



## Health Risk Assessment in Exposure to Methacrylic Monomers in Dental Practice

Maya Lyapina<sup>1\*</sup>, Maria Dencheva<sup>2</sup>, Assya Krasteva<sup>2</sup>, Mariana Tzekova<sup>2</sup>,  
Mariela Deliverska<sup>3</sup>, Angelina Kisselova<sup>2</sup> and Jeny Staikova<sup>4</sup>

<sup>1</sup>Department of Hygiene, Medical Ecology and Nutrition, Medical University, Medical Faculty, Sofia, Bulgaria.

<sup>2</sup>Department Oral and Image Diagnostic, Medical University, Faculty of Dental Medicine, Sofia, Bulgaria.

<sup>3</sup>Ministry of Education and Science, Sofia, Bulgaria.

<sup>4</sup>National Centre of Public Health and Analyses, Sofia, Bulgaria.

### Authors' Contributions

*This work was carried out in collaboration between all authors. Author ML conceived and designed the study, managed the analyses of the study and the literature search, performed the statistical analysis, wrote the first draft of the manuscript, edited and sent it to the journal for publication. Authors MD, AK and MT contributed to skin patch testing, data analysis and results interpretation. Author MD contributed in ethical aspects and written informed consent preparation. Author AK supervised all aspects of the study and reviewed results. Author JS contributed in data analysis. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** To evaluate the health status and to assess the risk of adverse health effects manifestation among occupationally exposed to methacrylic monomers dental professionals (dentists, nurses and attendants) and students of dental medicine and from the dental technician school, as well as to determine the incidence of sensitization to some methacrylic monomers in dental practice.

**Place and Duration of Study:** Department "Oral and Image Diagnostic", Medical University, Faculty of Dental Medicine, Sofia, Bulgaria, between January 2014 and July 2014.

**Methodology:** A questionnaire survey, including a review of medical summary of history was performed among 262 participants – 213 exposed to methacrylic monomers in dental practice and education (dental professionals, students of dental medicine and from Dental technician school), mean age 30.9, and 49 non-exposed healthy referents – dental patients, mean age 45.1. Skin patch testing with methyl methacrylate (MMA), triethyleneglycol dimethacrylate (TREGDMA), ethyleneglycol dimethacrylate (EGDMA), 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl] propane (BIS-GMA), 2-hydroxyethyl methacrylate (2-HEMA), tetrahydrofurfuril metacrylate and glutaraldehyde was performed.

**Results:** Significantly higher incidence and risk of manifestation of subjective symptoms from the skin (OR=2.20, CI=1.12 – 4.34, P = .020) and the upper respiratory tract (OR=2.26, CI=1.45 – 4.45, P = .017) were established among the referents group. Occupational and during education exposures to the tested methacrylic monomers and to glutaraldehyde didn't result in increased incidence of sensitization (P> .050). An increased incidence and OR for manifestation of concomitant sensitization to methacrylic monomers and glutaraldehyde was revealed, with very high significance, (P < .001, OR=4.52, CI=2.33 – 8.74). Men could be outlined as a group at risk of sensitization. Our results confirm the cross-reactivity of acrylic compounds – 43.9% of all the participants were allergic to more than one of the tested monomers.

**Conclusion:** No role of exposure to methacrylic monomers in dental practice and education for increased incidence and risk of manifestation of irritant effects, subjective symptoms and sensitization were established. An increased incidence and risk of concomitant sensitization to methacrylic monomers and glutaraldehyde and of cross-reactivity of acrylic compounds were observed.

*Keywords: Methacrylic monomers; glutaraldehyde; sensitization; cross-reactivity; dentistry; occupational exposure; risk assessment.*

## 1. INTRODUCTION

Dental professionals are occupationally exposed to numerous chemical agents while handling dental materials and medicines on a daily basis. Dental products contain a number of allergens and irritants that may give rise to health issues. The biological reactions can take place either at a local level or far removed from the site of contact (i.e., systemically) [1]. Both dental patients and dental personnel are exposed to potential health risks, with the patient being the recipient of the restorative materials, and dental students – during their practical education.

Acrylates are plastic materials produced by polymerization of monomers derived from acrylic or methacrylic acid. Polymerization may occur at room temperature or with heat [2].

Numerous acrylates have found applications in dental composite resins, medical devices - contact lenses, hearing aids and bone cement for orthopedic endoprostheses, in paints and adhesives, printing inks, artificial nails [3].

