} in the room was lower than that in the car because of the larger volume of the room. Although the estimated C_{air} in the car was larger than that in the room, the EHE calculated for the room was greater because the exposure time in the car was shorter.

All calculated MOE values exceeded target MOE (300), indicating that inhalation risks were negligible (Table 2). However, dermal exposure to CMI and MI should be considered because these species are significantly enriched in air fresheners. If consumers touch the inner surface of an air freshener after use to discard it without wearing personal protective equipment, they might be exposed to CMI and MI concentrations exceeding the regulated values for fresh products. Dermal contact via dust particles and room surfaces might be also of concerns.

In this study, only two liquid air fresheners, in which water was the major solvent, were tested. However, other organic solvents or mixtures are used in various types of liquid air fresheners. The relative volatilities of the solvent and active biocidal ingredients should be important in determining the volatilization. As was the case in this study, enrichment of the active ingredient should be

Table 2
Estimated air concentration (C_{air}), estimated human exposure (EHE), and margin of exposure (MOE) values calculated for two risk assessment scenarios—in a room and in a car—using model 1 and model 2 at two different time points (1 d and 270 d).

	Room			Car		
	Model 1 (t = 1 d)	Model 2 (t = 1 d)	Model 2 (t = 270 d)	Model 1 (t = 1 d)	Model 2 (t = 1 d)	Model 2 (t = 270 d)
C_{air} (μg L^{-1})	6.0×10^{-6}	4.0×10^{-6}	0.1×10^{-5}	4.5×10^{-5}	3.0×10^{-5}	6.8×10^{-5}
EHE	1.4×10^{-6}	9.1×10^{-7}	2.2×10^{-6}	3.2×10^{-4}	2.1×10^{-4}	4.8×10^{-4}
MOE	$4.4 \times 10^{+4}$	$6.6 \times 10^{+4}$	$2.6 \times 10^{+4}$	$1.9 \times 10^{+5}$	$2.8 \times 10^{+5}$	$1.2 \times 10^{+5}$

carefully considered when conducting exposure assessments if the solvent volatilizes much more rapidly than the solutes although this should be further validated under real use conditions.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemosphere.2015.10.136.

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