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Comparison of Sampling and Analytical Methods Used During the Preparation of Methyl Methacrylate Bone Cements

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Surgeons, surgical nurses, and other operating room staff are exposed to airborne concentrations of methyl methacrylate during the preparation of orthopedic bone cement. Three sampling and analysis methods have been used to measurement methyl methacrylate in this work environment: (1) direct-reading photoacoustic infrared spectrometry, (2) solid sorbent and gas chromatography with flame ionization detection, and (3) colorimetric detector tubes. Previous studies have measured operating room exposures and judged the efficacy of cement mixing wth little, if any, regard for method sensitivity, detection limits, precision, or accuracy. The present investigation was designed to allow concurrent monitoring of methyl methacrylate levels from the same air volume using each of the three methods. Three popular orthopedic bone cement products were mixed during a number of repeat preparations (n = 36). Airborne concentrations were monitored concurrently during each preparation. Attention was given to the proper treatment of detection limits, and the results are reported both as raw data and descriptive statistics. A one-way ANOVA using a Tukey-Kramer HSD comparison was performed on method-specific results indicating that the photoacoustic infrared spectrometry and solid sorbent, gas chromatography with flame ionization detection are in good agreement, but the colorimetric detector tube method reports significantly different airborne concentrations. It is concluded that previous assessments using the photoacoustic infrared spectrometry and solid sorbent, gas chromatography with flame ionization detection may be relied on, but the detector tube method underreports actual exposures. Accordingly, the results of past exposure assessments and mixing method efficacy studies using colorimetric detector tubes may not be reliable.

Keywords bone cement, detector tubes, gas chromatography, method comparison, methyl methacrylate, photoacoustic infrared spectrometry

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The release of methyl methacrylate (MMA) during the mixing and application of orthopedic bone cement has been extensively reported in the literature. These reports include both workplace exposure assessments and efficacy studies of various cement mixing methods. However, use of the results of these investigations is hampered by problems in experimental design and data interpretation. A major source of these problems is the use of different, if not inappropriate, sampling and analytical methods to quantify the airborne concentrations.

Three sampling and analytical techniques have been used to measure MMA concentrations in air during the previous investigations:(1) direct-reading photoacoustic infrared spectrometry, (2) solid-sorbent collection followed by gas chromatography with flame ionization detection, and (3) colorimetric detector tubes. Several of the key research efforts relied solely on colorimetric detector tubes.[1–3] It is only recently that investigators have turned to the more rigorous methods of spectrometry.[4–6] Given that users of bone cement have relied on this research to make decisions regarding both exposure characterization and workplace protection, it is important to assess and compare the performance of these methods. This is particularly true in the case of both the photoacoustic infrared spectrometry and colorimetric detector tubes, since the former is relatively new technology and the latter is recognized to be less rigorous and more susceptible to errors of interpretation. No less important is the fact that the results obtained using the detector tube method are the basis for claims of efficacy regarding different bone cement mixing appliances.

METHODS

To assess and compare the subject methods, MMA levels in air were monitored during the preparation of orthopedic bone cement. Direct-reading photoacoustic infrared (PAIR) spectrometry, solid sorbent and gas chromatography with

flame ionization detection (GC-FID), and colorimetric detector tube (DT) methods were concurrently employed to report MMA concentrations from the same sample air volumes. The following is a description of these sampling and analysis methods, the concurrent sampling apparatus employed, the cement mixing scenarios tested, and the statistical analyses performed.

Sampling and Analysis

The sampling and analytical techniques investigated include: an Innova AirTech PAIR spectrometer; the National Institute for Occupational Safety and Health (NIOSH) GC-FID method; and the Dräger DT method for methyl acrylate. Although not specifically designed to detect MMA, the methyl acrylate tube was the basis for previous investigations using the DT method. A detailed description of each method follows with a summary of key method components in Table I.

