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Original Article

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Characterization and Quantitation of Personal Exposures to Epoxy Paints in Construction Using a Combination of Novel Personal Samplers and Analytical Techniques: CIP-10MI, Liquid Chromatography–Tandem Mass Spectrometry and Ion Chromatography

Yalong Xue,[1] Anila Bello[2] and Dhimiter Bello[3,*,]

[1]Department of Chemistry, Kennedy College of Sciences, University of Massachusetts Lowell, Olney Hall 525, One University Ave. Lowell, MA 01854, USA; [2]Department of Public Health, Zuckerberg College of Health Sciences, University of Massachusetts Lowell, 61 Wilder St., O'Leary 540D, Lowell, MA 01854, USA; [3]Department of Biomedical and Nutritional Sciences, Zuckerberg College of Health Sciences, University of Massachusetts Lowell, 883 Broadway Street, Dugan Hall 108C, Lowell, MA 01854, USA

*Author to whom correspondence should be addressed. tel: +1-978-934-3343; e-mail: Dhimiter_Bello@uml.edu

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Abstract

Epoxy resins are extremely versatile products that are widely used in construction for coatings, adhesives, primers, and sealers. Occupational exposures to epoxies cause allergic contact dermatitis, occupational asthma, hypersensitivity pneumonitis (epoxy-resin lung) and acute decline in lung function. Despite these health concerns, there is a striking paucity of quantitative exposure data to epoxy resins in construction. The lack of practical analytical methods and suitable personal samplers for monitoring of reactive two-component epoxide systems in real-world applications has been an unmet challenge for decades. Sampling and analysis methods for epoxies should be able to collect the paint aerosols efficiently, stop polymerization reactions at the time of sample collection, and subsequently provide detailed multispecies characterization of epoxides, as well as the total epoxide group (TEG) content of a sample, to properly document the chemical composition of exposures to epoxide paints.

In this work, we present the development and application of two new complementary quantitative analytical methods—liquid chromatography–tandem mass spectrometry with online ultraviolet detection and ion chromatography (IC)—for multispecies characterization of raw products, as well as inhalation and skin exposures to epoxy formulations in real-world construction

What's important about this paper?

We have successfully developed and employed for the first time two complementary analytical methods to characterize reactive epoxy formulations in complex construction applications: (i) LC-ESI-MS/MS to measure the monomer BADGE and its higher oligomers with high sensitivity and resolution; and (ii) ion chromatography to quantify the total epoxy group (TEG). Both methods were used successfully, in conjunction with a new CIP-10IM personal sampler, to quantify epoxy resins during bridge painting. High inhalation and dermal exposures were documented. These methods will be instrumental in supporting future exposure measurements and intervention research to reduce epoxy-induced allergic contact dermatitis and other diseases.

applications. A novel personal sampler, CIP-10MI, was used for personal sampling of airborne epoxies. We report for the first time the results of personal inhalation and potential skin exposures to individual monomers and oligomers of bisphenol A diglycidyl ether (BADGE), as well as TEG, during metal structure coatings in construction; compare analytical results of the two analytical methods; and provide recommendations for method selection in future field studies. High inhalation and potential skin exposures to epoxies point to the need for interventions to reduce exposures among painters in construction.

Keywords: Bisphenol A Diglycidyl Ether (BADGE); CIP-10MI; epoxy paints; construction; inhalation and skin exposures; ion chromatography; liquid chromatography–tandem mass spectrometry

Introduction

Epoxy resins are commercially important products that are used widely in construction trades for their high versatility and excellent performance characteristics, including coatings, adhesives, primers, and sealers (Tavakoli 2003; Spee *et al.*, 2006; CPWR, 2008). The majority of commercial epoxy resins (75–95%) are mixtures based on bisphenol A diglycidyl ether (BADGE) and its respective higher oligomers formed from the condensation of two or more monomeric units, and ~7% are based on bisphenol F diglycidyl ether (BFDGE) monomer (Fig. 1) (Niklasson *et al.* 2009; Aalto-Korte *et al.*, 2014). Epoxies are reactive chemicals containing two or more oxirane groups, or epoxide groups, which can enter polymerization reactions (Fig. S1, available at *Annals of Occupational Hygiene* online) with various cross-linking agents leading to resin curing (Knudsen and Forsgren, 2017). Epoxy coatings products used for painting metal structures in construction are mostly two-component systems. Part one or A is the epoxy component, based on BADGE and its oligomers. Part two or B is a mixture of chemicals, including cross-linking agents (commonly polyamines such as triethylene tetra amine and diethylene triamine), and additional functional additives (anticorrosion agents, inorganic fillers, solvents, moth repellents, etc.). The two parts are mixed in the workplace right before painting, triggering a polymerization reaction that leads to epoxy-resin curing (Muskopf and McCollister, 2000; Knudsen and Forsgren, 2006). The paint is applied with brushes and/or rollers to first cover hard to reach corners/surfaces, followed by spraying. Construction painters could be exposed to epoxy paints via inhalation of overspray aerosols and vapors generated during painting and rolling/brushing, as well as the dermal route from direct contact with the raw uncured epoxy component during product mixing, painting and roller/brushing, contact with contaminated tools, cleaning and maintenance tasks, or from deposition of overspray aerosols directly onto surfaces and clothing.

Occupational exposures to epoxies have been associated extensively with allergic and irritant contact dermatitis (Tosti *et al.* 1992; Jolanki *et al.*, 1996; Dickel *et al.*, 2002; RøMyhr *et al.*, 2006; Geier J *et al.*, 2011; Bangsgaard *et al.*, 2012; Aalto-Korte *et al.*, 2014). Construction workers have one of the highest rates of occupational contact dermatitis, with a prevalence of 25–47% from self-reported data among Dutch construction workers (Timmerman *et al.*, 2016). In a study in Finland, painters were the largest occupational group (~20%) among 209 workers diagnosed with contact allergy to epoxy systems (Aalto-Korte *et al.*, 2015). Respiratory symptoms including occupational asthma and hypersensitivity pneumonitis (epoxy-resin lung) from epoxy systems have also been reported in case studies (Fawcett *et al.*, 1977; Meadway, 1980; Hannu *et al.*,