Methyl methacrylate (MMA) is a small molecular acrylate, a widely used monomer in dentistry and medicine. Methacrylates serve as bases for acrylic resins [4]. Resin-based dental materials are extensively used today in dentistry. Examples of applications of such materials in dentistry include general dental applications dentures (bases, liners, tissue conditioners, artificial teeth, temporary restoration, etc.), cavity restorative materials (composites – self / light curing), pulpal, cavity and margin sealants, impression materials (alginate, agar, elastomers, waxes, etc.), (resin based cements, dentin bonding agents, orthodontic appliances, habit breaking appliances (nail biting, thumb sucking, etc.), oral and maxillofacial appliances, cleft palate plates maxillary supports, etc. [5]. Numerous methacrylates, mostly used in dental bonding materials, printing inks, and artificial nails, are polymerized by exposure to UV light with help from a priming photo initiator. In dentistry, more than 98% of the restorations are made of polymers and monomers. Dental professionals are thought to be at higher risk of adverse reactions to monomers than the patients.

Experimental and clinical studies have documented that methacrylic monomers may cause a wide range of adverse health effects such as irritation to skin, eyes, and mucous membranes, allergic dermatitis, stomatitis, asthma, neuropathy, disturbances of the central nervous system, liver toxicity, and fertility disturbances [6-9]. The most important adverse health effects include respiratory tract irritation and sensitization.

The cytotoxicity and genotoxicity of some methacrylates were identified during the last decade. Many dental resins contain co-monomers such as triethylene glycol dimethacrylate (TEGDMA), 2-hydroxyethyl methacrylate (HEMA) and BisGMA which causes gene mutations in vitro, formation of micronuclei, indicative of chromosomal damage [10-14]. Studies demonstrated that monomers reduced the levels of the natural radical scavenger glutathione (GSH). Depletion of the intracellular GSH pool may significantly contribute to cytotoxicity, because a related increase in ROS levels can activate pathways leading to apoptosis [15].

The acrylates and, to a lesser extent, methacrylates (2-hydroxyethyl methacrylate - (2-HEMA), triethyleneglycol dimethacrylate (TREGDMA), and 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl]propane (BIS-GMA) are not only strong irritants, but also notorious allergens. These compounds were found at concentrations of 50 to 90% in unhardened dental adhesives and cements. Cured methacrylates can also volatilize, thereby causing the respiratory irritation as well as sensitization and allergic symptoms [3,16]. Completely polymerized acrylic plastics are inert and harmless. Numerous case reports documented allergic contact dermatitis to MMA. In 2012 (meth) acrylates were accessed by the American Contact Dermatitis Society to the rank of “allergen of the year” [3].

Numerous studies confirm the length promenade incidence of sensitization to methacrylates in dental professionals [17-26], as well as in patients undergoing dental treatment and exposed to resin-based materials [27,28]. Studies concerning health status evaluation and risk assessment in occupational (in dental practice and during education of dentistry) exposures to methacrylic monomers are relatively few.

The aim of this study is to evaluate the health status and to assess the risk of some adverse health effects manifestation among occupationally exposed to methacrylic monomers dental professionals (dentists, nurses and attendants) and students both of dental medicine and from the dental technician school, as well as to determine the incidence of sensitization to some methacrylic monomers in dental practice.

## 2. MATERIALS AND METHODS

### 2.1 Subjects

A total of 262 participants were included in the study, divided into two main groups – Group E, consisting of 213 occupationally exposed to methacrylic monomers individuals – 65 dental professionals, 110 students of dental medicine and 38 students from Dental technician school, and Group R – 49 referents - randomly chosen individuals of different gender, age and occupations, the main inclusion criteria being the lack of occupational exposure. Data regarding age and gender characteristics are presented in (Table 1). No statistically significant difference in the latter distribution was found ( $P > .050$ ).

**Table 1. General characteristics of the studied groups of individuals**

Groups of studied subjects	n / %	By gender		Age mean $\pm$ StD (years)
		Man n / %	Women n / %	
Occupationally exposed (Group E)	213 (81.3%)	71 (86.4%)	142 (93.4%)	30.9 $\pm$ 14.1
Referents (Group R)	49 (18.7%)	10 (13.6%)	39 (68.7%)	45.1 $\pm$ 18.3
Total	262 100%	81 (30.9%)	181 (69.1%)	39.9 $\pm$ 16.3

The study was supported by the Medical University – Sofia, Grant № 5-C/2013 and was approved the Medical Ethics Board at the Medical University of Sofia. All participants were informed about the purpose of the study and gave their written informed consent.

