Journal of Occupational and Environmental Hygiene, 4: 272–280
ISSN: 1545-9624 print / 1545-9632 online

DOI: 10.1080/15459620701223843

Control of Methyl Methacrylate During the Preparation of Orthopedic Bone Cements

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The use of methyl methacrylate (MMA) bone cement during orthopedic procedures has been seen as a potential exposure hazard to health care professionals. However, that assessment is based on a number of investigations with problems in experimental design, analysis, and data interpretation. The current investigation quantified differences in MMA vapors produced during the preparation of competing bone cements using various methods of preparation. Unlike previous investigations, this effort employs modern validated sampling and analytical methods, and considers the affect of censored results. Measurements of sufficient quality and number were collected to allow for a statistical treatment of the data. The ability of two controlled preparation techniques to reduce MMA emissions were compared with a traditional open container. The results confirmed that the preparation of bone cement releases MMA vapors into the breathing zone of the preparer. One preparation technique (Stryker Bowl) controlled emissions during mixing and curing and affected a 73% reduction in measured MMA concentrations. In addition to mixing and curing, the second technique (UltraMix System) also controlled the MMA during pouring of the monomer and affected a 90% reduction in MMA concentrations. An ANOVA test of interaction indicates that the reductions are attributable to the preparation technique regardless of the type of cement being used. Both a Fisher's PLSD and Games/Howell post hoc test of the results indicate that the mean differences between the uncontrolled open container and the controlled preparation techniques are significant ($p < 0.05$).

Keywords bone cement, exposure control, gas chromatography, methyl methacrylate, photoacoustic infrared spectrometry

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INTRODUCTION

The chemical properties that make methyl methacrylate (MMA) an attractive acrylic monomer for use in bone cement also contribute to its potential as an exposure hazard (Table I). MMA vapors can be detected by the human nose at concentrations near 0.049 ppm or 0.2 mg/m^3, whereas the irritation of the mucous membranes is reported to occur near 170 ppm (697 mg/m^3).[1] Industrial experience has shown that direct contact with the skin can cause irritation, burns, and allergic sensitization. Increases in airborne concentrations above 170 ppm have been reported to cause lung, liver, and kidney damage; headaches; dizziness; difficulty breathing; and a loss of consciousness.[2] Presently, the International Agency for Research on Cancer (IARC) reports that there is inadequate data to support evidence for carcinogenicity of MMA in humans or animals.[3] The American Conference of Governmental Industrial Hygienists (ACGIH®) recommends an 8-hr time-weighted average (TWA) of 50 ppm (205 mg/m^3) and a short-term exposure limit (STEL) of 100 ppm.[4]

Despite the occupational hazards associated with MMA, the simple avoidance of dermal contact and the maintenance of low airborne concentrations will reduce the substance's potential to cause harm. Indeed, MMA has been successfully used and controlled in a number of workplace environments.[5,6] It is this history of high-volume use in industrial settings that supports a reasonable presumption of safety when lower volumes of MMA are used in a medical setting. In attempts to confirm that presumption, past investigations have tried to quantify the release of MMA using controlled laboratory experiments and workplace simulations.

Laboratory Investigations

Two early laboratory investigations into the release of MMA focused on vapor emissions during cement preparation.[7,8] Although these studies established that MMA is released during preparation, the use of an unvalidated sampling and analytical method places the accuracy of the measurements into question. Since the performance of these early investigations, the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) have developed and validated sampling and analytical methods specific to MMA in air.[9,10] As presented in Table II, the analytical method employed during

TABLE I. Physical Properties and Other Information for Methyl Methacrylate

Property and Units	Value
Chemical abstract service number	80-62-6
Physical state at 20°C	Colorless liquid
Boiling point, °C	100
Density, g/mL at 20°C	0.944
Vapor pressure, mm Hg at 20°C	29
Odor description	Acrid, fruity
Odor threshold, ppm (mg/m^3)	0.049 (0.2)
Threshold limit value, ppm (mg/m^3)	100 (410)
Immediately dangerous to life and health (IDLH), ppm (mg/m^3)	1000 (4100)
Molecular weight	100.1
Formula	CH_2=CH-$COOCH_3$

the earlier investigations varies in almost every aspect from the procedures that were eventually validated.