Innova 1312 PAIR Multi-Gas Monitor

The Type 1312 Multi-gas Monitor[7] (Innova AirTech Instruments, Ballerup, Denmark) draws air into a hermetically sealed sampling chamber. Pulsating light from an infrared source is then directed through narrow-band optical filters and into the sealed chamber. The light transmitted by the filters is selectively absorbed by the MMA vapor causing the temperature of the gas to increase, momentarily increasing chamber pressure. The light pulsation produces a modulating pressure change that is detected by microphones in the chamber wall. The acoustical signal detected by the microphones is directly proportional to the concentration of MMA vapors present in the chamber—a relationship that remains linear over several orders of magnitude. The detection principle of this technology allows the spectrometer to measure chemical compounds that absorb light in a narrow infrared spectrum and to eliminate the affect of interferences.

During this investigation, narrow-band optical filters were installed into an Innova 1312 to allow for the detection of MMA in air at a center-band wavelength of 8.5 μm, while compensating for the presence of water vapor. Water vapor was the only other airborne substance with the potential to cause interference during the testing. The monitor was calibrated according to manufacturer's recommendations, including zero-point, humidity-interference, humidity-span, and MMA vapor concentrations between nondetect and 100 ppm (410 mg/m^3). The Innova 1312 reports airborne concentrations in mg/m^3.

NIOSH GC-FID Method

The NIOSH GC-FID method[8] for methyl methacrylate collects the air sample on solid sorbent tubes containing 400- and 200-mg sections of XAD-2 resin (ST 226-30-06; SKC, Eighty Four, Pa.). The first section of sorbent acts as the primary collection media, whereas the second section is a backup sorbent used to quantify the amount of breakthrough that occurs during sampling. The sorbent sections are separated by silylated wool and sealed in a glass sampling tube. The air sample is collected by drawing a known volume of air through the sorbent tube using a personal sampling pump (224-PCXR4; SKC). The sampling pump is calibrated at a flow rate of 0.01 to 0.05 L/min. The used sorbent tubes are stored on dry ice before desorption with reagent-grade carbon disulfide. The GC-FID is injected with sample aliquots of the desorption liquid. The reported masses of MMA on both the first and second (backup) sections are corrected for an empirically determined desorption efficiency and subtracted to determine the amount of breakthrough that may have occurred. Samples

TABLE I. Comparison of Sampling and Analytical Methods

Method Components	Innova Photoacoustic Multi-Gas Monitor (PAIR)	NIOSH Method 2537 (GC-FID)	Dräger Methyl Acrylate 5/a Detector Tube (DT)
Sampling media	NA	XAD-2 resin	Pd-molybdate complex coated resin
Sampling pump	Volumetric flow	Volumetric flow	Stroke
Flow rate, L/min	0.02[A]	0.01 to 0.05	0.3[B]
Inhibitor	NA	Dry ice	NA
Desorption agent	NA	Carbon disulfide	NA
Analytical technique	Photoacoustic infrared spectrometry	Gas chromatography with flame ionization	Colorimetric chemical reaction
Accuracy, %	±1	±12.6	Not reported
Precision, %[C]	±1	±6	±40
Range, mg/m^3	0.5–50,000	0.5–1,100	30.8–615

Note: NA = not applicable.

[A] Calculated as the auto sample volume of 0.014 liters per sample divided by a sample time of 0.75 min, or 0.02 L/min.

[B] The manufacturer prescribes a total air volume equal to 20 strokes at 0.1 L/stroke, which requires approximately 6.5 min of pump operation to produce an average flow rate of 0.3 L/min.

[C] Calculated as the relative standard deviation × 100 and reported as a percentage.

with less than 10% breakthrough are considered valid. The sum of the MMA reported in the two sections is divided by the collected air volume to produce a concentration in mg/m^3.

Dräger DT Method

The Dräger DT for methyl acrylate (MA) was the method of choice for several of the previously published investigations.[9] The detector tube contains an indicator layer that changes color when MA reacts with a Pd-molybdate complex and produces a blue reactant. The sample is collected by drawing air through the tube using a stroke pump (Accuro 2000; Dräger Safety, Pittsburgh, Pa.). The concentration in air is determined by comparing a blue stain in the indicator layer with gradation marks printed on the glass tube. The marks along the length of the tube are on a nonlinear scale from 5, 10, 50, to 200 ppm. The use of the MA detector tube for the determination of MMA is allowed. However, because of the low sensitivity of the colorimetric reagents to MMA, the manufacturer prescribes a correction factor of three be applied to tube ranges from 5 ppm through 50 ppm. This multiplier produces equivalent MMA concentrations of 15, 30, and 150 ppm. Using a conversion factor of 1 ppm equals 4.1 mg/m^3, the scale can also be read in concentrations 61.5 mg/m^3, 123 mg/m^3, and 615 mg/m^3. The detector tube is read by noting the scale marking nearest to the end of the blue discoloration.