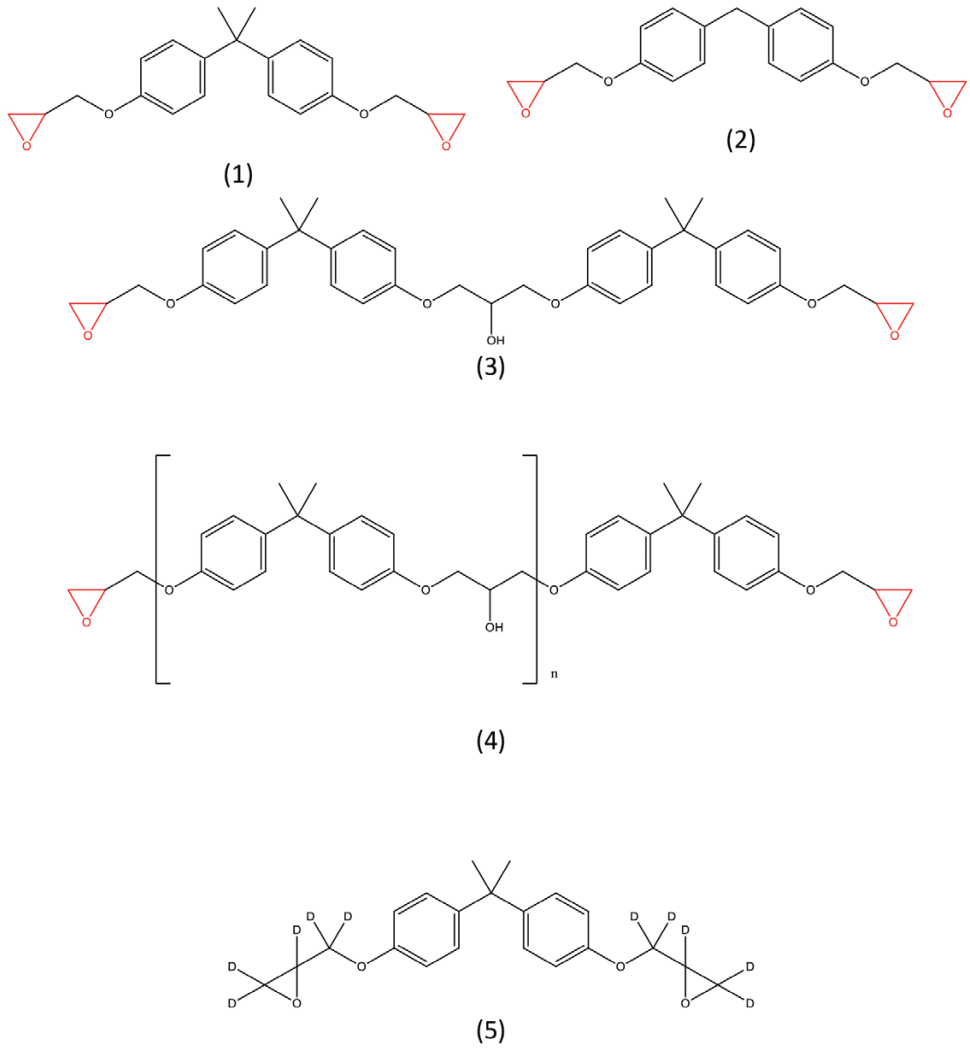

Figure 1. Chemical structures of main monomers and oligomers in commercial epoxy resins: (1) Bisphenol A diglycidyl ether (BADGE); (2) Bisphenol F diglycidyl ether (BFDGE); (3) BADGE dimer; (4) Generic structure of a BADGE-based polymer with 'n' monomeric units; (5) BADGE-d10, IS.

2009; Hines *et al.*, 2015). In earlier studies, painters' exposures to epoxy resins were found to lead to an acute decrease in the forced expiratory volume during the first second (FEV1) (Rempel *et al.*, 1991). The exact agents in the epoxy-resin formulations responsible for occupational asthma and other lung disorders remain unclear.

Despite strong evidence that epoxy systems cause respiratory and skin disease, quantitative investigations of exposures to epoxy formulations among construction workers are remarkably limited in the literature. Exposure data are essential in identifying agents responsible for the adverse health symptoms reported among construction workers in epidemiological studies, identifying workers with the highest exposures, in developing effective exposure prevention strategies and subsequent evaluation of the effectiveness of such interventions. An important impediment to quantitative assessment of occupational inhalation and skin exposures to epoxy paints is the lack of suitable sampling and analytical methods.

The only quantitative inhalation exposure data for epoxies can be found in two papers by Herrick and colleagues from three decades ago (Herrick and Smith, 1987; Herrick *et al.*, 1987) that focused on determining the epoxide content of aerosols during spray painting. Herrick's epoxy method required sampling with a

midget impinger flask filled with dimethylformamide (DMF) to collect and stabilize epoxies. Sample analysis followed the American Society for Testing and Materials (ASTM) D1652 method, which measures the total epoxy group (TEG) content in resin systems through titration with hydrogen bromide (HBr) (Fig. S2, available at *Annals of Occupational Hygiene* online). The excess bromide ion (Br^-) was determined with normal pulse polarography, instead of titration, with a reported method's limit of detection (LOD) of 1 µeq TEG/sample (170 µg BADGE). Neither the sampler, a DMF-loaded impinger, nor the analytical finish (polarography) are suitable for assessing personal inhalation and skin exposures to epoxies in complex (construction) environments and method sensitivity is rather low. The TEG method, however, provides a useful alternative exposure metric for reactive aerosols that contain variable quantities of unknown intermediate pre-polymeric species formed between the time of application and sample collection. A major limitation of the TEG method is that it does not provide specific compositional information for the sample.

More recently, sensitive analytical methods, most notably liquid chromatography–tandem mass spectrometry (LC–MS/MS), have been developed to determine BADGE, BFDGE, and bisphenol A (BPA), as well as other analogs in a variety of food samples, such as whole milk (Casajuana and Lacorte, 2004); canned foods (Leepipatpiboon *et al.* 2005; Gallart-Ayala *et al.*, 2011); drinking water (Lane *et al.*, 2015); and coating of cans used for food storage (Ether, 2003). A few studies have measured BADGE levels in indoor air and dust (Wang *et al.*, 2012), and sewage sludge (Xue *et al.*, 2016). However, there are no reports on the application of these methods for assessment of exposures to epoxy oligomers and no suitable personal samplers have been reported. Furthermore, there are no commercially available analytical standards for higher oligomers of BADGE and there is a real need for developing modern sampling and analytical methods for multi-analyte quantitation of epoxy paint components (monomers, oligomers) in real-world settings.

The main objectives of this work were: (i) to develop a new LC–MS/MS method to analyze BADGE and its oligomers in epoxy paint formulations; (ii) to develop an ion chromatography based TEG method for real-world epoxy paint formulations; (iii) and to apply both methods simultaneously for measurements of inhalation and potential skin exposures to epoxy paints in construction workers during bridge painting.

Methods

Field study sites and participants

Workplace sampling was performed during epoxy midcoat applications at four bridge painting sites in New England from October 2017 to October 2018. Workers performed spray painting in conjunction with rolling and brushing of difficult to reach surfaces, edges, and tight angles. Among the 17 study participants, 11 were painters involved directly with product application through spraying, rolling or brushing, 3 were helpers who performed product mixing and other auxiliary tasks, and 3 were bystanders (site supervisors).