### 2.2. Sociological Methods

Interviews and detailed, intentionally conducted questionnaire survey with an emphasis on family history, suspected or known allergies to the standard set of household or occupational allergens was performed.

To evaluate the overall health status of investigated subjects and to estimate the incidence of some possible adverse health effects of methacrylic monomers in dental practice exposure, questions concerning manifestation of subjective symptoms from the upper respiratory tract, respiratory system and skin, the digestive, cardiovascular, nervous and urinary systems have been included in the inquiries. A review of medical documentation was performed as well. A summarized questionnaire is presented in (Table 2).

### 2.3 Skin Patch Testing

Skin patch testing with methyl methacrylate (MMA), triethyleneglycol dimethacrylate (TREGDMA), ethyleneglycol dimethacrylate (EGDMA), 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl]propane (BIS-GMA), 2-hydroxyethyl methacrylate (2-HEMA), tetrahydrofurfuril metacrylate and glutaraldehyde was performed, according to the Jadassohn

& Bloch classical methods for diagnosis of contact allergy, by placing the allergens (0.2%/pet, Chemotechnique Diagnostics) in IQ-Ultra hypoallergenic patches of Chemotechnique Diagnostics (IQ Chambers ®, Vellinge, Sweden). Obligatory condition was lack of anti-allergic medication before placing the patches and during the study. Patches with allergens were applied and stayed on the back of the tested subjects; reading of the test was carried out on day 2, several hours after removing of the patches, with control revision on day 3.

**Table 2. Summarized questionnaire used in the study**

Questions	Questionnaire Answers
1. Past and present smoking habits.	- I've never smoked - Sometimes - Yes, regularly
2. Alcohol consumption.	- I don't use alcohol - Sometimes, on special occasions - 2-3 times a week - every day
3. Past exposure to chemical agents.	- No - Yes If "Yes" – point out the chemical agents and the duration of exposure
4. Medical history for past diseases (more than one answer is possible).	- no history; - frequent rhinitis; - allergic rhinitis; - frequent upper respiratory tract infections; - bronchitis; - pneumonia; - bronchial asthma; - other respiratory tract diseases; - hepatitis; - hypertension; - diabetes; - renal calculus; - eczema; - urticaria; - peptic ulcer; - other diseases (please, point out)
5. Family history of (more than one answer is possible).	- no history; - allergies; - respiratory system diseases; - hypertension; - diabetes; - other diseases (please, point out)
6. Chronic intake of medications (more than one answer is possible).	- no chronic intake; - anti-allergic drugs; - corticosteroids; - hypertension medications; - neuroleptics; - other drugs (please, point out)
7. Subjective upper respiratory tract symptoms (more than one answer is possible).	- no symptoms - irritation; - itching; - bouts of sneezing; - secretion; - difficulty breathing;
8. Skin symptoms (more than one answer is possible).	- no symptoms - itching; - redness; - cracking; - dryness; - rashes; - ulcerations; - rhagades
9. Respiratory system symptoms (more than one answer is possible).	- no symptoms - irritation; - dry cough; - cough with phlegm; - breathlessness; - shortness of breath during physical efforts
10. Cardiovascular system	- no symptoms - pain/tightness in the heart area; - heart palpitations; - arrhythmia; - hearth oppression; - easy fatigability; - swelling of the extremities
11. Digestive system	- no symptoms - lack of appetite; - pains; - nausea; - vomiting; - acid reflux symptoms; - burps; - constipation
12. Urinary system	- no symptoms - frequent urination; - urinary burning; - pain crises; - dull pains; -
13. Nervous system	- no symptoms - headache (occipital, temporal, paroxysmal, etc.); - dizziness; - irritability; - emotional instability; - sleep disorders; - change in mood; - morning fatigue; - easy fatigability

For the interpretation of the test result the following scheme was used (International Contact Dermatitis Research Group - ICDRG) (Table 3).

**Table 3. Scheme of ICDRG for interpretation of skin patch test results**

(-)	Negative reaction
?	Doubtful reaction (faint macular, no infiltration, homogenous erythema)
+	Weak reaction (non-vesicular)
++	Strong reaction (oedematous or vesicular)
+++	Extreme reaction (ulcerative or bullous)
IR	Irritant reaction (discrete patchy erythema without infiltration)

### 2.3 Statistical Methods

Available for cross-tabulation statistics were used: chi-square test, Fisher Exact Test for statistical significance, testing of the ratio of two probabilistic ones OR (Odds ratio). Values of  $p < .05$  were accepted as statistically significant.