Sampling Apparatus

The sampling apparatus is designed to allow for concurrent monitoring of the same air volume by each of the three methods. This design required the construction of a fixed stand to hold and position each of the method-specific sampling trains.

1. The sampling train for the PAIR spectrometer consists of a 45-μm pore pre-filter connected to a 1-meter Teflon sampling tube. The pre-filter is not part of the sample collection process but is used to prevent the introduction of dust or other particulate into the spectrometer. The sampling tube is connected to a microprocessor-controlled, multiport sampler that purges and supplies a sample to the spectrometer every 40 to 45 sec. This response time allowed for both the detection of MMA and compensation for water vapor.
2. The sampling train for the GC-FID method consists of the XAD-2 tube connected to an SKC personal sampling pump with Tygon tubing. Sampling of the air is continuous over the duration of each test.
3. The sampling train for the DT method consists of a methyl acrylate 5/a tube (Dräger) connected to an Accuro-2000 stroke pump (Dräger) using Tygon tubing. Sampling of the air is accomplished over a 20-stroke duration of approximately 6.5 min.

The point of collection for all three sampling trains is located at 50 cm over the opening of the container where the bone cement is prepared. This distance allows for the collection of a breathing zone sample while permitting unobstructed access to the container for preparation of the cement. The three method-specific sampling trains and structural supports of the sampling apparatus are presented in Figure 1. A view of the entire experimental setup including the sampling trains, structural supports, PAIR spectrometer, continuous-flow SKC sampling pump, and Accuro-2000 stroke pump is presented in Figure 2.

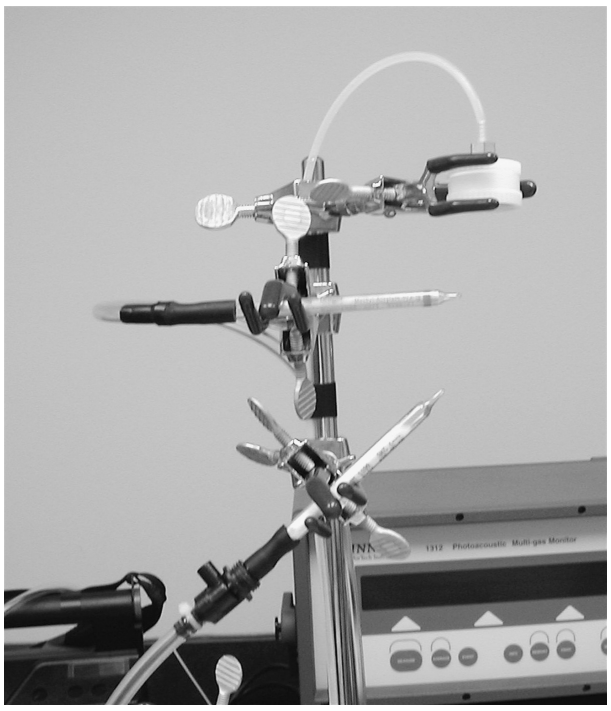

FIGURE 1. Sampling trains for PAIR, DT, and GC-FID methods

Test Scenarios

Three bone cement products were used as sources of MMA emissions during this experiment: (1) Endurance by DePuy Orthopaedics, Inc., Warsaw, Ind.; (2) Palacos R by Schering-Plough, Inc., Brussels, Belgium; and (3) Simplex P by Stryker Howmedica Osteonics, Limerick, Ireland. Each cement product was prepared and monitored 12 times under identical laboratory conditions. The laboratory ventilation was turned off during each test to prevent dilution of the MMA vapors during measurement. A special high-volume exhaust system with fresh air supply was used to evacuate the laboratory air between tests.

