کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی

در تدوین و چاپ مقاله
Local and Systemic Effects of Unpolymerised Monomers

Sulekha Siddharth Gosavi¹, Siddharth Yuvraj Gosavi¹, Rama Krishna Alla²

ABSTRACT
Methyl methacrylate (MMA), a widely used monomer in dentistry and medicine has been reported to cause abnormalities or lesions in several organs. Experimental and clinical studies have documented that 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.

Keywords: Allergic contact, Dermatitis, Methylmethacrylate, Stomatitis.

Received: February 2010
Accepted: April 2010

Introduction
A material may be said to be biocompatible when it has the quality of being non-destructive in the biological environment. It is important to appreciate that this interaction works in both ways such as the effect of the material on the biologic environment and the effects of the biologic environment on the material.¹ All dental biomaterials release substances into the oral and working environment to a varying degree. The biological reactions can take place either at a local level or far removed from the site of contact (i.e., systemically). The latter is a very important consideration. Because it may not always be readily apparent that clinical symptoms such as dermatological, rheumatic or neural reactions could be associated with a biomaterial. Both patients and the dental personnel are exposed to these interactions and the potential risks, with the patient being the recipient of the restorative materials and the dental personnel handing many of the materials on a daily basis. Resin-based dental materials are extensively used today in dentistry. Methyl methacrylate (MMA), a widely used monomer in dentistry and medicine, has been reported to cause abnormalities or lesions in several organs. Experimental and clinical studies have documented that 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.²⁻⁷ Monomer is highly used in the factory, reconstructive surgeries and dentistry. In dentistry, more than 98% of the restorations are done by the polymers and monomers. The dental staff is at higher risk of adverse reactions to monomers than the patients. The aims of this article are to focus on the toxic effects of different unpolymerized monomers on different systems of body. It will also concern about the prevention of the exposure of different monomers to the patients and the operators in the working field.

Applications of biopolymers in dentistry
General dental applications dentures (bases, liners, tissue conditioners, artificial teeth, temporary restoration in FPD, etc.), cavity restorative materials (composites self cure/light cure), sealants (pulpal, cavity and margin sealants), impression materials (alginate, agar, elastomers, waxes, etc.), cements (resin based cements), dentin bonding agents, orthodontic appliances, habit breaking appliances (nail biting, thumb sucking, etc.), oral and maxil-
lofacial appliances, cleft palate plates, and maxillary supports, etc., are the examples of Applications of biopolymers in dentistry.

**Genetic and Cellular Damage**

Several studies have investigated and identified the cytotoxicity and genotoxicity of some of these methacrylates during the last decade. Many dental resins contain a co-monomer such as triethylene glycol dimethacrylate (TEGDMA), which causes gene mutations in vitro. The formation of micronuclei is indicative of chromosomal damage and the induction of DNA strand breaks detected with monomers like TEGDMA and 2-hydroxyethyl methacrylate (HEMA). As a consequence of DNA damage, the mammalian cell cycle was delayed in both G1 and G2/M phases, depending on the concentrations of the monomers. Studies demonstrated that monomers reduced the levels of the natural radical scavenger glutathione (GSH), which protects cell structures from damage caused by reactive oxygen species (ROS). Depletion of the intracellular GSH pool may then significantly contribute to cytotoxicity, because a related increase in ROS levels can activate pathways leading to apoptosis. Complementary, cytotoxic, and genotoxic effects of TEGDMA, HEMA and Methacrylate are inhibited in the presence of ROS scavengers like N-acetylcysteine (NAC), ascorbate, and Trolox (vitamin E).^17^-^19^ 

In an in vitro study, Bereznowski reported that MMA exerts its toxic effects by interacting with the cell membrane. Additionally, mitochondria are intercellular target organelles and interaction of MMA with the mitochondrial membrane leads to structural and functional damage. The outer membrane was ruptured and the matrix structure was disorganized.^14^ Drozd et al.^15^ studied the toxicity of BisGMA and found it genotoxic for human lymphocytes. One study indicated that dentin adhesives were inducers of toxic-genetic events, with the mitotic recombination being the main mechanism of action.^16^