## 3. RESULTS

### 3.1 Studied Population

A statistically significant higher ( $P = .002$ ) was the mean age of the control group if compared with the one of occupationally exposed individuals – (Table 1). The mean age of the group of men was  $31.5 \pm 14.3$ , and of the group of women –  $34.4 \pm 16.5$ . No statistically significant difference in the latter distribution was found.

The gender distribution was not uniform, with a predominance of women in the overall distribution, due to the feminization of most occupations in dental medicine. Aiming bigger exactness of the analysis we performed a comparative statistical analysis of gender distribution in the sub-groups of investigated individuals, determined by type and duration of occupational exposure to methacrylic monomers (Table. 3). No statistically significant differences in this distribution were found ( $\chi^2 = 6.29$ ,  $P = .10$ ).

Concerning smoking habits, 43.3% individuals from the group of occupationally exposed dental professionals and students and 38,8% from the referents were smokers. No statistically significant differences and OR concerning smoking habits were observed ( $\chi^2 = 0.33$ ,  $P = .57$ ), odds ratio (OR) = 0.83, 95% Confidence Interval (CI) = 0.44 – 1.57. No significant difference between the groups determined by us were found, as well, concerning alcohol consumption – 24.5% from the group of occupationally exposed individuals and 20.8% from the reference used alcohol ( $\chi^2 = 0.29$ ,  $P = .59$ , OR=0.81, CI=0.34 – 1.74).

### 3.2 Questionnaire Survey

The results from the individuals who responded the questionnaire are presented in (Table 4). Obviously, subjective upper respiratory tract symptoms predominated in the referent group. Moreover, a significantly higher incidence and OR for manifestation of such symptoms were established among individuals aged over 40 years ( $\chi^2 = 16.95$ ,  $P < .001$ , OR=3.61, CI=1.93 – 6.78), without significance concerning gender distribution ( $\chi^2 = 1.11$ ,  $P = .291$ , RR=0.72, CI=0.39 – 1.33). It seems that no role of the occupational exposure could be speculated.

**Table 4. Distribution by gender in the sub-groups of investigated individuals, determined by type of occupational exposure to methacrylic monomers**

Group according type of exposure		Gender		Total
		Women	Men	
Referents	Count	39	10	49
	% within the group	79.5%	20.5%	100.0%
	% within men / women	21.3%	12.6%	18.7%
Students of dental medicine	Count	68	42	110
	% within the group	61.8%	38.2%	100.0%
	% within men / women	37.2%	53.2%	42.0%
Students of dental technician school	Count	29	9	38
	% within the group	74.3%	25.7%	100.0%
	% within men / women	15.8%	11.4%	14.5%
Dental professionals	Count	47	18	65
	% within the group	72.3%	27.7%	100.0%
	% within men / women	25.7%	22.8%	24.8%
Total	Count	183	79	262
	% within the group	69.8%	30.2%	100.0%
	% within men / women	100.0%	100.0%	100.0%

As presented in (Table 5), the incidence and OR of the subjective skin symptoms were significantly higher among the referent group, as well as among women ( $\chi^2=6.24$ ,  $P = .013$ ,  $OR=0.46$ ,  $CI=0.25 - 0.85$ ) and individuals over 40 years ( $\chi^2=12.16$ ,  $P < .001$ ,  $OR=2.90$ ,  $CI=1.58 - 5.33$ ).

In respect of subjective symptoms from the respiratory system, the only significant difference we established was their predomination among individuals over 40 years ( $\chi^2=21.79$ ,  $P < .001$ ,  $OR=4.52$ ,  $CI=2.34 - 8.74$ ).

Subjective symptoms from the cardiovascular system were reported by 29.2% of the occupationally exposed dental professionals and students, and by 51.1% of the referents, being significantly higher in the latter group ( $\chi^2=7.72$ ,  $P = .005$ ), as well as among women ( $\chi^2=20.68$ ,  $P < .001$ ) and among individuals over 40 years ( $\chi^2=38.08$ ,  $P < .001$ ). The incidence of subjective symptoms from the digestive system predominated among women ( $\chi^2=8.22$ ,  $P = .004$ ) and elderly individuals over 40 ( $\chi^2=18.18$ ,  $P < .001$ ), with no significant difference concerning occupational exposure ( $\chi^2=1.21$ ,  $P = .27$ ).