Exposure measurements among bridge painters

Personal airborne sampling was conducted with a novel CIP-10MI (CIP-Capteur Individuel de Poussiere; M-microbiologic; I-inhalable) sampler (Arelco, Fontenay-Sous-Bios Cedex, France) that collects aerosols inside a small cup filled with a liquid of choice, in this case 2 ml of *N*,*N*-dimethylformamide (DMF). The cup rotates at 7600 rpm, producing a collection flow rate of 10 l/min (Gorner *et al.*, 2006), and collecting aerosol droplets by impaction. This sampler has been used successfully for sampling of aliphatic isocyanate aerosols during painting of bridges (Bello *et al.*, 2020). The sampler offers the advantages of an impinger sampler for direct sampling of reactive aerosols in a liquid, and the convenience of a passive sampler-like system (no tubing and external pumps). Because exposures to vapors of BADGE and other higher oligomers are negligible, inhalation exposure is primarily to spray paint aerosols. For example, BADGE has a vapor pressure of 2.55×10^{-6} mmHg and a boiling point of 500°C at 760 mmHg, but it may decompose before reaching its boiling point (Welinder *et al.*, 1988). Air sampling duration ranged from 20 to 230 min with a median of 90 min, corresponding to the actual task duration. At the end of sampling, the liquid media was transferred into clean amber glass vials and transported to the lab in coolers with ice packs. Samples were stored at –20°C until chemical analysis.

Potential skin exposure to hands was assessed by measuring the amount of epoxy accumulated on workers' gloves used during painting tasks followed by immediate post-sampling field extraction and reaction inhibition in DMF solution. This sampling approach was made possible by the fact that epoxy formulations applied in bridges are slow curing systems, with curing times in the order of several hours to over a week. Workers provided their regular gloves at the end of the painting tasks. Most workers wore cotton gloves coated

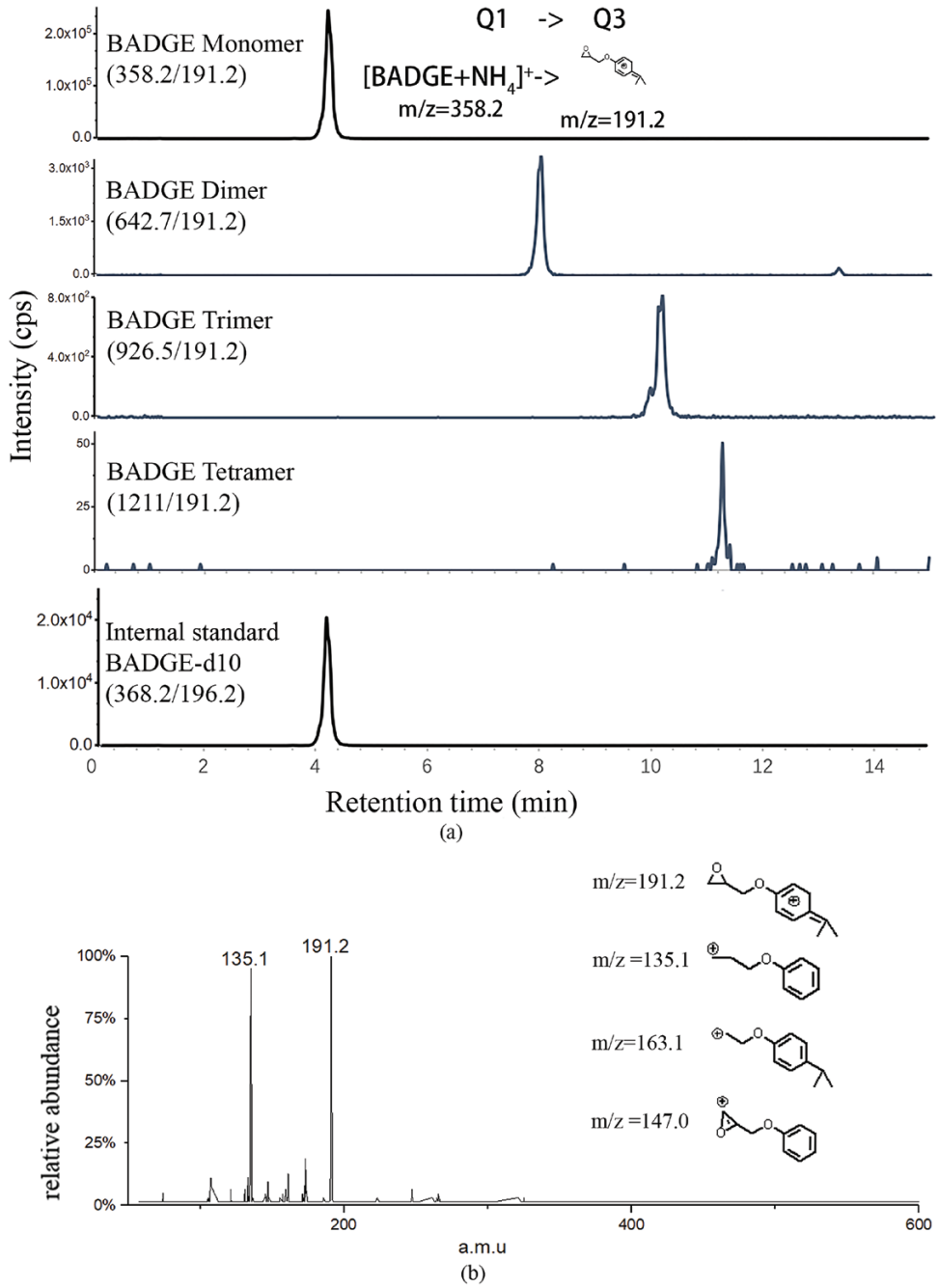

Figure 2. (a) Example chromatograms from LC–MS/MS analysis of a glove sample. (b) Mass spectrum for the BADGE monomer and the proposed structures of major product ions.

with a polymer on the Palmar side (n = 10). The rest of the workers wore thick cotton gloves (n = 1), thin nitrile gloves (n = 1), rubber gloves (n = 1), or no gloves at all (n = 1). Gloves were transferred immediately into 150 ml capacity jars that contained 100 ml DMF solution. The left- and right-hand gloves were placed in separate jars and vortexed to ensure full soaking of the glove with DMF. The jars were capped with a PTFE-lined lid, stored and transported to the lab in a cooler with ice packs, and stored at –20°C until ready for chemical

analysis. Eleven glove pairs were collected, after 20–240 min (median 90 min) task duration.

Analytical method development

Liquid chromatography with tandem mass spectrometry (LC–MS/MS) method chemicals

BADGE (CAT# D3415), glycidyl end-capped poly (Bisphenol A-co-Epichlorohydrin) or poly-BADGE (CAT# 387703), and ammonium acetate (CAT# 73594) were acquired from Sigma Aldrich (St. Louis, MO, USA); isotope-labeled BADGE-d10 [Fig. 1, internal standard (IS), CAT# DLM-9193-1.2] was purchased from Cambridge Isotopes Laboratories (Tewksbury, MA); and MS grade methanol (CAT# BDH85800) from VWR (Radnor, PA).