- A key issue addressed by both agencies was the propensity of MMA to rapidly polymerize into an unrecoverable polymer. OSHA addresses the polymerization problem by treating the charcoal sorbent with an inhibiting agent, whereas the NIOSH solution involves collection on a synthetic sorbent followed by storage on dry ice. It is significant that the early investigations used neither of these precautions, nor did they address, account for, or provide other protection against polymerization.
- Another noteworthy difference is the detector technology that was used during the early analyses. The early investigations used a thermal conductivity detector (TCD), a technology no longer employed in gas chromatographic analysis of MMA because of its poor sensitivity (Table II). Both the OSHA and NIOSH methods use the newer flame ionization detector (FID) technology. The impact of the TCD sensitivity is evident when interpreting censored data during the early investigations. All sampling and analytical methods have limits of detection (LOD). However, the early investigations neglected to publish the results of calibrations against known standards, report the LOD that was achieved, or address the handling of censored data. Given that TCD is up to three orders of magnitude less sensitive than current FID technology, the theoretical detection limit of the TCD method would include LOD values above many of the reported measurements.[11]

Given the aforementioned sampling and analytical problems, the conclusions drawn in these earlier investigations regarding differences in vapor concentrations produced by competing bone cements and the efficacy of their respective preparation techniques may be questioned.

Workplace Simulations

The first efforts at simulating workplace exposures to MMA were made with the use of a detector tube (DT) method.[12,13] Although attempts were made to justify the use of DT method by claiming a correlation with gas chromatographic results, no DT method has ever been validated by OSHA or NIOSH for use in characterizing exposures. Indeed, a recent study demonstrates that the DT method employed during these early simulations underestimates airborne concentrations and produces results significantly different from those reported using validated gas chromatographic methods.[14]

The most recent simulation attempts to address the efficacy of various preparation techniques using both a GC-FID method and a modern direct-reading instrument.[15] Although an improvement over previous DT efforts, the study unfortunately employed a dated sampling and analytical method (Methylmethacrylate BIA 7940).[16] As summarized in Table II, the BIA method for methyl methacrylate does not address the key issue of polymerization and uses an older version (dual

TABLE II. Comparison of Sampling and Analytical Methods

Parameter	Darre et al.	BIA[A]	OSHA	NIOSH
Sampling media	Charcoal	Charcoal	Coated charcoal	XAD-2 resin
Inhibitor	None	None	4-*tert*-butylcatechol	Dry ice
Desorption agent	Carbon sulfide [*sic*]	Diethyl ether	Toluene	Carbon disulfide
Column packing	Chromosorb 102	Dual columns of silica and Carbowax	Film-fused silica	Film-fused silica
Instrument	GC with TCD[B]	GC with FID[C]	GC with FID	GC with FID
Injection temp., °C	185	200	250	250
Detection temp., °C	210	230	300	300
Column temp., °C	185	180	100	100
Accuracy, %	Not reported	Not reported	±5.8	±12.6
Detection limit, mg	Not reported	0.07[D]	.002	.01

[A] Berufsgenossenschaftliches Institute fur Arbeitsschutz.[16]
[B] A gas chromatograph equipped with a thermal conductivity detector.
[C] A gas chromatograph equipped with a flame ionization detector.
[D] Reference 15.