**Table 5. Distribution of subjective symptoms manifestation among the group of occupationally exposed to methacrylic monomers and the referents (\* $P < .05$ )**

Occupational exposure	Group E With symptoms n / %	Group R With symptoms n / %	Odds ratio (OR) 95% confidence Interval (CI) Statistical significance (P)* $P < .05$
Upper respiratory tract	59/27.7%	23* /46.9%	<b>OR=2.26 CI=1.45 - 4.45* <math>P = .017</math></b>
Respiratory system	50/23.5%	14 /28.6%	OR=1.38 CI=0.66 - 2.86 $P = 0.393$
Skin symptoms	75/35.2%	27* /55.1%	<b>OR=2.20 CI=1.12 - 4.34* <math>P = .020</math></b>

The incidence and OR of subjective symptoms from the nervous system were significantly higher among women ( $\chi^2=22.91$ ,  $P < .001$ ), individuals over 40 ( $\chi^2=19.31$ ,  $P < .001$ ) and occupationally exposed dental professionals and students ( $\chi^2=5.79$ ,  $P = .016$ ).

Similarly, subjective symptoms from the urinary tract predominated among women ( $\chi^2=9.19$ ,  $P = .002$ ) and individuals over 40 years ( $\chi^2=12.25$ ,  $P < .001$ ).

### 3.3 Skin Patch Tests

Data concerning the incidence of sensitization to the investigated methacrylate in the population investigated by us is summarized in (Table 6). According to the results achieved in the present study, occupational and during education exposures to the listed above methacrylic monomers doesn't result in increased incidence of sensitization.

**Table 6. Distribution of positive and negative skin patch test reactions to methacrylic monomers among the studied groups**

<b>Contact hypersensitivity to METHACRYLATE (MMA)</b>				
<b>Studied group according to occupational exposure</b>	<b>Negative n / %</b>	<b>Positive n / %</b>	<b>Total n / %</b>	<b>p(*P&lt; .05)</b>
Occupationally exposed dental professionals and students	172 80.8%	41 19.2%	<b>213</b> 100%	$P = .52$
Referents	38 77.6%	11 22.4%	<b>49</b> 100%	
<b>Contact hypersensitivity to TREGDMA</b>				
Occupationally exposed dental professionals and students	159 74.6%	54 25.4%	<b>213</b> 100%	$P = .99$
Referents	37 75.5%	12 24.5%	<b>49</b> 100%	
<b>Contact hypersensitivity to EGDMA</b>				
Occupationally exposed dental professionals and students	170 79.8%	43 18.2%	<b>213</b> 100%	$P = .86$
Referents	39 79.6%	10 20.4%	<b>49</b> 100%	
<b>Contact hypersensitivity to Bis – GMA</b>				
Occupationally exposed dental professionals and students	166 77.9%	47 22.1%	<b>213</b> 100%	$P = .40$
Referents	36 73.5%	13 26.5%	<b>49</b> 100%	
<b>Contact hypersensitivity To 2-HEMA</b>				
Occupationally exposed dental professionals and students	170 79.8%	43 20.2%	<b>213</b> 100%	$P = .39$
Referents	37 75.5%	12 24.5%	<b>49</b> 100%	
<b>Contact hypersensitivity to Tetrahydrofurfuryl methacrylate</b>				
Occupationally exposed dental professionals and students	172 80.8%	41 19.2%	<b>213</b> 100%	$P = .19$
Referents	36 73.5%	13 26.5%	<b>49</b> 100%	
<b>Contact hypersensitivity to METHACRYLATES (Mma+2-Hema+ Tetrahydrofurfuryl methacrylate)</b>				
Occupationally exposed dental professionals and students	121 56.8%	92 43.2%	<b>213</b> 100%	$P = .44$
Referents	25 51.0%	24 49.0%	<b>49</b> 100%	



The results about the sensitization rates to glutaraldehyde are summarized in (Table 7). No significant differences between the groups defined by us were established.