**1) Nose**

The monomers used in dental resin-based materials are volatile and it is usually possible to smell them in dental clinics. MMA is highly volatile with a vapor pressure of 36–47 hPa at 20°C. MMA is used as a basic material for different resins and plastics, either as a monomer or as a polymer (poly-methyl methacrylate). MMA is an irritating and corrosive substance. The nasal olfactory epithelium is the first target tissue and mucosal degeneration and necrosis are reported at low concentrations. The MMA metabolite methacrylic acid causes lesions of olfactory epithelium. These metabolites are formed enzymatically by carboxylesterase.\(^{17,-19}\)

**2) Respiratory systems**

Monomer vapor is irritating to the respiratory system. Repeated inhalation may be harmful; lung irritation and serious central nervous system disorders may result.\(^{20}\) In an animal study, Sokmen and Oktener showed that when rats were exposed to low concentrations (0.45 ppm) of methylmethacrylate monomer vapor, histopathological manifestations of lungs and trachea were observed. The statistically significant pathologic changes were loss of cilia of trachea and bronchial respiratory epithelium, hyperplasia of peribronchial lymphoid follicles, and respiratory capillary hyperemia. At (sub) lethal concentrations, pulmonary lesions were seen including emphysema, edema, and collapsed lungs. These results demonstrated the importance of ventilation in working places for people who use methylmethacrylate.\(^{21}\) Lozewicz et al. reported a case of asthmatic reaction immediately occurring following provocation by MMA. After several years of this work, he developed chest tightness, dyspnea, and cough which persisted for several hours after exposure to even small amounts of MMA.\(^{22}\)

**3) Irritant contact dermatitis**

Depending on the concentration and exposure time, the reaction can vary from erythema to necrosis. The monomer may exert a direct cytotoxic effect on the cells in the superficial skin or mucosa, most often corresponding exactly with the site of application. Repeated contact with low doses of primary irritants over extended time periods can develop cumulative insult dermatitis, and is caused by a gradual deterioration of the natural barriers. Such exposure conditions are mainly seen in occupational settings.\(^{23,-24}\)

One example is the ‘three-finger syndrome’: this type of reaction is often seen on the first three fingers of the left hand, in right-handed persons. These three fingers are exposed to spray from bonding resins when used to reflect the patients’ lips during treatment and may also have been in

---

*Archive of SID*  
Gosavi et al. *Local and Systemic Effects of Unpolymerised Monomers*  
Dental Research Journal (Vol. 7, No. 2, Summer - Autumn 2010)
contact with the remnants of spills on the outside of squeeze-bottles containing the liquid monomers.\textsuperscript{25-27} Gloves used for prevention of microbial contamination do not protect from exposure to monomers in dental materials. The monomers penetrate vinyl and latex gloves within a few minutes, and may therefore be in contact with the skin for an extended time period.\textsuperscript{28-31}

4) Allergic contact dermatitis
Most components of dental materials are of low molecular weight. By acting as haptens and combining with body proteins, they may form complete antigens capable of inducing sensitization of immune-competent cells. The risk of sensitization depends on various factors such as the type and concentration of the substance and the type and condition of the contacting tissues.\textsuperscript{32} The actual contact site with the allergen is usually the first place where clinical symptoms develop. However, contact-sensitized individuals may develop a number of symptoms when exposed to the allergen systematically, either orally or by inhalation, infusion, transcutaneous or transmucosal absorption.\textsuperscript{28,33-36}

5) Neuropathy
A direct neurotoxic action is possible in dental technicians, who handle monomeric methylmethacrylate resin with bare fingers. Methyl methacrylate is absorbed through the skin and is known to affect the myelinated nerve function.\textsuperscript{37} Methylmethacrylate is a cutaneous irritant and penetrates skin effectively. Sensory conduction velocities in the finger nerves were slowed in conjunction with the reported numbness. The neurological complaints were more common among those with a longer career and heavier exposure. Biopsies from a dental laboratory technician who had been preparing dental prostheses for more than 30 years have shown direct pathological effects of methyl methacrylate on nerve fibers, resulting in a sensorimotor peripheral neuropathy.\textsuperscript{38,39}