TABLE III. Comparison of Direct-Reading Instrumentation

Parameter	Rae Systems, Inc. Photo Ionization Detector (PID)	Innova Photoacoustic Multi-Gas Monitor (PAIR)
Detection method	Ultraviolet (UV) photoionization detector (PID)	Photoacoustic infrared spectrometer
Construction	Hand-held portable	Laboratory stationary
Sampling pump	Volumetric flow	Volumetric flow
Flow rate, L/min	0.5[A]	0.02[B]
Calibration standard	Isobutylene	Methyl methacrylate
Precision, %[C]	Not reported	±1
Accuracy, %	Not reported	±1
Detection limit, mg/m^3	0.02	0.5

[A] Reference 15.
[B] Calculated as the auto sample volume of 0.014 L per sample divided by a sample time of 0.75 min, or 0.02 L/min.
[C] Calculated as the relative standard deviation ×100 and reported as a percentage.

column) of the current GC-FID technology. Finally, the direct-reading instrument employed in the simulation is a photo ionization detector (PID; RAE Systems, Inc., San Jose, Calif.). The PID meter is not specific to or directly calibrated for MMA. As summarized in Table III, the PID relies on a corrected calibration using isobutylene to estimate the instrument's response to MMA.

As with the laboratory experiments, problems associated with the sampling and analysis methods used during the workplace simulations call into question any conclusions drawn from these investigations.

EXPERIMENTAL DESIGN

This investigation addressed the key deficiencies identified in the previous studies. Differences in the release of MMA were determined during the preparation of competing bone cements using both controlled and uncontrolled techniques. Measurements were taken using valid sampling and analytical methods under controlled laboratory conditions, with a consideration of censored results. A sufficient number of replicates were performed to allow for the construction of descriptive statistics, an analysis of variance (ANOVA), and a test of significance between the measured differences in mean air concentrations created during uncontrolled and controlled preparations of bone cement.

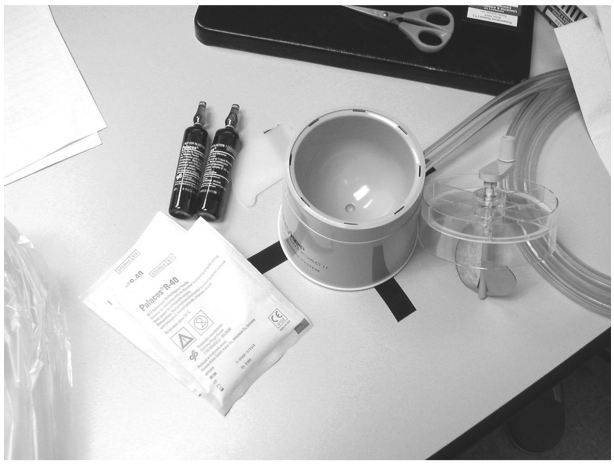
Bone Cement Products and Preparation Techniques

Three bone cement products were tested: Endurance by DePuy Orthopaedics, Inc., Warsaw, Ind.; Palacos R by Schering-Plough, Inc., Brussels, Belgium; and Simplex P by Stryker Howmedica Osteonics, Limerick, Ireland. Each of the cement preparations consists of a liquid component in a glass ampoule that is primarily MMA monomer (96–98%) and a powder component in a plastic bag that is polymethyl methacrylate or a related copolymer (84–90%). The specific compositions of the three cements are presented in Table IV.

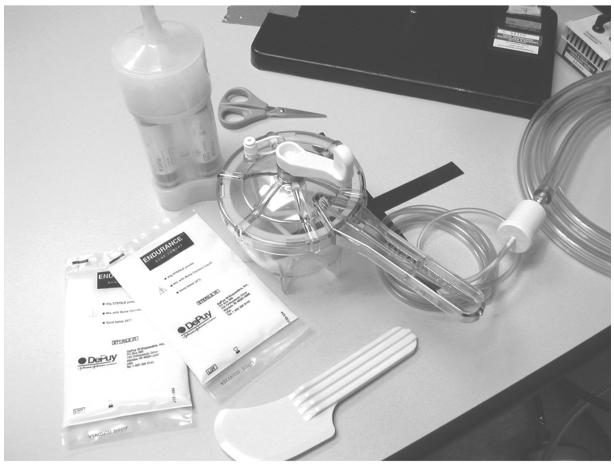
TABLE IV. Composition of Bone Cement Products (%)