Standard and sample preparation

Standard solutions were prepared using high purity BADGE dissolved in methanol at ten concentrations in the range of 0.1–1000 ng/ml. Each standard was spiked with 10 µl of 10 µg/ml BADGE-d10 (I.S., final concentration 100 ng/ml) before the analysis. Following warming at room temperature and mixing, field samples were diluted 100× with methanol. Then, 10 µl of a 10 µg/ml BADGE-d10 IS was spiked to each sample prior to the chemical analysis (final concentration 100 ng/sample).

Instrumentation

The LC–MS/MS system consisted of a Shimadzu LC coupled to an AB SCIEX API4000 triple quadrupole mass spectrometer, equipped with a Turbo V Ion Spray electrospray ionization ion source. The Shimadzu system included two solvent delivery units (LC-20AD), degasser (DGU-20A3), autosampler (SIL-20 AC), column oven (CTO-20AC), and an online diode array detector (DAD, SPD-M20A). The system used in these analyses was an LC-UV-ESI-MS/MS (liquid chromatography with an online DAD detector coupled to a triple quadrupole mass spectrometer operated in positive electrospray ionization mode). For simplicity, we will refer to the system as LC–MS/MS. The mass spectrometer was supplied with high purity N_2 gas from a Peak Scientific AB-3G generator, which was used as the nebulizing (gas 1), heating (gas 2), and curtain gas. Chromatographic separation was performed on a Kinetex C18, 2.6 µm, 100 × 4.6 mm column, with a matching C18 guard column (Phenomenex, CA).

LC–MS/MS analysis

The mobile phases used for the BADGE and other oligomers present in commercial epoxy samples were: A, 0.15% (w/v) ammonium acetate in water; and B, 0.15% (w/v) ammonium acetate in methanol. Epoxy compounds were eluted with a flow rate of 0.6 ml/min using a linear gradient from 60% B to 95% B during the first 10 min, held at 95% B for another 5 min, followed by 3 min post-analysis re-equilibration at 60% B. Column oven temperature was set to 40°C, and the sample injection volume was 10 µl. Mass spectrometry analysis was conducted in the multiple reaction monitoring (MRM) mode. MS source parameters included curtain gas (CUR) 30, collision gas (CAD) 5, ion spray voltage 5500 V, source temperature 600°C, ion source gas 1 and 2 (GS1, GS2) 60 and 30, respectively, and interface heater was ON. The optimized compound parameters for each specific analyte are shown in Table S1 (available at *Annals of Occupational Hygiene* online).

Analysis of the BADGE monomer was performed using calibration curves with BADGE-d10 as the IS. For quantitation of BADGE oligomers (dimer and trimer), for which there are no commercially available analytical standards, we used the monomer calibration curve in MS/MS, adjusted with a compound-specific response factor in MS/MS derived from the online DAD detector (see Supplmentary section 2.3, Table S2 and Fig. S3, available at *Annals of Occupational Hygiene* online). The correction factor (CF) for the dimer was 3.05, which means that the BADGE response factor in MRM was divided by 3.05. Quantification of the trimer followed the same procedure as quantification of the dimer. The CF for the trimer was 10.38. The CF for the tetramer was 29.72. It is important to note that CFs are compound and instrument-specific and they should be derived and verified each time there is a change in the instrument, or MRM method settings. Two typical bulk epoxy products used in the field were also characterized in detail (Table 2).

Reproducibility in analytical results was investigated by conducting repeated independent analysis of 10 randomly selected samples over a range of concentrations by repeating the whole sample processing cycle and using a new set of standard solutions for each sample batch. Sample storage stability was evaluated by reanalyzing a set of 5 random samples from the original solution that were stored for six months at −20°C, using a fresh set of standards for each analytical batch.

Ion chromatography (IC) method for the TEG

Chemicals

HPLC grade DMF, BADGE, Poly (Bisphenol A-co-epichlorohydrin), glacial acetic acid (>99.99%, trace metals basis), analytical standard grade 0.1 M perchloric

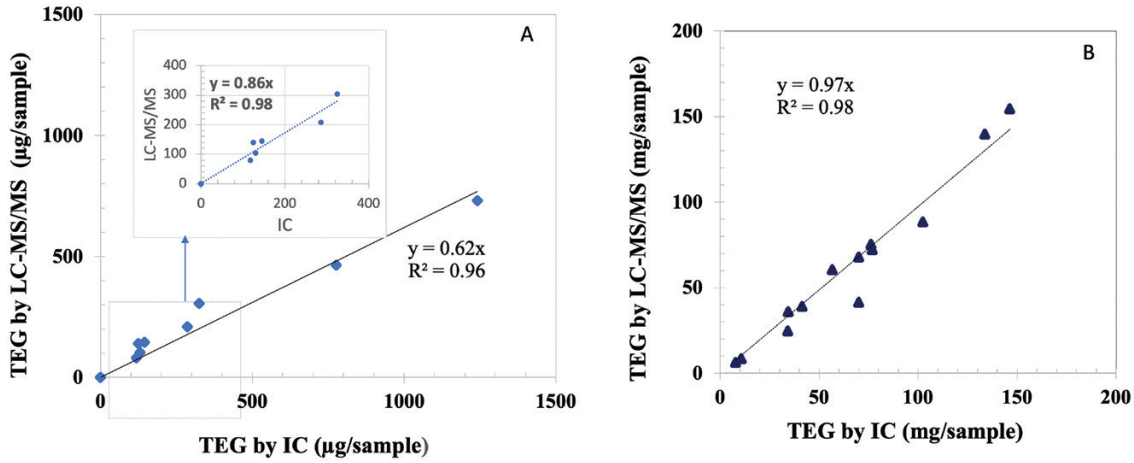

Figure 3. Comparison of total epoxide group (TEG) in field samples by the LC–MS/MS (estimated) and the IC method. (a) Air samples; (b) Glove samples up to 150 mg/sample.

Table 1. Accuracy and precision for BADGE and its oligomers (n=3/concentration) in LC–MS/MS. The nominal values for dimer (50–1000 ng/ml) and trimer (60–1200 ng/ml) in test solutions, for which no pure analytical standards exist, were determined by accurately weighing different amounts of reference bulk material (in Table 2), and using the % dimer or trimer content that was determined independently by LC–UV analysis to calculate their final expected concentrations.

Analyte	Nominal concentrations (ng/ml)	Accuracy (%)	RSD (%)
BADGE	500	99.8	2.3
	100	105	0.8
	10	96.0	1.2
	Average	**100.2**	**1.4**
Dimer	1000	100	0.3
	500	97.0	1.2
	50	88.2	1.5
	Average	**95.1**	**1.0**
Trimer	1200	96.5	5.3
	600	94.1	4.6
	60	103	5.3
	Average	**97.8**	**5.1**

acid in acetic acid solution, and tetraethylammonium bromide (TEAB), were all purchased from Sigma Aldrich (St. Louis, MO).