Sadoh DR reported a case of occupational exposure of monomer in which a dental technician, who was in the profession for 14 years, developed a generalized neuropathy.\textsuperscript{40}

6) Contact stomatitis
Contact allergy results from a delayed hypersensitivity reaction that occurs when antigens of low molecular weight penetrate the skin or mucosa of susceptible individuals. When allergic reactions were noted, they were described as white, necrotic lesions on the mucosa; either as small, multiple lesions or as large ulcers mimicking aphthous stomatitis.

Although allergic responses to the methacrylate in general are rare, mostly, auto-polymerizing (self-cure) resins cause these reactions more often rather than by the heat-cured ones.\textsuperscript{41} These antigens combine with epithelial-derived proteins to form hapten that bind to Langerhan’s cells, migrate to the regional lymph nodes and present the antigen to T lymphocytes, which become sensitized and undergo clonal expansion. After re-exposure to the antigen, sensitized individual develop an inflammatory reaction confined to the site of contact.\textsuperscript{42} Contact stomatitis is unknown, but it is believed to be significantly less common than contact dermatitis for the following reasons:

a. Saliva quickly dilutes potential antigens and physically washes them away and digests them before they can penetrate the oral mucosa.

b. Since the oral mucosa is more vascular than the skin, potential antigens that do penetrate the mucosa are rapidly removed before an allergic reaction can be established.\textsuperscript{43}

Direct application of relining materials in the oral cavity and subsequent release of high concentrations of monomers from the initially cured resins may severely irritate the mucosa.\textsuperscript{44,45} By immersion of acrylic resin dentures in hot water (50°C) for one hour before insertion into the oral cavity can minimize the possible risk of sensitization or allergic reactions by acrylic dentures. This procedure is particularly important with the auto-polymerized resins used either for rebasing or as a denture base material.\textsuperscript{43}

7) Effects on bone
The effects on bone includes inhibition of proliferation, alkaline phosphatase (ALP) activities, the expression of osteocalcin, and mineralized tissue formation at 200 microgm/L or more with HEMA. These results indicate that HEMA at the concentrations similar to that observed in elution tests affected osteoblastic proliferation, differentiation, and mineralization, suggesting that elution of unreacted HEMA could be the main component of the adverse effects of resin-modified glass-ionomer (RMGIC) on osteoblast-like cells and influences of resin restoratives on the osteoblasts are possibly
dependant on release characteristics of unpolyme-
rised monomers.66

8) Gastrointestinal system
Tansy et al. observed an inhibition of gastrointes-
tinal motility by breathing the methylnethacrylate
monomer.27 They assumed that this effect might be
occurring due to the cardiopulmonary mechanism.
Ingestion can cause gastrointestinal irritation, nau-
sea, vomiting and diarrhea. Ingestion of this pro-
duct may also result in adverse central nervous sys-
tem effects including headache, sleepiness, dizziness,
slurred speech and blurred vision.

9) Genital tissue
It is believed that the liver couldn’t metabolize the
MMA at both high (32%) and low (4%) concentra-
tion by its nonspecific carboxylesterase enzyme.
The MMA that circulates in the blood is associated
to the seminal vesicle atrophy either through its
direct action on testosterone secretion or its possi-
ble indirect action on testosterone through the hy-
pophysis. This hypothesis is still to be demonstrat-
ed by further studies which will address the con-
comitant effects of MMA on the pituitary gland,
the testis and the seminal vesicle.2

10) Effect on embryo
Exposure of pregnant women to a working envi-
ronment containing these esters is always a poten-
tial health threat, since these monomers have been
found to act as embryotoxic and teratogenic agents.67 Clinically there have been no reports indi-
cating that dental monomer directly affects the fe-
tus. However, judging from the fact that BISGA-
MA and MTYA have been shown to exhibit some
degrees of cytotoxicity, appropriate consideration
need to be taken while developing the product us-
ing this monomer.3,9,49,51