Component (CAS No.)	Endurance	Palacos R	Simplex P
Liquid			
Methyl methacrylate (80-62-6)	98.00	96	97.4
N,N-dimethyl-p-toluidine (99-97-8)	2.00	2	2.6
Hydroquinone (123-31-9)	75 ppm	Present	75 ppm
Chlorophyll-copper complex (none)	—	2	—
Peanut oil (8002-03-7)	—	Present	—
Powder			
Polymethyl methacrylate (9011-14-7)	67.05	—	15.0
Methacrylate/styrene copolymer (none)	21.10	84 to 85	75.0
Benzoyl peroxide (94-36-0)	1.85	1 to 2	—
Barium sulfate (7727-53-7)	10.00	—	10.0
Zirconium dioxide (1314-23-4)	—	15	—

(a)



(b)



(c)

FIGURE 1. Preparation appliances and bone cement products

The preparation techniques tested in this investigation are presented in Figure 1 and include an open container (uncontrolled scenario), a container designed to control emissions during mixing and curing (Stryker Bowl, Stryker Howmedica Osteonics), and an apparatus designed to control emissions from pouring, mixing, and curing (UltraMix System, DePuy Orthopaedics).

- The open container (Figure 1a) consists of a simple open-faced plastic bowl with a plastic mixing spatula. The components of the cement are added to the bowl and mixed without a lid, enclosure, or other precaution.
- The Stryker Bowl (Figure 1b) consists of a container equipped with a vacuum exhaust to evacuate the air volume of the container during mixing and curing. The container lid houses a mixing paddle and hand crank. The cement components are added to the Stryker Bowl, the lid is attached, vacuum is applied to the container, and the cement is mixed inside the container by turning the crank. The Stryker Bowl attempts to control emissions during the mixing and curing phases of preparation.
- The UltraMix System (Figure 1c) consists of a container equipped with a vacuum exhaust plenum and a lid with a mixing paddle and hand crank. The UltraMix System also incorporates an enclosed monomer delivery device. Unlike the previous two preparation techniques, the UltraMix System uses the monomer delivery device to dispense the liquid monomer directly into an enclosed, vacuum exhausted container. The UltraMix System attempts to control emissions during pouring, mixing, and curing phases of preparation.

Test Events

Each cement preparation was a two-dose configuration as prescribed by the manufacturers, i.e., 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 loading of each container with powder, pouring in the MMA monomer, mixing, and curing of the polymer. The prescribed product-related timelines for the preparation of the bone cements and the test timeline used during this investigation are presented in Table V. Each cement preparation and test event was conducted under identical environmental conditions. Temperature, humidity, and pressure

TABLE V. Cement Preparation Tasks and Test Timeline at 20–22°C

	Endurance (Min)	Palacos R (Min)	Simplex P (Min)	Test Timeline (Min)
Loading of powder	—	—	—	0.5
Pouring of monomer	—	—	—	0.5
Mixing	0.75	0.5 to 1	—	0.5 to 0.75
Curing	0.25 to 1	0.25 to 0.5	1.5 to 2	0.5 to 1.25

levels were maintained to within specified ranges of 20°C to 23°C, 30% to 40%, and 1060 kPa to 1080 kPa, respectively.

Sampling and Analytical Methods

Two methods were used to measure airborne concentrations of MMA during cement preparation: photoacoustic infrared (PAIR) spectrometry and NIOSH gas chromatography (GC-FID). The PAIR spectrometry method allowed for the collection of nearly instantaneous measurements specific to MMA in air; the NIOSH GC-FID allowed for the collection and analysis of integrated time-weighted average samples using a validated procedure.

- The 1312 PAIR Multi-Gas Monitor (Innova AirTech Instruments, Ballerup, Denmark)[17] 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 a potential to cause interference during the testing. The Innova 1312 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[9] for methyl methacrylate collects the air sample on solid sorbent tubes containing 400-mg and 200-mg sections of XAD-2 resin (ST 226-30-06 or equivalent). 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 sample is collected by drawing a known volume of air through the sorbent tube using a personal sampling pump (224-PCXR4 or equivalent). 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 with less than 10% breakthrough are considered valid. The sum of the MMA reported in each of the two sections is divided by the collected air volume to produce a concentration in mg/m^3.