**Table 7. Distribution of positive and negative skin patch test reactions to glutaraldehyde among the studied groups**

<b>Contact hypersensitivity to <i>GLUTARALDEHYDE</i></b>				
Occupationally exposed dental professionals and students	163	50	<b>213</b>	<i>P</i> = .58
	76.5%	24.5%	100 %	
Referents	36	13	<b>49</b>	
	73.5%	26.5%	100%	

The results concerning the sensitization rate to both methacrylic monomers and glutaraldehyde are presented in (Table 8). The statistical analysis revealed, with very high significance, an increased incidence and OR for manifestation of co-sensitization to methacrylic monomers and glutaraldehyde ( $\chi^2=25.05$ ,  $P < .001$ , OR=4.52, CI=2.33 – 8.74).

**Table 8. Distribution of positive and negative skin patch test reactions both to methacrylic monomers and to glutaraldehyde among the studied groups**

<b>Contact hypersensitivity to methacrylates – MA (MMA+2-HEMA+ Tetrahydrofurfuryl methacrylate)</b>	<b>n</b>	<b>Contact hypersensitivity to <i>glutaraldehyde</i> (GA)</b>		<b>Total</b>	<b>Odds ratio (OR) 95% confidence interval (CI) *<i>p</i> &lt; 0,05</b>
		<b>Negative</b>	<b>Positive</b>		
<b>Negative</b>		<b>129</b>	<b>18</b>	<b>147</b>	<b>OR=4.52 (CI=2.33 – 8.74) * <i>P</i> &lt; .001</b>
	% within <b>MA negative</b>	87.8%	12.2%		
	% within <b>GA neg / pos</b>	64.8%	28.6%		
<b>Positive</b>		<b>70</b>	<b>45</b>	<b>115</b>	
	% within <b>MA positive</b>	60.9%	39.1%		
	% within <b>GA neg / pos</b>	35.2%	71.4%		
<b>Total</b>	<b>n</b>	<b>199</b>	<b>63</b>	<b>262</b>	

Due to the unequal distribution by gender and our previous observations about increased incidence of sensitization to methacrylic monomers among women, further we performed a gender analysis. Results are presented in (Table 9).

Generally, high rate of sensitization to two or more of the tested methacrylic monomers - 115 (43.9%) of all the participants was established. The statistical analysis demonstrated, with high significance, increased incidence and OR of sensitization to most of the tested methacrylic monomers (e.g. TREGDMA, EGDMA, BIS-GMA, 2-HEMA and tetrahydrofurfuryl methacrylat), as well as to glutaraldehyde in the group of men.

**Table 9. Distribution of positive and negative skin patch test reactions to methacrylic monomers and glutaraldehyde by gender**

<b>Contact Hypersensitivity to METHACRYLATE (MMA)</b>					
Studied group by gender	Negative n / %	Positive n / %	Total n / %	P (*P < 0,05)	Odds ratio (OR) Confidence Interval (CI)
Women	150 82.9%	31 17.1%	<b>181</b> 100%	P = .15	OR=1,59 (CI=0.85 – 2.96)
Men	61 75.3%	20 24.7%	<b>81</b> 100%		
<b>Contact hypersensitivity to TREGDMA</b>					
Women	142 78.5%	39 21.5%	<b>181</b> 100 %	* P = .013	* OR=2,05 (CI=1,15 – 3.64)
Men	52 64.2%	29 35.8%	<b>81</b> 100%		
<b>Contact hypersensitivity to EGDMA</b>					
Women	159 87.8%	22 12.2%	<b>181</b> 100 %	* P < .001	* OR=4.08 (CI=2.19 – 7.57)
Men	50 61.7%	31 38.3%	<b>81</b> 100%		
<b>Contact hypersensitivity to BIS – GMA</b>					
Women	153 84.5%	28 15.5%	<b>181</b> 100 %	* P < .001	* OR=3.42 (CI=1.89 – 6.20)
Men	50 61.7%	31 38.3%	<b>81</b> 100%		
<b>Contact hypersensitivity to 2-HEMA</b>					
Women	147 81.2%	34 18.8%	<b>181</b> 100 %	P = .224	OR=1.47 (CI=0.79 – 2.72)
Men	60 74.1%	21 25.9%	<b>81</b> 100%		
<b>Contact hypersensitivity to Tetrahydrofuryl methacrylate</b>					
Women	150 82.9%	31 17.1%	<b>181</b> 100 %	* P = .047	* OR=1.85 (CI=1.00 – 3.42)
Men	58 71.6%	23 28.4%	<b>81</b> 100%		
<b>Contact hypersensitivity to METHACRYLATES (mma+2-hema+ Tetrahydrofuryl methacrylate)</b>					
Women	106 58.6%	75 41.4%	<b>181</b> 100 %	P = .187	OR=1.42 (CI=0.84 – 2.40)
Men	41 50.6%	40 49.4%	<b>81</b> 100%		
<b>Contact hypersensitivity to GLUTARALDEHYDE</b>					
Women	147 81.2%	34 18.8%	<b>181</b> 100 %	* P = .005	* OR=2.27 (CI=1.27 – 4.05)
Men	52 64.2%	29 35.8%	<b>81</b> 100%		