Ways of reducing exposure61,45,52
1. In dental laboratories and operating room, mo-
nomers vapors shall not exceed 100 ppm, and ex-
hausting systems should be used following Occu-
pational Safety and Health rules.
2. Wear protective work clothing, laboratory coat
or apron, safety glasses and wear impervious
gloves.
3. Containers should be tightly covered, to prevent
evaporation.
4. Exposure indication batches should be made to
indicate the amount of monomer exposure in the
working area.
5. Wash thoroughly immediately after exposure to
monomer and at the end of the work shift.
6. Flush away with running water immediately af-
ter contact with them through eye or skin contact.
7. Remove contact lenses if it can be done safely
and immediately flush eyes with water for at least
15 minutes, while holding eyelids open.
8. Move affected individual to non-contaminated
air. Loosen tight clothing such as collar, tie, belt or
waistband to facilitate breathing.
9. In case of spill, clean up spill using appropriate
sorbent materials.
10. Resin-based materials should be adequately
cured.
11. Vacuum mixing system for monomer should be
used as compared to handmixing, to reduce the
monomer fumes.52
12. Posthazard and warning information in the
work area should be install.
13- Seek medical attention when any symptom
devlops and persists.

Conclusion
Resin-based dental restorative materials are exten-
sively used today in dentistry. However, significant
concerns still remain regarding their biocompati-
bility. In spite of their good physical and mechan-
ical properties and excellent esthetic characteristics,
may, in turn, cause some side effects. The side ef-
fects may lead to severe lesions in oral cavity or far
from the application place of the materials. Tech-
niques should be employed to reduce patients, doc-
tors, nurses and other medical staff contact with
monomer exposure during dental procedures in
order to reduce the risks of possible complications.