Sampling Apparatus

The sampling apparatus allows for concurrent monitoring of the same air volume, and its fixed stand holds and positions each of the method-specific sampling trains.

- The sampling train for the PAIR spectrometer consists of a 45-m pore prefilter connected to a 1-m Teflon sampling tube. The prefilter 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 45 sec. This response time allowed for both the detection of MMA and compensation for water vapor.
- 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.

The point of collection for both sampling trains is located 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.

RESULTS

The monitoring was performed to obtain two types of information regarding the release of MMA during the preparation of bone cements using the various preparation techniques: real-time measurements and integrated airborne concentrations.

- The PAIR spectrometer was used to report real-time concentrations of MMA in mg/m^3 at 45-sec intervals. This real-time data was used to construct a plot of airborne concentrations of MMA over time and is presented as an emission-time profile in Figure 2.
- The NIOSH GC-FID method was used to obtain airborne concentrations of MMA in mg/m^3 as integrated over the 3-min sampling period (i.e., during loading, pouring, mixing, and curing phases of the cement preparation). The data was used to calculate descriptive statistics of the MMA concentrations by preparation technique and is presented in Table VI.

The number of tests performed with each preparation technique represents the sum of four replicates conducted on each of the three cement products (n=12). The number of results for the UltraMix System differs by one replicate