Each cement preparation was a two-dose configuration as prescribed by the manufacturers, that is, two 40-g packets of polymer powder were dispensed into a container and mixed with two 18.88-g ampoules of liquid monomer. Monitoring was conducted during the entire cement preparation timeline that included loading a container with powder, pouring in the MMA monomer, mixing, kneading and working, and allowing for the setting of the polymer. The prescribed product-related timelines for the preparation of the bone cements and the

FIGURE 2. Photoacoustic infrared spectrometer, sampling apparatus, sampling pumps, and bone cement preparation with mixing container

test timeline used during this investigation are presented in Table II. The test timeline chosen for this experiment was 13 min in duration. Although the photoacoustic spectrometer should detect the presence of MMA during all time regimes, the Dräger and NIOSH methods have detection limits that could be impacted by shorter sampling intervals. Each cement preparation and monitoring event was conducted under identical environmental conditions in an industrial hygiene calibration laboratory. Temperature, humidity, and pressure levels were maintained to within specified ranges of 20°C to 23°C, 30% to 40%, and 1060 kPa to 1080 kPa, respectively.

TABLE II. Preparation Tasks, Product-Specific Timelines, and Test Timeline (min)

Tasks	Endurance	Palacos R	Simplex P	Test
Load powder	NS	NS	NS	0.5
Pouring	NS	NS	NS	0.5
Mixing	0.75	0.5–1	NS	0.75
Kneading	0.25–1	0.25–0.5	1.5–2	—
Working	1–1.5	4–5	2	—
Setting	11–13	2.75–3.75	8–14	11.25
Total duration	13–16.25	7.5–10.25	11.5–18	13

Note: Product-specific timelines as prescribed by the manufacturers in the product preparation instructions were used for the preparation of the bone cements. NS = duration of task is not specified or prescribed by the manufacturer.

Data Analysis

Descriptive statistics were calculated and presented in the form of an arithmetic mean, median, standard deviation, and relative standard deviation for monitoring data produced by each of the sampling and analytical methods. Values for skew and kurtosis were also determined for each of the test data distributions. Statistical analysis in the form of a one-way analysis of variance (ANOVA) tested by a Tukey-Kramer honestly significant difference (HSD) comparison was performed using the statistical software Statview, Version 5.0.1 by SAS Institute, Inc. The ANOVA provided the statistical tool necessary to compare multiple means, while the Tukey-Kramer HSD provided a test of difference that attempts to avoid the occurrence of a Type I error.

RESULTS

The results of the monitoring for MMA during the experiment are presented in Figure 3 and summarized in Table III. The univariate chart in Figure 3 presents the raw monitoring data in units of mg/m^3 by sampling and analytical method. Table III provides descriptive statistics for each method: sample size (n), measures of central tendency (arithmetic mean and median value) in units of mg/m^3, measures of distribution (skew and kurtosis), and an estimate of variability (standard deviation). Additionally, an estimate of precision (relative standard deviation) was calculated for each method. To address the problem of how to treat and interpret the detection limit of the DT method, two sets of descriptive statistics were calculated and presented in Table III. The first set of DT statistics uses a zero value to represent events of nondetection. The second set of DT statistics uses an imputed concentration for these events. The imputed concentration was calculated using the NIOSH L/2 approach.[10] This approach assumes that the concentration of a nondetect event is estimated as a concentration halfway between true zero and the effective lowest recordable value from the DT tube, that is, 15/2 ppm or 7.5 ppm (30.8 mg/m^3) of MMA.