Standard and sample preparation

All standards were prepared by dissolving BADGE in DMF solution at a range of concentrations from 0.05 to 50 µM. In each standard solution, we added 3 ml of 100 µM TEAB, 300 µl of 1 mM v/v perchloric acid in acetic acid, and 10 mg of $NaHCO_3$. Standards were prepared fresh with each batch of field samples. Sample preparation included the following steps: 300 µl of a field sample (air or glove) was added to each of three different polypropylene tubes (7 ml capacity), each containing 3 ml of 1, 10, and 100 µM of TEAB in acetic acid; each tube was spiked with 3, 30, and 300 µl, respectively, of 1 mM perchloric acid in acetic acid, and vials were capped and allowed to react overnight. Then, 10 mg of $NaHCO_3$ was added to each sample, and samples were evaporated under a gentle nitrogen flow over several hours, completely dried inside a vacuum oven (up to 2 days), and then dissolved in 3 ml of the mobile phase (as specified below).

IC analysis

IC analyses were performed on a Dionex™ ICS-1000 instrument that contained a Dionex™ IonPack™ AS11A anion separator column, equipped with a guard column. The eluent flow rate was 1 ml/min of 0.6 mM NaOH. The sample loop was 25 µl and the column temperature was set at 35°C. Quantitation of TEG was performed using external calibration curves plotting the peak area of excess Br^- ion as a function of different concentrations of TEG in BADGE standards. Of note, this relationship is inverse in that more TEG consumes more Br^- resulting in progressively less residual/excess Br^-.

To evaluate method recovery, we used a range of 0.1–100 µM NaBr solution as the standard at 0.1, 1, and 10 µM BADGE concentrations. This allows calculation of the theoretical residual concentration of Br^- ion,

Table 2. Compositional analysis of two typical bulk products used at sampling sites and the reference material [Poly (Bisphenol A-co-epichlorohydrin), glycidyl end-capped]. Linear regression fit: TEG (by IC) = 1.18 × TEG (by LC–MS/MS), R^2 = 0.999.

Materials	% w/w				% TEG eq. by LC–MS/MS (w/w)	% TEG by IC (w/w)	TEG ratio IC:MS/MS
	Monomer	Dimer	Trimer	Tetramer			
Reference: material	71.9	26.2	1.9	0.2	23.9	28.3	1.18
Product I: Mid-Coat	19.3	5.9	1.4	0.6	4.7	5.2	1.10
Product II: Primer	18.9	3.5	9.3	10.2	7.0	8.7	1.24

since BADGE will react completely with bromide ions. Concentration of the remaining Br^- ion was determined by IC and the recovery was calculated as the ratio of the measured remaining Br^- concentration over the theoretical residual Br^- concentration. Method reproducibility was assessed by randomly reanalyzing the original stock of 5 field samples 6 months later using new sample aliquots, and a new set of analytical standards.

Statistical analysis

Airborne concentrations of BADGE and its oligomers were calculated based on the analytical results for each sample, sampling duration, and the flow rate of the sampler, and expressed as μg analyte/m^3 air. The amount of epoxy paint accumulated on workers' gloves was determined for each glove pair (sum of left and right hand). Results were expressed as mg analyte/pair of gloves. To account for variable task duration, glove results were also expressed as normalized amounts, mg analyte/glove pair/min.

The TEG exposure metric derived from the IC analysis was compared to the estimated TEG from the LC–MS/MS. The latter one was calculated as the sum of epoxy group content across all measured epoxy species (monomer, dimer, trimer) (see Supplementary material, section 2.3.2, available at *Annals of Occupational Hygiene* online).

Exposure data from the field were examined for the underlying distributions and log transformed data were used for subsequent statistical analysis using SAS 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics, including geometric mean (GM), geometric standard deviations (GSDs), ranges and inter-quartiles, were generated for inhalation and skin exposures of individual analytes and TEG. Linear mixed effects models (proc mixed) were utilized to investigate association of airborne exposures with the task performed (spraying, rolling) using site ID as a random effect. The data were considered statistically significant at $\alpha = 0.05$. Regression analysis was used to evaluate method reproducibility and assess association between different analytes (BADGE, dimer) and TEG exposure metrics.

Results

Performance of the LC–MS/MS method

Quantitation of BADGE and its oligomers in the standards mixture was accomplished in the MRM mode by monitoring the following Q1/Q3 transitions: monomer, 358.2/191.2 and retention time (RT) of 4.2 min; dimer, 642.7/191.2, RT 7.6 min; trimer, 926.5/191.2, RT 9.8 min; and tetramer, 1211/191.2, RT 11.2 min (Fig. 2). The most common Q3 ion fragment of BADGE and its oligomers was that of [(*p*-isopropylphenoxy) methyl] oxirane, with an *m/z* of 191.2 (Fig. 2).

Quantitation of BADGE was performed by the internal standard method with BADGE-d10 as IS. The calibration curve was linear over the 0.5–2000 ng/ml range (R^2 = 0.999). Field samples were diluted typically 100× for air samples and 1000× –10,000× for gloves. The LOD for BADGE, determined as a signal-to-noise ratio >3:1 for the lowest detectable standard in a field blank matrix was 0.25 ng/ml. Except for the (field and lab) blank samples, all field samples were above the LOD for BADGE. The LODs for dimer and trimer were similarly estimated at 1.0 and 1.8 ng/ml, respectively. Additional quality control and verification measures included spikes of field blank aliquots at 1× to 3× LOD BADGE (final dilution) and with known amounts of a well characterized epoxy bulk material.

Analysis of three sets of quality control standards, representing low (~10 ng/ml), medium (~100 ng/ml), and high concentration (~500 ng/ml) covering the linear range of the calibration curve in an equivalent field blank matrix, were used to assess the accuracy of the LC–MS/MS analysis. The average accuracy ranged from 95 to 101% across three test concentrations, with a relative standard deviation of 1.0–5.1% (Table 1).

Table 3. Personal breathing zone (PBZ) and potential skin exposures to epoxy measured in construction metal structure coating tasks.