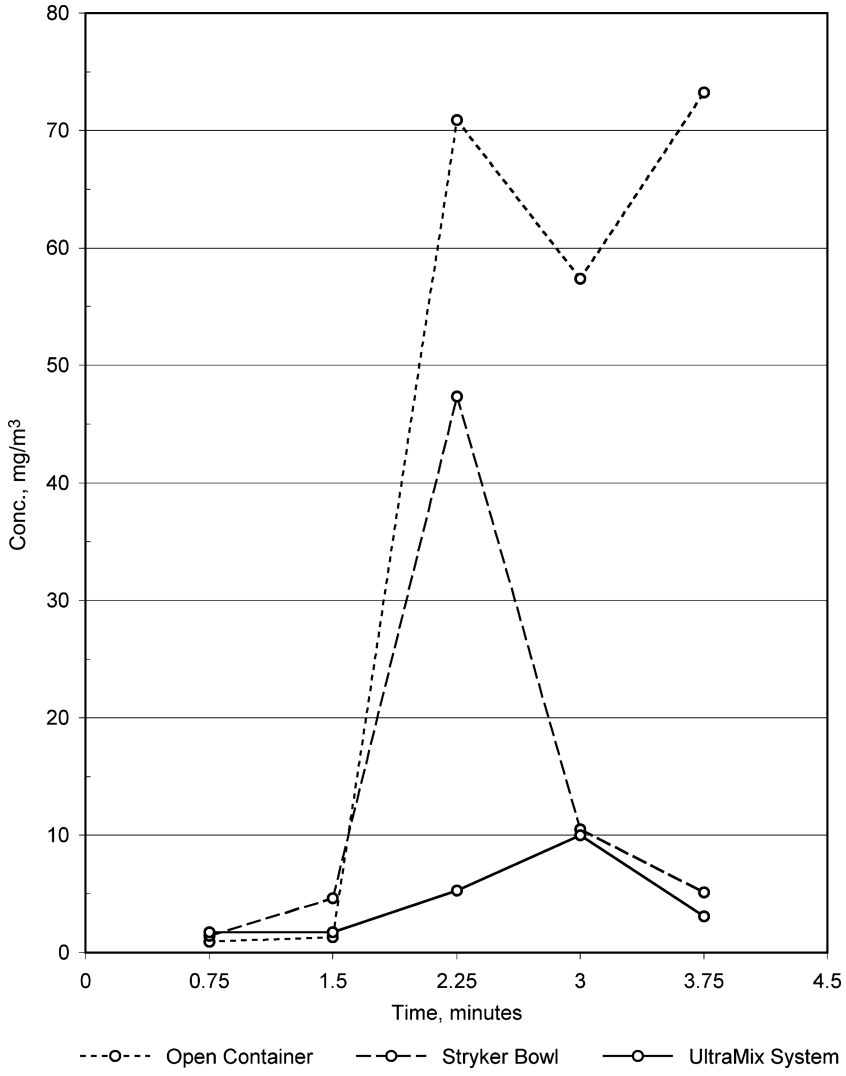


FIGURE 2. Emission-time profiles of mean MMA concentrations

because the first test of the Palacos R cement failed. During the failed test event, the Palacos R monomer in one of the two ampoules would not drain. This failure caused a significant alteration in the timeline and required that the delivery device be disassembled to free the remaining monomer. The failure to drain appears due to differences in monomer viscosity. Although a similar failure did not reoccur during any of the subsequent tests, the Palacos R monomer dispensed the slowest of the three cement products.

TABLE VI. Concentrations of MMA by Preparation Technique

Parameters	n	Mean, (mg/m^3)	Standard Deviation	Average Efficiency (%)
Open container	12	81	58	—
Stryker Bowl	12	22	14	73
UltraMix System	11	8	12	90

DISCUSSION

The treatment of the NIOSH GC-FID data and descriptive statistics included an assessment of sample distributions, an ANOVA, and post hoc tests of significance using StatView Version 5.0.1 statistical software by SAS Institute, Inc., Cary, NC.

Sample Distributions

The measured vapor emissions from the uncontrolled preparation were a continuous variable that is normally distributed. However, the emissions from the controlled preparations became more skewed and lognormal in character as the control