DISCUSSION

Because all monitoring was conducted concurrently under identical conditions and from the same air volume, one would expect the methods to report nearly identical concentrations and similar descriptive statistics. However, even a casual examination of the monitoring results in Figure 3 reveals that the DT method produced the lowest values during all but one (i.e., 17) of the 36 test measurements. This anomalous result cannot be assigned a specific cause from either the monitoring conditions present or the cement product tested. Nor does information exist to fault the use, handling, or interpretation of the tube. Although manufacturing flaws or intralot differences

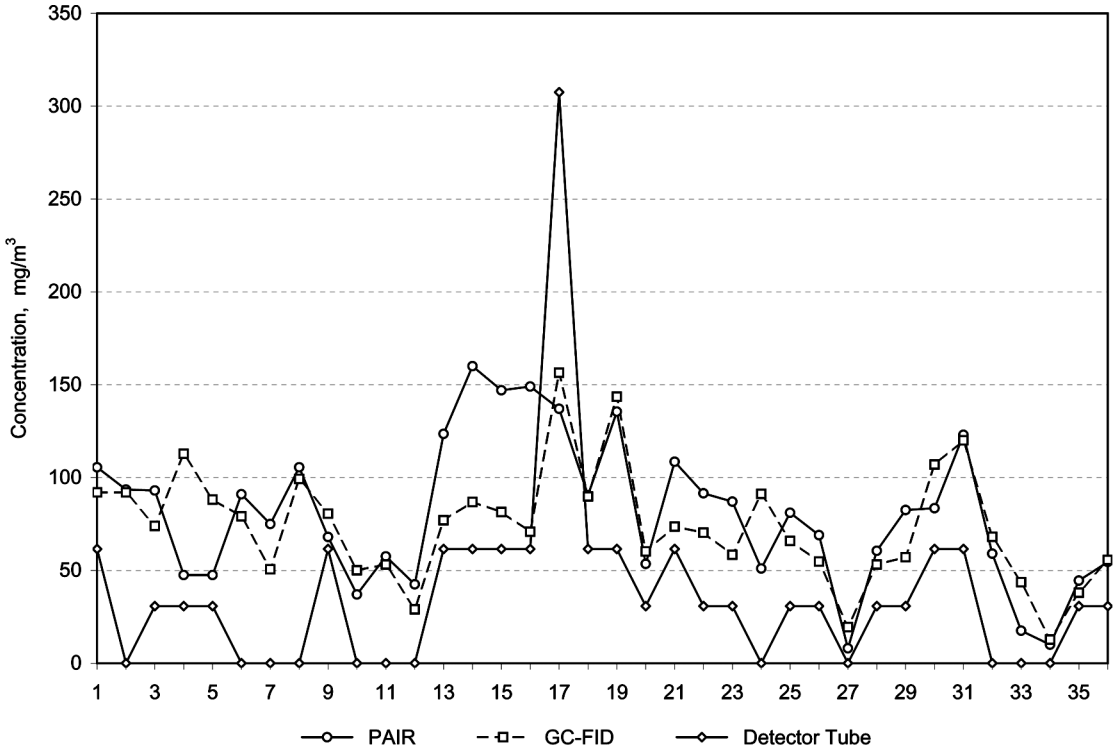

FIGURE 3. Univariate chart of method-specific sampling and analytical results

in the tubes are possible, no data was collected that would address those issues. Accordingly, the suspect result is retained during the statistical analysis, but its impact is discussed in the conclusions.

The PAIR and GC-FID methods produced very similar sample statistics in Table III. However, these comparable results were markedly different from those obtained using the DT method. The relationships between methods are consistent throughout the investigation, regardless of the descriptive statistic being considered.

- The PAIR method produced the highest mean airborne concentration followed by the GC-FID results. This agreement is in contrast to the mean values for either treatment of "nondetection" using the DT data. Both DT treatments reported substantially lower mean values. The same comparison is true for the median statistic.
- The measures of central tendency for the PAIR and GC-FID results are similar in magnitude and suggest that both methods report sample populations that are normally distributed. The measures of central tendency for the DT results do not exhibit the same degree of normality. This similarity between PAIR and GC-FID sample populations is supported by the estimates of skew. Skewness values for the PAIR and GC-FID results are near zero and describe a sample distribution with a high degree of symmetry. The DT method reports values skewed to the right of the mean, a result that is consistent with the large number of nondetects and the manufacturer's warning that the detector tube is less sensitive to MMA than MA. A difference is also found in the measure of kurtosis. The PAIR and GC-FID values are near zero and reflect a mesokurtic distribution of the data, whereas the DT statistics display a marked leptokurtic arrangement.