Epoxy species[a]	Inhalation exposures[c] (n = 9)				Potential skin exposures[d] (n = 11)						
	Non-detects n' (%)[b]	*Breathing zone concentrations (μg/m³)*			Non-detects n', (%)	*Glove loading (mg/pair)*			*Glove loading (mg/pair/min)*		
		GM	(GSD)	Range		GM	(GSD)	Range	GM	(GSD)	Range
BADGE **MW = 340.42**	0 (0)	802.7	(3.2)	111–3,850	0 (0)	547.2	(2.9)	55–1,963	8.9	(3.3)	0.6– 34.2
DimerMW = 624.77	0 (0)	26.4	(7.2)	1.6–478	0 (0)	10.7	(4.5)	0.5–70.7	0.2	(6.0)	<0.1– 1.3
TrimerMW = 909.13	1 (11)	13.1	(10.2)	nd[c]–325.8	1 (9)	8.3	(3.0)	0.6–23.0	0.1	(5.0)	<0.1– 1.3
TEG, IC [e]	0 (0)	276.9	(3.9)	30–1,551	0 (0)	173.1	(3.0)	18.4–752	2.8	(3.3)	0.2– 10.2
Calc. TEG, LC–MS/MS	—	211.8	(3.4)	28.6–1,044	—	141.1	(2.9)	14.0–506	2.3	(3.3)	0.2–8.9

[a]MW, molecular weight (g/mol); the tetramer was not detected in any of the samples.
[b] Number of non-detectable samples.
[c]Air sampling duration, which continued for the duration of the task, had a median of 90 min (20–230 min).
[d] Glove sampling duration had a median of 90 min (15–240 min).
[e] TEG, Total Epoxy Group (equivalent weight, 43 g/mol).

Results of storage stability of field samples (n = 5) at –20°C indicate that BADGE concentration decreased by 12–19% over a 6-month period. Therefore, epoxide analysis of samples stored in DMF as the inhibition medium should proceed as soon as possible, preferably within 1 month. Storage of samples at room temperature is not recommended.

The reproducibility of analytical results for BADGE was satisfactory (Fig. S4a, available at *Annals of Occupational Hygiene* online), with a linear regression coefficient (beta) of 1.09 and R^2 = 0.99. Compositional analysis by LC–MS/MS of two epoxy formulations used in the field and a reference epoxy material is presented in Table 2.

Performance of the ion chromatography method

A typical chromatogram obtained from the study samples analyzed with the IC method is provided in Fig. S5 (available at *Annals of Occupational Hygiene* online). The bromide ion peak, at RT of ~6.7 min, is well separated from the acetate peak. The fact that we could not see the perchlorate ion could be related to its long retention time when using 0.6 mM NaOH.

The LOD for the IC method was calculated from the lowest concentration of sodium bromide standard with a signal-to-noise ratio of >3:1. For the Dionex™ ICS-100 ion chromatograph, the LOD of the bromide ion was 10 ng/ml. This LOD corresponds to residual bromide in a sample, which is inversely related to the TEG content of a sample. At high epoxide loads, the residual bromide content is very low, and measured with poor reproducibility. However, at low epoxide loads, the residual bromide is very high and minor changes in Br^- content are difficult to quantify with accuracy. Therefore, reproducibility in measuring Br^- is an important consideration in determining the equivalent epoxide LOD. The LOD of the IC method, for which good reproducibility can be achieved, was estimated to be equivalent to 0.1 μM BADGE (34 ng BADGE/ml, or ~8.6 ng epoxy group/ml).

The reproducibility of total epoxide group analysis by IC was satisfactory (Fig. S4b, available at *Annals of Occupational Hygiene* online, linear regression coefficient, 0.87; R^2 = 0.96). The recovery of TEG based on known spikes of BADGE was satisfactory for the range of tested standards (0.1–10 μg TEG/ml) (Table S3, available at *Annals of Occupational Hygiene* online), with absolute recoveries in the range of 107–112% and relative standard deviation of 3.2–12.2%.

Airborne exposures among bridge painters

Airborne sampling results are summarized in Table 3. High airborne exposures were measured for the BADGE monomer: GM of 802.7 μg/m³ and GSD of 3.2. Exposures to the dimer had a GM of 26.4 μg/m³ (GSD 7.2), whereas the trimer had a GM of 13.1 μg/m³ (GSD 10.2). BADGE and its dimer were detected in 100% of the samples. The trimer was detectable in all but one sample (89%). The highest personal exposures were measured during spraying inside a tarp-enclosed bridge, as follows: BADGE, 3850 μg/m³; dimer, 478 μg/m³; and trimer, 185 μg/m³. No BADGE or higher oligomers were detected in multiple field blank air samples and laboratory blanks.

The TEG measured by IC had a GM of 276.9 (GSD 3.9) μg/m^3 and a range of 30–1551 μg/m^3.

Spraying was associated with higher exposures to BADGE compared to rolling or brushing tasks (Fig. S6a, available at *Annals of Occupational Hygiene* online), although the results were not statistically significant (*P*-value = 0.55). Airborne exposures to the dimer were higher during spaying than brushing/rolling ($P = 0.09$, Fig. S6b, available at *Annals of Occupational Hygiene* online). Trimer levels were slightly higher during brushing than spraying, but not statistically significant (Fig. S6c, available at *Annals of Occupational Hygiene* online; $P = 0.83$).

Potential skin exposures among bridge painters

BADGE and its dimer were detected in 100% of the samples, whereas the trimer was detectable in all but one sample (91%) (Table 3). Exposures to the BADGE monomer had an overall GM of 547.2 mg/pair (GSD 2.9); dimer GM 10.7 mg/pair (GSD 4.5); and trimer GM 8.3 mg/pair (GSD 3.0). The maximum amounts of epoxy compounds accumulated on the glove dosimeters were 1963.0 mg/pair for BADGE, 70.7 mg/pair for the dimer, and 23.0 mg/pair for the trimer. The total TEG (by IC) accumulated on painters' gloves ranged from 18.4 to 752.0 mg epoxy group/pair of gloves (GM 173.1 mg epoxy group/pair; GSD 3.0). No BADGE or higher oligomers were detected in blank nitrile and cotton gloves processed as samples.

Comparison of TEG content by the two methods

The TEG content measured by IC is expected to be higher than that calculated based on LC–MS/MS because it includes several non-chromatographable species, and many structurally unknown intermediate products. The BADGE monomer accounted for 79% (w/w) of the reference material, and ~19% (w/w) of the raw materials collected in the field (Table 2). The content of higher oligomers was between 1 and 10% w/w. The TEG content of two field products were 5.2 and 8.7%, respectively. The IC method yielded 11–24 % higher TEG content than LC–MS/MS. More commercial materials should be analyzed in future studies to better assess the overall bias in TEG estimation by LC–MS/MS.

The TEG exposure metric in field samples, calculated from the LC–MS/MS analysis, compared favorably to the TEG values determined by IC. Figure 3 plots the correlation of TEG values between the two methods for air and glove samples. The regression coefficient for air samples was $\beta = 0.86$ and $R^2 = 0.98$ (lower agreement at higher sample loads, Fig. 3a), whereas for glove samples it was $\beta = 0.98$ and $R^2 = 0.95$ (Fig. 3b). BADGE (as TEG equivalent) correlated strongly with TEG by IC for air (TEG by IC = 1.10 × BADGE; R^2=0.95) and glove samples (TEG = 1.44 × BADGE; $R^2 = 0.92$; Fig. S7a and b, available at *Annals of Occupational Hygiene* online).