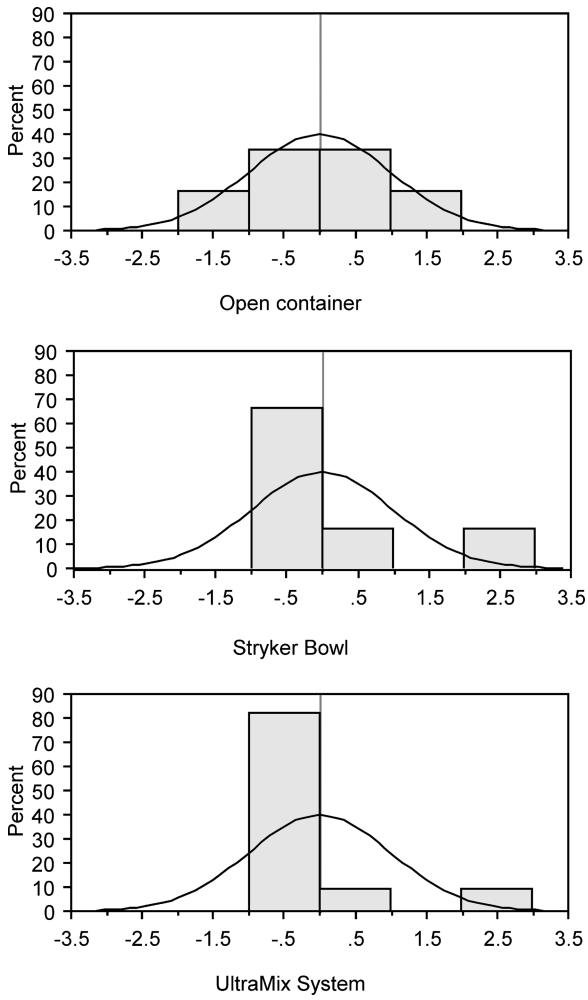


FIGURE 3. Z-score histograms of concentrations of MMA by preparation technique

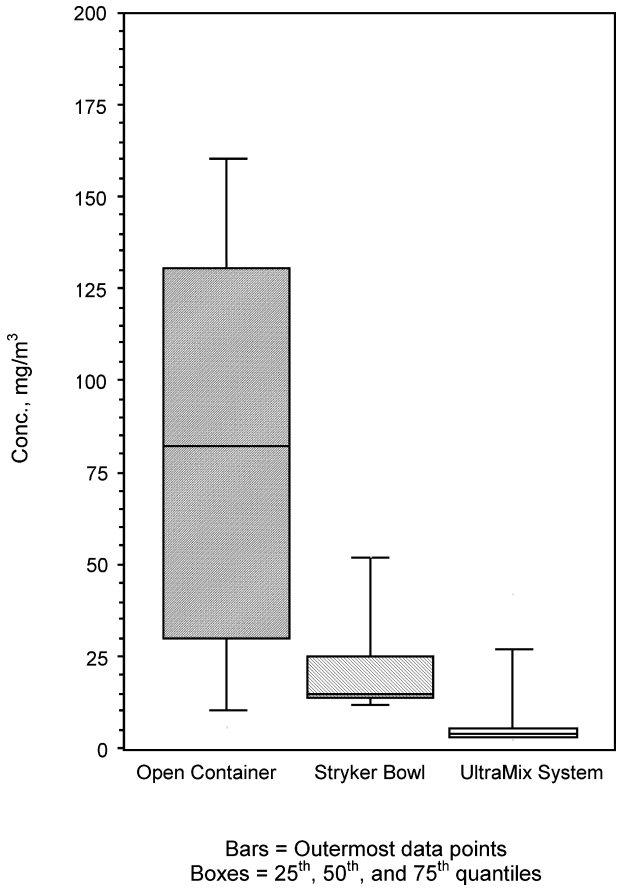


FIGURE 4. Box plot of concentrations of MMA by preparation technique

efficiency improved. This change in distribution has important implications both for our interpretation of the results and when selecting post hoc tests of significance.[18] The distributions of the test data are presented as z-score histograms in Figure 3 for each of the sample populations.

The results for the open container are normally distributed about the sample mean. This distribution changes markedly during the use of both the Stryker Bowl and UltraMix System as the preparation techniques are successful at altering the amount of vapor released into the air. A box plot of the test results in Figure 4 shows that the Stryker Bowl and UltraMix System have a marked impact on airborne concentrations, with the Stryker Bowl achieving on average a 73% reduction in airborne concentrations of MMA, whereas the UltraMix System achieved an average reduction of 90%.

Analysis of Variance

One critical question to be answered is how much of the variability in the airborne concentrations of MMA can be explained by the effect of the preparation technique. It is hypothesized that the type of preparation technique used can account for most of the variability in MMA airborne concentrations. However, the possible effect of different types of cements cannot be overlooked, particularly given the viscosity problems that were associated with Palacos R. It was recognized that a statistical treatment that tests only the main effect of the preparation technique could hide or "average out" the impact of cement type. Accordingly, the impact of cement type on the measured MMA was addressed using an interaction analysis of "preparation technique by cement" (preparation

TABLE VII. ANOVA for Concentrations of MMA by Preparation Technique and Cement

Effect	Degrees of Freedom	Mean Square	F-Value	p-Value
Preparation technique	2	17240	12.6	<0.05
Cement	2	297	0.2	0.81
Preparation technique*Cement	4	1063	0.8	0.55
Residual	26	1368		

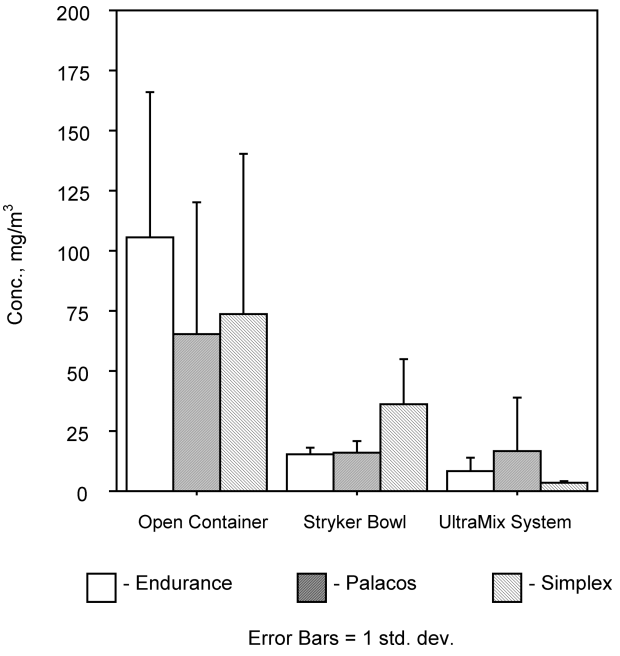


FIGURE 5. Interaction bar plot for concentrations of MMA by preparation technique and cement