TABLE III. Descriptive Statistics of MMA Results by Sampling and Analytical Method

Method	n	Mean (mg/m^3)	Median (mg/m^3)	Skew	Kurtosis	Std. Dev.	Relative Std. Dev.
PAIR	36	80.3	81.8	0.19	−0.57	38.9	48
GC-FID	36	73.8	72.2	0.52	0.59	30.8	42
DT							
Nondetect as 0	36	37.6	30.8	3.83	17.56	52.6	140
Nondetect as ≤30.8	36	56.8	46.1	4.64	22.85	48.9	86

- The variability of the results, when reported as a standard deviation, is smallest for the PAIR and GC-FID methods and greatest for treatments of the DT data. Furthermore, the relative standard deviations suggest a greater degree of scattering in the measured results as one proceeds from PAIR to GC-FID to DT method. Some of the scatter associated with the DT method may be ascribed to the use of nonlinear tube gradations and the difficulty interpolating color changes.

CONCLUSIONS

The one-way ANOVA assesses whether the methods are equally capable of detecting and reporting airborne concentrations of MMA. This expectation would result in the calculation of mean differences near zero, i.e., a value of zero is equivalent to the null hypothesis that there is no difference between methods.

- The outcome of the one-way ANOVA indicates that this hypothesis of equality between method means should be rejected ($p = 0.0002$).
- The Tukey-Kramer HSD is a multiple comparison that tests which pairs of means are significantly different. Positive values, which indicate a significance difference between the means being compared, where found for PAIR vs. DT and GC-FID vs. DT.

Table IV presents the mean difference and Tukey-Kramer value (mean difference, calculated HSD) for each comparison ($q = 2.6$, $\alpha = 0.05$).

This statistical analysis indicates that the PAIR and GC-FID results are not in agreement with results of the DT method and that the difference is statistically significant. The analysis also indicates that the PAIR and GC-FID results are in agreement and that any disparity between these methods is do to chance and not effect. Regardless of which of the more rigorous methods (i.e., PAIR or GC-FID) is used as a control (i.e., standard of measurement), the DT method significantly underreports airborne concentrations of MMA. However, the magnitude and significance of the underreporting depends on how one treats and interprets the detection limit of the DT method (i.e., 0 vs. $\leq$30.8 mg/m^3).

The use of imputed values, for events of nondetection, improves the performance of the DT data during an ANOVA. However, this change is deceptive since it affects only the negative outcomes (events of nondetection) and can have no impact on the DT method's ability to more accurately report recordable values ($>$30.8 mg/m^3). Finally, the disagreement between the more rigorous methods and the DT is further confirmed when the test run containing the anomalous DT value (i.e., 17) is removed: a subsequent one-way ANOVA also rejects the null hypothesis ($p < 0.0001$) and the Tukey-Kramer HSD test indicates that all mean differences between the PAIR or GC-FID methods, and both treatments of the DT data are significant.

TABLE IV. Tukey-Kramer HSD Comparison of Means

Comparison	Mean Difference	Tukey-Kramer Mean Difference –HSD[A]
PAIR vs. DT, nondetect = 0	42.7	16.0
GC-FID vs. DT, nondetect = 0	36.2	9.4
PAIR vs. DT, nondetect ≤30.8	23.5	−3.2
GC-FID vs. DT, nondetect ≤30.8	17.0	−9.8
PAIR vs. GC-FID	6.5	−20.2

[A]A positive value indicates a significance difference between the method means being compared ($q = 2.6$, $\alpha = 0.05$).

FINDINGS AND RECOMMENDATIONS

During this investigation, the colorimetric detector tubes reported different MMA air concentrations when compared with either the more rigorous direct-reading photoacoustic infrared spectrometry or the NIOSH gas-chromatographic method. This difference was found to be statistically significant. The results of the analysis suggest that past studies based on the subject detector tube technology may underreport MMA exposures. Finally, given the weaker precision of the DT method (see Table I) and apparent inaccuracies associated with the DT results (see Tables III and IV), any past exposure assessments of operating room personnel or comparisons of mixing methods using airborne concentrations of MMA measured by the DT method should be viewed with skepticism.

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