## 4. DISCUSSION

### 4.1 Studied Population

A total of 262 participants were included in the present study – 213 occupationally exposed to methacrylic monomers dental professional and students, and 49 referents without

occupational exposure. The number of subjects from the control group was smaller compared to the one of subjects from the generalized group of occupationally exposed dental professionals and students, but it equals to the sub-groups of investigated individuals, determined by type and duration of occupational exposure to methacrylic monomers. The final results is no believed to be strongly affected (detailed statistical intra-group analysis is to be presented in a next manuscript).

Due to the feminization of most occupations in dental medicine, the distribution of the participants by gender was not uniform, with predominance of women in all defined sub-groups, but without statistical significance. Since no statistically significant differences and OR between the groups determined by us were concerning smoking habits and alcohol consumption were observed those factors are not supposed to affect seriously the results concerning the discussed below parameters reflecting the overall health status of investigated individuals.

## 4.2 Subjective Symptoms Reported in the Questionnaire Survey

The monomers used in dental resin-based materials are volatile and are known to be irritating substances. The nasal olfactory epithelium is the first target tissue and mucosal degeneration and necrosis were reported in exposure to low concentrations. The lesions of olfactory epithelium are caused by the metabolite of MMA methacrylic acid [29,30]. Monomer vapor is irritating also to the respiratory system. After repeated inhalation lung irritation and central nervous system disorders may result [31]. Histopathological alterations of lungs and trachea (loss of cilia of trachea and bronchial respiratory epithelium, hyperplasia of peribronchial lymphoid follicles, and respiratory capillary hyperemia) were observed in an animal study after exposure to low concentrations of methyl methacrylate monomer vapor [32]. Increased incidence of respiratory irritation and sensitization among dental professionals were reported, as among the most common causes are the methacrylates [33-36].

Aiming to evaluate some parameters reflecting the overall health status of the studied population we performed an intentional questionnaire survey, aimed to collect data about subjective symptoms from upper respiratory tract, respiratory system, skin, cardiovascular, digestive and nervous systems and from the urinary tract.

The results obtained by us in the present study confirm our previous observations that both occupational and during the course of education in dentistry exposures to methacrylates didn't result in an increased incidence of subjective upper respiratory system symptoms [37]. Significantly increased incidence and OR for manifestation of such symptoms we established among individuals over 40 years. No role of occupational exposure was established concerning the incidence and OR of manifestation of subjective skin symptoms – they predominated significantly among women and individuals over 40 years.

In summary, the results from the present study didn't confirm the irritant action of methacrylic monomers in dental practice.

An inhibition of gastrointestinal motility after inhalation exposure to methyl-methacrylate monomer was observed, that might be due to the cardiopulmonary mechanism [38]. Ingestion can cause gastrointestinal irritation, nausea, vomiting and diarrhea [39] and may also result in adverse central nervous system effects including headache, sleepiness, dizziness, slurred speech and blurred vision. Methyl methacrylate affects the myelinated

nerve function. A Direct neurotoxic action in dental technicians, handling methyl methacrylate resin with bare fingers is possible. The neurological complaints were more common among those with a longer exposure [40].

Aiming to evaluate the overall health status of the investigated participants, questions concerning manifestation of subjective symptoms from cardiovascular, digestive and nervous systems and from the urinary tract and were also included. No role of occupational exposure to methacrylic monomers for manifestation of subjective symptoms from the cardiovascular and digestive systems, and from the urinary tract was established. Such role was found for the manifestation of unspecific subjective symptoms from the central nervous system (headache, dizziness, irritability, sleep disorders, change in mood, easy fatigability). Basing on the findings that women over 40 were more vulnerable, we consider that these symptoms could not be at smaller extent related with the occupational exposure to methacrylates.