technique*cement) to test the null hypothesis that the effect of the technique is the same regardless of the cement being used.

The results of this interaction ANOVA are presented in Table VII. The ANOVA indicates that the effect of preparation techniques on MMA vapors is significant, that it accounts for differences between means, and is not appreciably impacted by the type of cement being used. The test results are also presented as an interaction bar plot in Figure 5.

Post Hoc Tests

Once established that the type of preparation technique accounted for the differences in airborne concentrations, it was of interest to determine whether the differences in MMA emissions were significant. As mentioned previously, the study did not produce sample populations uniformly compatible with any single statistical technique (Figure 3). Rather than making arbitrary or poorly supported assumptions with regard to population characteristics, both a Fisher's PLSD and Games/Howell post hoc test were performed on the data. These tests expose the results to assessment of significance using different criteria:

- The Fisher's PLSD assumes a significant F-ratio, homogeneity of variance, equal *n*, and normality. Although a significant F-ratio has been defined, the sample sets (n) are slightly different and may inflate the probability of a Type I error.
- The Games/Howell test also assumes a significant F-ratio but is more robust to unequal values of n, heterogeneous variances, and non-normality. The Games/Howell test accepts unequal values of n, difference variances, and violations of normality by defining a different value for each comparison to exceed for significance.

The post hoc tests indicate that the reduction in MMA vapors from the cement preparation is significant for both the Stryker Bowl and UltraMix System. However, the vapor releases from the UltraMix System, although demonstrably lower, were not significantly different from the Stryker Bowl. The outcome of the Fisher's PLSD and Games/Howell tests of significance are presented in Tables VIII and IX, respectively.

TABLE VIII. Fisher's PLSD Test of Concentrations of MMA by Preparation Technique

Comparison	Mean Difference	Critical Difference	p-Value
Open Container vs. Stryker Bowl	59	30	<0.01[A]
Open Container vs. UltraMix System	73	30	<0.01[A]
Stryker Bowl vs. UltraMix System	14	30	0.36

[A]Significant at 5% level.

TABLE IX. Games/Howell Test of Concentrations of MMA by Preparation Technique

Comparison	Mean Difference	Critical Difference
Open container vs. Stryker Bowl	59	46[A]
Open container vs. UltraMix System	73	46[A]
Stryker Bowl vs. UltraMix System	14	14

[A]Significant at 5% level.

CONCLUSIONS

The preparation of orthopedic bone cement releases MMA vapors into the breathing zone of the preparer at concentrations that can approach the ACGIH 8-hr. TWA exposure limit during uncontrolled pouring, mixing, and curing. Control solutions designed into appliances used during cement preparation successfully reduce the amount of MMA vapor released. The Stryker Bowl affected a 73% reduction in MMA concentrations in the breathing zone of the preparer during mixing and curing. The UltraMix System affected a 90% reduction in breathing zone concentrations of MMA during pouring of the monomer, mixing, and curing.

An ANOVA test of interaction indicates that the reductions are attributable to the preparation technique regardless of the type of cement being used. Both a Fisher's PLSD and Games/Howell post hoc test of the results indicate that the mean differences between the open container and the controlled preparation techniques are significant. Although the UltraMix System affected a demonstrably greater average reduction in

MMA vapors than that of the Stryker Bowl, the difference between these two controls was not statistically significant.

ACKNOWLEDGMENTS

Funding for this investigation was provided through a contract with DePuy Orthopaedics, Inc., Warsaw, Indiana, a Johnson & Johnson Company.

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