References
1. Atai Z, Atai M. Side Effects and Complications of
Dental Materials on Oral Cavity. Am J Applied Sci
2007; 4(11): 946-9.
2. Fakhouri J, Sarkis R, Chababi-Atallah M, Aftimos
G. Toxic effects of methyl methacrylate monomer
on male genital tissues. In vitro study in rats. J Med
Liban 2008; 56(1): 22-6.
3. Keyf F, Keyf I. Harmful effects of methylmethacry-
late and formaldehyde from acrylic resin denture
base materials. Saudi Dental Journal 1998; 10(1):
23-8.
4. Leggat PA, Kedjarune U. Toxicity of methyl methacrylate in dentistry. Int Dent J 2003; 53(3): 126-31.
5. Mizunuma K, Kawai T, Yasugi T, Horiguchi S, Takeda S, Miyashita K, et al. Biological monitoring and possible health effects in workers occupationally exposed to methyl methacrylate. Int Arch Occup Environ Health 1993; 65(4): 227-32.
6. Leggat PA, Smith DR, Kedjarune U. Surgical applications of methyl methacrylate: a review of toxicity. Arch Environ Occup Health 2009; 64(3): 207-12.
7. Bhola R, Bhola SM, Liang H, Mishra B. Biocompatible denture polymers-a review. Trends in Biomaterials and Artificial Organ 2010; 23(3): 129-36.
8. Cimpan MR, Cressey LI, Skaug N, Halstensen A, Lie SA, Gjertsen BT, et al. Patterns of cell death induced by eluates from denture base acrylic resins in U-937 human mononoblastoid cells. Eur J Oral Sci 2000; 108(1): 59-69.
9. Schweikl H, Spagnuolo G, Schmalz G. Genetic and cellular toxicology of dental resin monomers. J Dent Res 2006; 85(10): 870-7.
10. Mavrogonatou E, Eliades T, Eliades G, Kletsas D. The effect of triethylene glycol dimethacrylate on p53-dependent G2 arrest in human gingival fibroblasts. Biomaterials 2010; 31(33):8530-8.
11. Fujisawa S, Kadoma Y. Prediction of the reduced glutathione (GSH) reactivity of dental methacrylate monomers using NMR spectra - Relationship between toxicity and GSH reactivity. Dent Mater J 2009; 28(6): 722-9.
12. Eckhardt A, Muller P, Hiller KA, Krifka S, Bolay C, Spagnuolo G, et al. Influence of TEGDMA on the cytotoxicity of ingredients of varnish and acrylic ocular prostheses. Orbit 2009; 28(6): 339-41.
13. Bakopoulou A, Papadopoulos T, Garefis P. Molecular toxicology of substances released from resin-based dental restorative materials. Int J Mol Sci 2009; 10(9): 3861-99.
14. Bereznowski Z. Effect of methyl methacrylate on mitochondrial function and structure. Int J Biochem 1994; 26(9): 1119-27.
15. Drozdz K, Wysokinski D, Krupa R, Wozniak K. Bisphenol A-glycidyl methacrylate induces a broad spectrum of DNA damage in human lymphocytes. Arch Toxicol 2010.
16. Arossi GA, Dihl RR, Lehmann M, Cunha KS, Reguly ML, de Andrade HH. In vivo genotoxicity of dental bonding agents. Mutagenesis 2009; 24(2): 169-72.
17. Mainwarling G, Foster JR, Lund V, Green T. Methyl methacrylate toxicity in rat nasal epithelium: studies of the mechanism of action and comparisons between species. Toxicology 2001; 158(3): 109-18.
18. Hext PM, Pinto PJ, Gaskell BA. Methyl methacrylate toxicity in rat nasal epithelium: investigation of the time course of lesion development and recovery from short term vapour inhalation. Toxicology 2001; 156(2-3): 119-28.
19. Parizi JL, Bai LA, Batalla CF, Lopes CC, Rizzo MF, Falcone CE, et al. Assessment of methyl methacrylate vapor toxicity on the rat tracheal epithelium. Braz Oral Res 2005; 19(3): 223-7.
20. Waltcher UI, Walther SC, Liebl B, Reichl FX, Kehe K, Nilius M, et al. Cytotoxicity of ingredients of various dental materials and related compounds in L2- and A549 cells. J Biomed Mater Res 2002; 63(5): 643-9.
21. Sokmen S, Oktemer M. Histopathological examinations of rat lungs that exposed to low concentration of methylmethacrylate monomer vapor. J Hacettepe Fac Dent 1988; 12:1-4.
22. Lozewicz S, Davies RJ. Inflammatory cells in allergic rhinitis. Respir Med 1991; 85(4): 259-61.
23. Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R. Methacrylate and acrylate allergy in dental personnel. Contact Dermatitis 2007; 57(5): 324-30.
24. Kanerva L. Cross-reactions of multifunctional methacrylates and acrylates. Acta Odontol Scand 2001; 59(5): 320-9.
25. Rajorani R, Tola S. Subjective symptoms among dental technicians exposed to the monomer methyl methacrylate. Scand J Work Environ Health 1985; 11(4): 281-6.