### **4.3 Sensitization Rates to Methacrylic Monomers**

A multitude of acrylic monomers is used in dentistry, and when dental personnel, patients or students of dentistry become sensitized, it is of great importance to identify the dental acrylic preparations to which the sensitized individual can be exposed. The most commonly positive allergens in dentists and dental nurses were to 2-hydroxyethyl methacrylate (2-HEMA), ethyl acrylate (EA), triethylene glycol dimethacrylate (TREGDMA), and 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl]propane (BIS-GMA). 2-HEMA is considered to be the most important allergen in dentists and dental nurses, and MMA and EGDMA in dental technicians. Reactions to BIS-GMA, DEGDA, TREGDA, EMA and EA were relevant in some patients [41-43]. We performed patch-testing with methacrylic monomers, included in Dental Materials Staff (DMS-1000) series.

In the present study, the overall sensitization rates to methacrylates are comparatively high both among occupationally exposed dental professional and the referents – contact hypersensitivity to one or more of the monomers MMA, 2-HEMA and tetrahydrofurfuryl methacrylate was observed in 43.2% from the group of dental professionals and student and even higher - 49% in the control group. According to the results achieved, occupational exposure to the listed above methacrylic monomers doesn't result in increased incidence of sensitization. No increased sensitization rates to glutaraldehyde in occupational exposure were established.

The latter findings confirm our previous observations about relatively higher incidence of sensitization to the listed above methacrylates among the occupationally unexposed individuals. Possible explanation is could be the specificity of the control group – the mean age of the participants is relatively high (45.1 years), they have history for multiple exposures to resin-based materials during dental treatments and to methacrylates in their various customer applications, some of them are with suspected sensitization to dental materials. The high incidence of sensitization to glutaraldehyde could be explained with the statement above, together with a possible role of multiple exposures to glutaraldehyde in their everyday environment. Also, we could suggest role of improved working conditions, application of effective educational programs and strict use of proper personal protective equipment in occupational exposure.

Basing on literature data and our previous finding about co-reactivity between formaldehyde and another commonly used in dental practice aldehyde - glutaraldehyde, as well as for

concomitant sensitization to formaldehyde and methacrylic monomers [37], in the present study we aimed to evaluate the possible concomitant sensitization to methacrylic monomers and glutaraldehyde. According to our results, an increased incidence and OR (with very high statistical significance) for manifestation of concomitant sensitization to methacrylic monomers and glutaraldehyde are observed in dental practice. No similar findings in the available literature were reported.

Interesting data were achieved when gender analysis of sensitization rates was performed. In contrast to our previous findings, in the present study we could determine as a group at significantly higher risk of sensitization to most methacrylic monomers (TREGDMA, EGDMA, BIS-GMA, 2-HEMA and tetrahydrofurfuryl methacrylat), as well as to glutaraldehyde the one of men. We could speculate that women are more strict and precise when following the accepted rules of good and safe working practice. On other hand, a possible role of "hyposensitization" of women when using methacrylate-containing cosmetic products, e.g. nail polishes and artificial nails could be suggested.

Acrylic monomers often cross-react – that is, allergic sensitization induced by one acrylic compound extends to one or more other acrylic compounds. Therefore, sensitized individuals are often multiallergic and, accordingly, cannot be exposed to any of the compounds [19-21,42,43]. The results from our study also confirm manifestation of cross-reactivity of acrylic compounds – 43.9% of all individuals, were allergic to more than one of the tested compounds.

Important aspect for dental practice is that product declarations of dental acrylic materials show all acrylic compounds presenting in the products – even acrylic monomers/impurities with lower concentrations than 1%. This could help to select a product that the sensitized individual could use [44].

Skin patch testing should be performed during the regular medical examinations of individuals, occupationally exposed to sensitizing chemical agents for early diagnosis of occupational sensitization.

#### **4. CONCLUSION**

No role of exposure to methacrylic monomers in dental practice and education for manifestation of irritant effects and for increased incidence of subjective symptoms from the skin, respiratory, cardiovascular and digestive systems, and from the urinary tract was established. Such role was found for the unspecific subjective symptoms from the central nervous system, women and individuals over 40 years being more vulnerable groups. Occupational and during education of dentistry exposures to the tested methacrylic monomers and to glutaraldehyde didn't result in increased incidence of sensitization, but men could be outlined as a group at risk. An increased incidence and OR for concomitant sensitization to methacrylic monomers and glutaraldehyde were established. Our results confirm manifestation of cross-reactivity of acrylic compounds.

#### **ETHICAL APPROVAL**

All authors hereby declare that all experiments have been examined and approved by the Medical Ethical Committee of the Medical University of Sofia and have therefore been

performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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