Discussion

In this work, we developed and evaluated two complementary analytical methods for quantifying BADGE and its higher oligomers (dimer, trimer, tetramer), as well as the TEG in representative commercial products collected at construction sites. Furthermore, the two methods were employed to assess personal airborne and potential skin exposures to epoxy resins among construction painters performing metal structure coatings. This is the first report on quantitation of airborne inhalation and potential skin exposures to BADGE and higher oligomers in epoxy paints, as well as TEG in these same samples. This work addresses an important analytical and sampling need for monitoring of occupational and consumer exposures to epoxies. The LC–MS/MS method (with an online DAD detector) for BADGE and higher oligomers is highly sensitive and reproducible. The BADGE and its dimer were quantified in 100% in all air and glove samples. Similarly, the trimer was quantified in all but one air/glove sample (~90%). Furthermore, the IC method for epoxies resulted in successful quantitation of TEG in airborne and glove samples, as well as in representative bulk products from the study sites. The TEG analysis by IC was compared favorably with the calculated TEG based on LC–MS/MS analysis. While direct quantitation of BADGE may not be considered challenging because BADGE standards and IS are commercially available, quantitation of the BADGE oligomers in MS/MS (dimer, trimer, tetramer) without commercial standards is of notable practical importance. It is possible that HPLC with UV detection can be used to quantify these analytes in commercial samples, using the BADGE calibration curve. However, from our previous experience with isocyanates and exploration of current epoxy glove and air samples, HPLC-UV lacks specificity, resolution, and sensitivity and is unable to reliably quantify these analytes in extremely complex matrices, such as is the case of glove samples collected at construction sites (Harari *et al.* 2016; Bello *et al.*, 2020). Furthermore, the sensitivity of HPLC-UV is often insufficient for detecting and quantifying the dimer and trimer in air samples.

Inhalation exposures and implications

The only exposure data for epoxies, dating back to 1988, report TEG in area samples collected during steel structure painting at levels that range from 2.86 to 11.7 μeq TEG/m^3 or (×43 μg/μmol) 123–503 μg TEG/m^3 (Herrick *et al.*, 1988; Herrick and Smith, 1988). The GM airborne TEG in our study was 277 μg TEG/m^3, comparable to the Herrick's values. However, we measured much higher TEG values in several personal samples, 3× higher than that maximum, or 1551 μg TEG/m^3. The similarly of our results with Herrick *et al.*, 1988 suggest that the CIP-10MI sampler is a valid substitute to impinger sampling, the latter not preferred by workers due to high risk of liquid spilling. The high centrifugal force in CIP-10MI prevents spilling even when the sampler is turned upside down, making it easy to use by the workers. Furthermore, CIP-10MI unit collects >95% of aerosol particles with aerodynamic diameter >2.8 μm and >50% for particles >1.8 μm (Gorner *et al.*, 2006). The mass median aerodynamic diameter of spray aerosols in these applications is around 15–20 μm (Herrick and Smith, 1988; Brosseau *et al.*, 1992). Although a true particle size distribution of paint aerosols using real-time instrumentation has not been reported (likely due to the risk of permanently damaging expensive instrumentation), the submicron size fraction of the aerosol is expected to be negligible. The CIP-10MI sampler with DMF as the collection liquid can be used routinely for monitoring personal exposures to epoxies in construction.

There are no occupational standards for airborne epoxy exposures to compare our results with. The sampling results clearly document activities associated with high airborne exposures to epoxy paints. Most of the painters (~70%) used half-facepiece organic vapor respirators, while the rest did not use any respirators. Workers often did not wear respirators during roller/brush painting, including inside tarp-enclosures, for which considerable airborne epoxide exposures were measured (Fig. S6a–c, available at *Annals of Occupational Hygiene* online).

Skin exposures and implications

There is extensive peer-reviewed literature documenting allergic contact dermatitis from exposures to epoxy-resin systems, but no quantitative exposure data. Hands and upper extremities are the most impacted body parts, represented ~69% (n = 209) of all occupational contact allergy cases in Finland. Statistics on the occupational disease burden, including contact dermatitis, among painters in the US are scarce. In our study, we measured the potential for skin exposures to the hands of workers using an interception technique (workers' own gloves) and found high epoxy loads (mg to grams), suggesting high potential for skin exposures via hands. Skin exposure to other body parts is highly likely since we frequently observed contamination (colored mid-coats) of head and forearms, which was more noticeable when workers wore short sleeve shirts. Quantitation of skin exposures to other body parts was not attempted in this study due to logistic constraints and will be addressed in future studies. However, in previous studies of spray polyurethane foam applicators we found that the head and forearms had higher isocyanate loads than hands, which represented the second most contaminated anatomical site (data not reported). The thick cotton gloves and cotton gloves (dorsal side) coated with a polymer on the Palmar side can serve as a sponge for epoxy paints and, for this reason, they are not recommended for use during epoxy painting applications (CPWR 2008). Our glove loading results confirm this concern. For workers who did not wear any gloves during painting, the glove results would represent actual skin exposure. The development of analytical methods for epoxies enables future studies to address more directly the actual skin contamination with epoxies, including under gloves and other fabrics. High potential for skin exposure to epoxy components is directly related to the predominance of transfer mechanisms from direct contact with raw materials, contaminated surfaces and tools (Van-Wendel-de-Joode *et al.*, 2003) and calls for further investigations into exposure sources and controls.

High likelihood for skin exposure to epoxies is concerning. In addition to the well-known acute contact dermatitis, BADGE can be absorbed slowly from the (mouse) skin (Climie *et al.*, 1981a, 1981b) to enter systemic circulation. Workers' exposures to BADGE have been associated with increased blood levels of the follicle stimulating hormone (FSH) (Hanaoka *et al.*, 2002). Exposure to BADGE (and its hydrolysis byproducts) has been implicated in potential reproductive and development toxicity (Hanaoka *et al.*, 2002), and adipogenesis in human and mouse multipotent mesenchymal stromal stem cells (MSCs) at low nanomolar concentrations (Chamorro-García *et al.*, 2012). Marqueno *et al.* (2019) emphasized 'the need to monitor human exposure to these compounds, at least as intensely as BPA [bisphenol A] is monitored' (Marqueño *et al.*, 2019). Our urinary biomonitoring results in this cohort of workers confirms a 2.9× cross-shift increase in the mean concentration of the main BADGE biomarker (BADGE·2H$_2$O) (post-shift to pre-shift, unpublished data). High exposures to epoxies and high uptake are occurring in this cohort of workers and systemic health effects remain largely unknown.

Limitations of the IC method

Although IC gives an accurate assessment of the TEG content and a single, easy to interpret number, it has several disadvantages. Of note, the sample preparation process is laborious. The process involves several steps and a considerable number of chemicals, such as dimethylformamide, perchloric acid, acetic acid, sodium hydroxide, and BADGE. The initial steps are time consuming. For example, the reaction of Br^- with BADGE requires an overnight step to ensure reaction completion. The removal of excess acetic acid under vacuum, required up to 2 days. In a multistep procedure, the amount of residual Br^- than can be lost with every processing step increases, resulting in potentially significant errors in the TEG estimation and the overall accuracy of the method. Because the IC method calculates TEG based on the amount of consumed bromide (as a difference), its accuracy at very low and very high epoxide concentrations is reduced considerably due to the increased difficulty in accurately determining such differences. Unlike HPLC, IC is not found as frequently in modern analytical laboratories.

TEG exposure metric: insights into polymerization chemistry and sampling needs

Sampling and chemical analysis of reactive resin systems, such as epoxies, isocyanates, and the like, present unique challenges originating from ongoing polymerization reactions that lead to formation of new intermediate species. The rate of these polymerization reactions varies widely with the type of product formulation—from slow curing over 7 or more days to very fast curing under 1 h—and environmental conditions, including temperature, relative humidity, and UV light. The polymerization reaction rates are accelerated by 2× or more for every 10°C increase in ambient temperatures. Epoxy formulation encountered at sampling sites in this study had curing times that varied from 7 days or more for primers to 2 h or more for topcoats. Furthermore, lack of commercially available standards for higher oligomers complicates their quantitation.

Direct comparisons between the TEG measured by IC and that calculated in LC–MS/MS for raw products, air samples, and glove samples can offer unique insights into polymerization chemistry of epoxy coatings used in construction and can inform future sampling and analytical needs. The expectation is that the higher the reactivity of the paint system, the higher the discrepancy between the measured TEG by IC and the calculated TEG by LC–MS/MS. For the raw materials (one component system), we found high correlation between TEG measured by IC and that calculated by MS/MS ($R^2 > 0.95$ in all cases) (Table 2) and only 18% underestimation of the TEG by LC–MS/MS. For air samples, good agreement was observed between the two methods ($R^2 = 0.96$ or more), however the calculated TEG was on average 80% of the measured TEG for most samples when calculated from individual data points and 86% as the slope of the fitted regression line (Fig. 3a). This discrepancy could be due to the extent of ongoing polymerization during aerosolization of epoxide spray paints, which may reflect well mixed reactants, aerosolization of liquid into small droplets with a larger surface area, and the relatively high ambient temperatures during paint application (commonly over 30°C/86°F). In the case of glove samples, the calculated TEG was nearly the same (97%) as the measured TEG (Fig. 3b). One possible explanation for the better agreement in TEG values between the two methods may be related to the fact that skin exposure may be happening to a larger extent through direct contact with raw epoxide component (part A) on epoxide containers and contaminated tools. Inhalation of part A epoxy constituents with very low volatility is unlikely. It is also possible that the fabric material in gloves somehow may hinder polymerization reactions. Similar to TEG findings for potential dermal and inhalation exposure to epoxides in coatings applications, the calculated total reactive isocyanate group (TRIG) of slow curing aliphatic isocyanate topcoat applications in bridges and autobody shops differed by <10% of the measured TRIG by titration (Bello *et al.*, 2002a, 2002b, 2020). In contrast to aliphatic isocyanates and epoxies, the measured TRIG (by the 1,8-diaminonaphthalene or DAN method) of fast curing two-component isocyanate systems in spray polyurethane foam applications (SPF) was almost 10 times higher than the calculated TRIG based on the LC–MS/MS method (Bello and Streicher, 2013; Streicher *et al.*, 2006). The slow curing rates of epoxy systems enable successful application of reagentless samplers, such as collection of gloves, or the possible use of removal techniques (wipes and tape stripping) from the skin or reagentless interception media (e.g. a filter) under clothing/garments, as long as the samples are immediately field extracted.

The ratio of different oligomers can further provide insights into polymerization chemistry of epoxy paints. The BADGE monomer/dimer ratio in the two bulk products encountered in the field ranged between 3.3 and 5.4 (Table 2). In samples, the median BADGE monomer/dimer ratio was 27 for air samples and 40 for gloves and the distributions of these ratios were similar. The dimer/

trimer ratios in two field bulks were 0.38–4.2 (Table 2). In air samples, the median dimer/trimer ratio was 2.97, whereas in gloves it was 1.7. While the median dimer/trimer ratio in samples is within the expected range in bulks, the BADGE monomer appears to be enriched by 10-fold or more, relative to the dimer content in air samples, and even more so in glove samples. One possible explanation that is supported by DAD exploration of relative peak heights of various oligomers in air and glove samples, is that BADGE may be reacting slower than the dimer and trimer. These observations require further investigations and confirmation.

The diversity of two-component epoxy systems in various applications suggests that further TEG assessment by both methods is required in order to better understand the behavior, polymerization chemistry, and associated sampling and analytical errors in quantitation of exposures to epoxides. Collective evidence from this work indicates that the higher molecular weight oligomers (beyond tetramer) make up only a small percentage of the epoxy polymer mixtures used in coating applications. If only one method must be used, we recommend the highly sensitive, more specific and reproducible LC–MS/MS as the method of choice. Further improvements to the LC–MS/MS method can be made by engaging in producing purified forms of the dimer, trimer and tetramer for use as standards, as well as in developing their corresponding labeled internal standards. Another important area for further epoxy method development should be to change the current strategy from using an inhibitor solvent to using a suitable derivatizing reagent that can effectively stabilize epoxides, as is done successfully with isocyanates. Such an approach could be particularly beneficial for quantifying epoxide inhalation and dermal exposures for fast curing formulations.

Conclusions

In this work, we have successfully developed two analytical methods for quantitation of epoxy content in raw epoxy materials and applied them to personal air and glove samples collected from construction sites that used two-component formulations. The LC–MS/MS method provides highly sensitive multi-analyte detection and quantitation of BADGE, and its two major oligomers—the dimer and the trimer. Furthermore, a complementary ion chromatography TEG method was also developed and applied to the same samples. The TEG content measured by IC correlated highly with the calculated TEG content, and in two out of the three comparisons, the agreement was within 20%. Furthermore, BADGE monomer was highly correlated with the TEG and represented ~90% of TEG in air samples and 70% of TEG in glove samples. BADGE can serve as a good surrogate marker for TEG and epoxy exposures.

We report herein for the first time high personal inhalation exposures to BADGE and its oligomers during spray painting of bridges, as well as high potential for skin exposures to epoxy paints. These methods and personal sampling approaches can be used routinely for monitoring personal exposures to epoxies in construction. We hope this successful application of the CIP-10MI sampler and the subsequent analytical methods for epoxies will end the 'long drought' in quantitative exposure data needed to guide interventions in the construction industry and to reduce the high prevalence of allergic contact dermatitis and other disorders. In a follow-up article, we report on the urinary biomonitoring results for BADGE in this cohort of workers and document a 2.9-fold increase in the average post-shift BADGE·$2H_2O$ biomarker levels relative to pre-shift, indicating the need for improved exposure controls at these sites.

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Conflict of interest

All authors declare that they have no conflict of interest.

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