26. Estlander T, Rajorani R, Jolanki R. Hand dermatitis in dental technicians. Contact Dermatitis 1984; 10(4): 201-5.
27. Goon AT, Isaksson M, Zimerson E, Goh CL, Bruze M. Contact allergy to (meth)acrylates in the dental series in southern Sweden: simultaneous positive patch test reaction patterns and possible screening allergens. Contact Dermatitis 2006; 55(4): 219-26.
28. Munksgaard EC. Toxicology versus allergy in restorative dentistry. Adv Dent Res 1992; 6: 17-21.
29. Lonnroth EC, Wellendorf H, Ruyter E. Permeability of different types of medical protective gloves to acrylic monomers. J Oral Sci 2003; 11(5): 440-6.
30. Nakamura M, Oshima H, Hashimoto Y. Monomer permeability of disposable dental gloves. J Prosthet Dent 2003; 90(1): 81-5.
31. Fan PL, Meyer DM. FDI report on adverse reactions to resin-based materials. Int Dent J 2007; 57(1): 9-12.
32. Goldberg M. In vitro and in vivo studies on the toxicity of dental resin components: a review. Clin Oral Invest 2008; 12(1): 1-8.
33. FisherAA. Allergic sensitization of the skin and oral mucosa to acrylic denture materials. J Am Med Assoc 1954; 156(3): 238-42.
34. Patel V, Allen D, Morley AM, Fecopph RM. Features and management of an acute allergic response to acrylic ocular prostheses. Orbit 2009; 28(6): 339-41.
35. Cao LY, Sood A, Taylor JS. Hand/face/neck localized pattern: sticky problems--resins. Dermatol Clin 2009; 27(3):227-49.
36. Liljelind IE, Hagenbjoerk-Gustafsson A, Nilsson LO. Potential dermal exposure to methyl methacrylate
among dental technicians; variability and determinants in a field study. J Environ Monit 2009; 11(1): 160-5.
37. Bohling HG, Borchard U, Drouin H. Monomeric methylmethacrylate (MMA) acts on the desheathed myelinated nerve and on the node of Ranvier. Arch Toxicol 1977; 38(4): 307-14.
38. Seppalainen AM, Rajaniemi R. Local neurotoxicity of methyl methacrylate among dental technicians. Am J Ind Med 1984; 5(6): 471-7.
39. Donaghy M, Rushworth G, Jacobs JM. Generalized peripheral neuropathy in a dental technician exposed to methyl methacrylate monomer. Neurology 1991; 41(7): 1112-6.
40. Sadoh DR, Sharief MK, Howard RS. Occupational exposure to methyl methacrylate monomer induces generalised neuropathy in a dental technician. Br Dent J 1999; 186(8): 380-1.
41. Giunta J, Zablotsky N. Allergic stomatitis caused by self-polymerizing resin. Oral Surg Oral Med Oral Pathol 1976; 41(5): 631-7.
42. Baker S, Brooks SC, Walker DM. The release of residual monomeric methyl methacrylate from acrylic appliances in the human mouth: an assay for monomer in saliva. J Dent Res 1988; 67(10): 1295-9.
43. Lai YL, Chen YT, Lee SY, Shieh TM, Hung SL. Cytotoxic effects of dental resin liquids on primary gingival fibroblasts and periodontal ligament cells in vitro. J Oral Rehabil 2004; 31(12): 1165-72.
44. Rickles NH. Allergy in surface lesions of the oral mucosa. Oral Surg Oral Med Oral Pathol 1972; 33(5): 744-54.
45. Ohlson CG, Svensson L. Prevention of allergy to acrylates and latex in dental personnel. Swed Dent J 2002; 26(4): 141-7.
46. Imazato S, Horikawa D, Nishida M, Ebisu S. Effects of monomers eluted from dental resin restoratives on osteoblast-like cells. J Biomed Mater Res B Appl Biomater 2009; 88(2): 378-86.
47. Tansy MF, Martin JS, Benhaim S, Landin WE, Kendall FM. GI motor inhibition associated with acute exposure to methyl methacrylate vapor. J Pharm Sci 1977; 66(5): 613-9.
48. Autian J. Structure-toxicity relationships of acrylic monomers. Environ Health Perspect 1975; 11: 141-52.
49. Singh AR, Lawrence WH, Autian J. Embryonic-fetal toxicity and teratogenic effects of a group of methacrylate esters in rats. J Dent Res 1972; 51(6): 1632-8.
50. Arossi GA, Lehmann M, Dihl RR, Reguly ML, de Andrade HH. Induced DNA damage by dental resin monomers in somatic cells. Basic Clin Pharmacol Toxicol 2010; 106(2): 124-9.
51. Schwengberg S, Bohlen H, Kleinsasser N, Kehe K, Seiss M, Walther U, et al. In vitro embryotoxicity assessment with dental restorative materials. J Dent 2005; 33(1): 49-55.
52. Schlegel UJ, Sturm M, Eysel P, Breusch SJ. Pre-packed vacuum bone cement mixing systems. A further step in reducing methylmethacrylate exposure in surgery. Ann Occup Hyg 2010; 54(8): 955-61.
گزارش‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله