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respiratory sensitisation of cold and hot cure acrylic resin

A Project Submitted to

The College of Dentistry, Al-Mustansiriyah University Department of Prosthodontics In Partial Fulfillment for the Bachelor of Dental Surgery

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CERTIFICATION OF THE SUPERVISOR

I certify that this project entitled

"***respiratory sensitisation of cold and hot cure acrylic resin"***

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in partial fulfillment The graduation requirements for the Bachelor

degree in dentistry

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Dedication

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Work is dedicated to my family, and my friends for

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Abbreviation	Description
PFTs	Pulmonary function test
PERF	Peak expiratory flow rate
NSIC	Non specific inhalation challenge
NR	Test were not reported

Introduction

Up until now, acrylic resins have been the most widely used material in orthodontics and prosthetics.

They have a well-documented history of use as biomaterials in the manufacturing of different types of dental appliances

It has long been known that it is used in denture bases and many other dental, medical, and industrial products. MMA, methacrylic acid and Other methacrylLong-chain homopolymers and co-polymers are easily formed by the polymerization of MMA, methacrylic acid, and other methacrylates. f methacryDental prosthetics are made of specialized meth-acrylate polymers. e used for Dental prostheses. Although MMA monomer is widely used in dentistry, not much is known about its toxicity.however little is known about its toxicity.

Concerns concerning potential sensitivity have been raised regarding its use in dentistry, affecting both the patient and the dentist. Dental patients are also exposed to MMA leached from Some dental appliances and the effects, at least in vitro, appear toxic to Cells and may cause local mucosal irritation or even an allergic reaction. When exposed to MMA in the dental clinic, dentists and other dental staff

Occasionally appear to experience local neurological symptoms, hypersensitivity, asthmatic reactions, irritant reactions, and local dermatological reactions. After being exposed to MMA, latex gloves' integrity could also be jeopardized. During dental procedures. MMA is not thought to be carcinogenic to Humans under normal conditions of use. Techniques should be employed To reduce patients' exposure to MMA during dental procedures in order to Reduce the risks of possible complications. Dental personnel should minimize room

ventilation and refrain from direct contact with MMA.**Kedjarune U, Leggat AustN Z 1998**

Aim of study

This report reviews studies respiratory sensetizstion of acrylic resin and harmful effect of methylmethaclyte

Definition

The German chemist Rohn created acrylic resin for the first time in 1900, and since Kultzer's patent in 1940, it has been extensively utilized in dentistry and medicine. Methyl methacrylate (MMA) is polymerized in an aqueous medium to produce the polymer. This process results in the formation of very small poly(methyl methacrylate) .(PMMA) balls with a diameter of 40-100 μm .**(Sastri, V.R. 2010)**

However, MMA synthesis needs to be done quickly in order to advance polymer production technology. Such a method of quick synthesis was introduced by Crawford in the early 30s. This method involves the applicationof commonly available chemicals such as acetone, hydrocyanic acid, methanol, and sulfuric acid. Currently, this process is widely used for synthesizing PMMA(**Brydson, J.A.)**The polymer synthesized by this method is resistant to isopropyl alcohol (IPA) and lipids. PMMA's high white light transmittance of roughly 92%, which gives the denture a natural appearance, is one of its most important characteristics. Based on the structure, an acrylic multipolymer can be sterilized with ethylene oxide, gamma radiation, or e-beam(**Sastri, V.R. 2010.)**

Classification of Denture Base resins

Denture bases in partially or fully edentulous arches are primarily made of acrylic denture base polymers. The part of a denture that sits on top of the oral cavity's soft tissues is called the denture base.**(McCabe 2013)**and Wallsclassified denture base polymers into five types

the classification of denture base polymers:

type	*class*	*description*
1	*1*	*Heat cure/self processing polymer (Powder and liquid)*
1	*2*	*Heat cure self processing polymer (plastic cake form)*
2		*Self cure /auto polymerized(powde and liquid)*
3		*Thermoplastic type*
4		*Light activated type*
5		*Microwave cured type*

Composition of acrylic denture base material.*(McCabe 2013)*

component	constltuents
Powder Polymer Initiator Pigment	 Polymethyl meth-Acrylate beads Aperoxide such benzoyl peroxide Salt of cadmium such iron dyes
Liquid Monomer Cross linking agent Inhibitors Activator	 Methylmethaclyte Ethyleneglycol dimethac-Rylate Hydroquinone N N_dimethyle_p_toludine

It has been observed that compared to heat-cured denture base resins, self-cured/auto-polymerized acrylic resins extract more leftover monomer.**[Baker *et al*.]**

They discovered throughout their experiment that the people wearing dentures c omposed of self-cured or auto

polymerized base resins had higher levels of methyl methacrylate (MMA) in the ir saliva.**Kedjarune et al**. claimed that the polymerization process and the powder-to-liquid (P/L) ratio utilized in the material mixing actually determined the amount of residual monomer. In order to prevent mucosal irritation brought on by leachable residual monomer molecules,

They recommended that practitioners counsel their patients not to wear newly pr oduced dentures overnight and that it be guaranteed that the amount of residual monomer is decreased before the dentures are implanted.

Hot and cold cure acrylic resin

At present, two main types of acrylic materials exist:

- Material that polymerizes at room temperature (RT)
- Material that requires processing at a high temperature (HT).

Differense between hot and cold cure acrylic materials

- First, there is a class of materials known as self-curing resins. In theCase of these materials, the powder has a higher content of Dibenzoyl peroxide as a reaction catalyst. The liquid consists Of MMA, with a small amount of ethylene glycol dimethac-Rylate (EGDMA) and tertiary amines or ammonium salts.These are used in a relatively small concentration (below2%), as low-temperature polymerization catalysts.

- Dimethacrylates (concentration less than 5%) are present in high-temperature materials; these compounds decrease sorption and solubility while increasing the hardness of acrylic materials. **Indian J. Dent. Res., 2017**)(**Arioli 2011**

The mechanical properties of acrylic

- materials thermally polymerized are superior
- . high-temperature resins have a fracture resistance of 80 to 95 Mpa,
- self-curing materials have a fracture resistance of 60 to 70 Mpa.

the ability to obtain products that do not quickly discolor in the oral environment is made possible by the color stability, sorption, and solubility as well as the ability to cure at a higher temperature without the need of a high concentration of dibenzoyl peroxide and tertiary amines. **Gurbuz. OHDMBSC, 2010,**

Polymerization reaction

The polymerization reaction in denture base resins is an addition reaction that involves the activation of the initiator. Generally, heat polymerization (also known as heat-curing), auto-polymerization (also known as self-curing), and light polymerization are used (.singRD2013) The polymerization reaction, also known as the curing process, turns MMA into poly-MMA, converting the monomer molecules into polymers. A portion of the monomer molecules remain unpolymerized because not all of them are converted during this process.(**Mccabe2013**) The unreacted monomer that may seep into the saliva is what actually causes the cytotoxic effects in the oral cavity.(**Bural et all 2011)** The detrimental effects will increase with the amount of unreacted monomer.

The P/L ratio of the materials is one of the crucial elements that needs to be taken into account when manipulating denture base resins. Researchers Jorge et al. (2003) discovered that less residual monomer was present in resins made in the lab with higher levels of the polymer (found in the powder) content, i.e., to a ratio of 5:3. In this work, the P/L ratios of these resins during manipulation were investigated. Lower the quantity of remaining monomer, the lower the cytotoxic consequences would be.

Another important factor that determines the degree of cytotoxic effects is the polymerization temperature.The quantity of unreacted monomer left behind is greatly decreased with longer pLonger polymerization times reduce the amount of unreacted monomer that rembe carried out at the highest temperatures for at least 30 minutes, and that the denture bases that have undergone heat curing ought to be submerged in water for one to two days before being supplied to the patients. performed for a minimum of 30 minutes at the highest temperatures, and that the denture bases that have undergone heat curing should be kept in water for 1-2 days prior to being given to the patients. This is expected to reduce the cytotoxic effects caused due to residual monomer to a significant extent.**Jorge JH**Self-cured denture bases which are additionally polymerized in water at 60°C and are kept in water at room temperature for a period of 1-day show significantly decreased amounts of residual monomer content.**Bayraktar2006**

Polymerization inhibitors

For the safe transportation and storage of MMA, polymerization inhibitors (such as hydroquinone, meth-Oxy hydroquinone, or their derivatives) are added to the monomer liquid at a concentration of 50–100 ppm. Without their presence, The monomer may self-polymerize on exposure to sunlight or
An elevated temperature. Inhibitors also act as free-radical Scavengers
(Kostic, ., 2017,.)(Becker,2006,

Biocompatibility of acrylic reins

There are various ways to approach this problem, starting with the materials that go into making and processing acrylic plastics. While PMMA is a safe and bio-Compatible material, the MMA monomer is not. After Polymerization, MMA remains in the material as a residual Monomer, with a concentration ranging from 0.2% (thermal-Ly polymerized denture) up to 6-10% (materials cured at RT) (**Muhsin, S.A2017)(Goldibi, F.; Asghari2009)**

Uncured MMA can cause wearers of dentures to experience a variety of allergic reactions. **(Bayraktar 2006) (hadyaoui2015)**It can even

cause inflammation in the lips and oral mucosa soon after the prosthesi is placed.

Dentists and dental technicians who work with pure MMA are also susceptible to allergic reactions. More than 20–30% of dental technicians report that their hands' skin has changed as a direct result of MMA (epi-dermal cracks, redness). Frequent contact with MMA also Facilitates its absorption through the respiratory tract, which Is mostly possible in poorly ventilated areas. Exposure to MMA may occasionally, and at higher concentrations, result in coughing. **(lyapina2013) leggat2007**)

Chemistry of MMA

In dentistry, acrylic resin is derived from a polymerization reaction that occurs between the liquid and powder components. The main ingredients of the powder are polymethyl methacrylate (PMMA) beads, colorants, and dibenzoyl peroxide.

Property	Description
Chemical name :	2_methyle_2_propenoic acid methyl Easter
IUPAC systematic type :	Methylacrylic acid . methyl ester
Synonyms:	2_(methoxycarbony)_1_propene: Methyl 2_methaacrylate: Methyl 2_methyl_2_propenoate
Abbreviation:	MMA
Boiling point:	100_101c
Melting point:	_48Ec
Flash point:	11Ec

Simulate the pigmentation in the Case of denture base or in tempo-Rary crown resin. Benzoyl peroxide Serves as the initiator for polymeri-Sation. The main component of the liquid portion is typically MMA (monomer), along with hydroquinone and glycol dimethacrylate (GDMA). MMA provides the Building blocks for polymerisation, Whereas GDMA serves as a cross-Linking agent. Hydroquinone is added as an inhibitor to prevent the liquid from unintentionally polymerizing (**Phoenix 1996)**. There are two major ways of Converting MMA Into PMMA Predicted on the polymerization process; self-curing/cold-curing

acrylic resin; heat-curing and autopolymerization. MMA is an integral part of many dental prostheses, including impression trays, orthodontic appliances, temporary bridges or crowns, and denture bases

The harmful effect of MMA

Professionals are reporting more and more allergic reactions to dental materials, and patch testing has shown to be a dependable and simple method of identi Unreacted fying these possible reactions.**Rai.Dinakar et all**As a clinical specialty, prosthodontics creates both traditional fixed and removable partial dentures and dentures that are implant-supported. Patients may also experience allergic reactions to these prostheses because the primary component is acrylic resin MMA monomer infiltration into the oral cavity can trigger harmful effects and allergic reactions, as evidenced in the context of an inadequately cured prosthesis. Previous literature has extensively documented research on substantial cellular harm affecting lymphocytes, mitochondria, and cell membranes.. **Drozdz k2011**

During the manipulation of acrylic resin, the vaporization of MMA monomer occurs, posing potential risks through inhalation that may cause irritation to lung tissues and affect the central nervous system (CNS). In a particular study, rats were subjected to MMA vapor exposure, revealing evident histological alterations such as lung collapse, edema, and emphysema..**sokmen** In order to minimize and ideally prevent negative effects like dyspnea, coughing, and asthma triggers Dental technicians must always work in a well-ventilated environment when handling acrylic resin.**Lozewicz** It is best not to hold the resin in your bare hands while mixing because MMA can have direct neurotoxic effects. MMA has the ability to pierce skin. Direct skin absorption of MMA has been shown to impact myelinated nerve functions and may result in neuropathies. **BohlingHG**

A condition known as contact allergy, which results from a delayed hypersensitivity reaction, is observed in denture wearers. Since self-cured acrylic resins have more effects than heat-cured ones, as was previously mentioned, it is crucial to stress that burning mouth and/or soreness symptoms could also be brought on by a variety of other problems, like badly fitting dentures and poor oral hygiene.**lamey PJ**Saliva acts as a diluting agent to potentially harmful antigens before they enter the oral mucosa, thereby providing the necessary defensive barrier in the oral cavity. The oral mucosa's high vascularity also lessens the impact of irritants that have penetrated That being said, a lot will depend on how much residual monomer is present.**Van t Hof w 2014 et all** Relining materials based on resin are applied during the chairside relining process. They are usually hard or soft reliners, and using them should be done carefully. when using them because any leftover monomer will quickly leach out and may irritate the oral mucosa. The immersion of auto-polymerized resins in water before insertion into the patient's mouth is particularly important. **Ata So 2009**

Dental technicians and lab students may experience direct skin reactions from the monomer used when manipulating acrylic resins. These effects are primarily occupational and typically depend on the duration of exposure.**Kanerva 2001** It While handling acrylic resin, MMA monomer vaporizes, presenting inhalation hazards that could irritate lung tissues and influence the central nervous system (CNS). In a specific investigation, rats exposed to MMA vapor exhibited notable histological changes, including lung collapse, edema, and emphysema.**Nakamura 2003**Whether taken on purpose or by accident, MMA can also cause systemic side effects related to the gastrointestinal tract and the central nervous system (CNS), such as headaches, fatigue, and blurred vision.

Respiratory sensitisation of acrylic resin

The best way to characterize asthma is as an inflammatory respiratory tract disease marked by wheezing and airway narrowing. According to estimates, up to 20% of adult cases of asthma are thought to be related to workplace exposures, or occupational asthma (OA) (**Malo et al. 2015; Maestrelli et al. 2020**).Rather than being defined in terms of the pathogenic processes that lead to the development of the disease, it is often defined as a function of symptoms connected to exposures in the workplace.

Workplace asthma is linked to two main categories of mechanisms.

- One is allergic asthma, which by definition necessitates the induction of a particular immune response because it is caused by allergic sensitization of the respiratory tract.
- The second condition is non-allergic asthma, which is brought on by non-immunological means. **Kimber 2017; Maestrelli et al. 2020**

It is regrettable that it is frequently difficult to distinguish between asthma brought on by non-immunological mechanisms and allergic asthma. Regulatory definitions reflect this lack of differentiation between these two broad classes of OA (**Kimber et al. 2001).**

According to that guidance, an agent that can cause airway hypersensitivity after inhalation exposure is referred to as a "respiratory sensitizer." Hypersensitivity is defined as a term that encompasses both immunological and non-immunological mechanisms that lead to asthma **(ECHA 2017a).**

The consideration of available human data must therefore be relied upon in the lack of validated predictive tests, a method that is not without serious interpretive difficulties. The value and constraints of human data for the precise identification of genuine chemical respiratory allergens, as well as the necessity of cautious data interpretation, have recently been reviewed by the present authors (**Pemberton and Kimber 2021).**

The goal of the analyses presented here was to thoroughly and rigorously review the human data that was available in order to determine whether MMA can cause allergic sensitization of the respiratory tract and respiratory allergies (**comprising worker surveys, case studies and clinical investigations)**

Cohort studies

Part of the examination included a self-administered questionnaire that concentrated on complaints related to the throat and nose. Further questions focused on the respiratory system, allergic skin reactions, and "asthmatic reactions." The sole physical examination carried out involved an anterior rhinoscopy using a speculum as guidance. If symptoms preceded MMA exposure, occurred at home, or had identifiable non-work-related causes (such as hay fever or a deviated nasal septum), they were deemed unrelated to MMA. Among those who are most exposed at work (30–40 ppm; n = 56)

Instances of "rhinitis," "dry nose," and "impaired nasal breathing" reported in association with MMA exposure have not been conclusively linked. Among workers in lower exposure categories, nasal symptoms attributed to MMA were reported with a frequency ranging from 1% to 10%. These effects were transient and correlated with instances of high-peak exposure, typically ranging from 100 to 680 ppm for durations of 5 to 15 minutes.

Four employees reported having a "reduced sense of smell" (2/128 at 10–20 ppm and 2/20 at 20–30 ppm); two of those employees (one case from each exposure group) were current smokers.Mixed martial arts caused "eye irritation" (burning, itching, or lacrimation), according to three employees.Only 2 workers with low-level MMA exposures and exposure times of 3 and 36 years were reported to have "chronic bronchitis." Furthermore, no reports of skin or respiratory sensitization linked to MMA exposure were found, and a review revealed no solid proof of any effects on the nasal epithelium.

There was no evidence of respiratory sensitization in workers with long-term moderate to high-level MMA exposure, but this study did show evidence of reversible irritation to the eyes, nose, and upper respiratory tract linked to short-term MMA peaks >100 ppm. s .The strength of these findings is limited by their subjective nature (self-reported “asthmatic reactions”) Because all work- ers were rotated through different areas, and potentially exposed to high peaks, it is also difficult to draw conclu- sions regarding the role of exposure levels and dose

. This research identified reversible irritation in the nasal passages, eyes, and upper respiratory tract linked to short-term MMA concentrations exceeding 100 ppm. However, there was no indication of respiratory sensitization among workers with prolonged moderate to high-level MMA exposure. The subjective nature of these findings, particularly the reliance on self-reported "asthmatic reactions," compromises their reliability. Drawing conclusions regarding the relevance of exposure levels and dosage is also complicated due to the rotational nature of workers across different areas, potentially leading to exposure to elevated peaks.

structure–activity relationship (SAR)

MMA electrophilic reactions are lower than those of ester acrylic, and the methyl group on the α-carbon in double acrylate bonds has decreased sensitivity, according to this analysis, which uses computer methods to identify features of sub-molecular structures. Because MMA only contains one functional reactive group—α-methyl—that can replace double bonds, it is regarded as inactive and not a respiratory sensitizer.

However, SAR analysis's utility in determining sensitivity is still restricted, and it cannot determine whether a given material is hazardous.

Research on the upper respiratory tract's reaction to an acute exposure to 50 ppm MMA has only shown a slight irritation of the nose and no other negative effects. **Muttray at all 2015.** Moreover, no variations were observed in the IL-8 expression levels between the treatment and control groups. However, these results cannot be extrapolated to those of chronic exposure **soykut et all2016** At low levels of MMA exposure, an adaptive response can occur **sudiana et all 2017**

In vivo study

A histological characteristic revealed that mice's lungs may contain more inflammatory cells as a result of MMA exposure. There were comparatively few inflammatory cells in the control group. The number was marginally higher than in the control group after 40 minutes of exposure. Following a 120-minute exposure, numerous broken alveolar septa and inflammatory cells, particularly monocytes and PMN, were seen. More erythrocyte permeation was seen after 160 and 200 minutes of exposure, along with a large number of inflammatory cells—though not as many as after 120 minutes. Thus, exposure to MMA can cause inflammation in the lung tissue.

Both endogenous and exogenous stimuli have the power to start an inflammatory reaction. In the present case, MMA is an irritant **Borak et all 2011**When there are irritant-induced lesions, there is active hyperemia, which results in increased blood flow to the damaged area, capillary dilatation, and the delivery of inflammatory and leukocyte cells. Neutrophils are the first leukocytes to be detected in the early stages of the inflammatory response.

Dental exposure

(Lozewicz et al., 1985) seven cases of occupational asthma were reported, two of which involved MMA-containing materials.Patient 6 was a male dental assistant, 40 years of age, with several years of experience working with dental prosthetic trays.He started to have work-related symptoms, including tightness in his chest, coughing, and dyspnea, after combining "pMMA powder with MMA liquid." These symptoms persisted for several hours. He disclosed no prior history of wheezing or dyspnea, aside from the incidents linked to his job. Non-specific inhalation challenge (NSIC) and When the patient was not working, PEFR was normal and spirometry was not reported. After mixing "PMMA powder with MMA liquid" monomer for 20 minutes to simulate a workplace exposure, the SIC was positive (24% fall in PEFR that resolved within 2 hours).A week later, the same result was obtained from repeat testing. No placebo testing was done.

Findings from 3152 reported in 1993 on patients evaluated for occupational respiratory disease (excluding pneumoconiosis). Three of the 880 cases with an OA or respiratory disease diagnosis were linked to MMA exposure.Among those three, a dental technician was one. **Savonius et al.**

Asthma had kept the 65-year-old woman hospitalized for 12 years, during which time she was treated chronically with corticosteroids (**Basker et al., 1990)**. Not long after she was fitted for acrylic dentures for the first time, she developed asthma. She described wheezing and skin irritation from asthma attacks she had experienced when exposed to cigarette smoke, gasoline fumes, and perfume.

responses following exposure to acrylic textiles. The PEFR was negative, and there was no provision of NSIC or spirometry data. She also reported having facial pain, sore mouth, and burning in her throat.Radioallergosorbent test (RAST) NOS and IgE test results were both "normal." After she stopped wearing her dentures, her asthma "subsided gradually."Dentures composed of three distinct base materials presented a challenge for the patient: vulcanite,Flexiplast (nylon 12), and "clear heat-cured pMMA"; however, SIC were not performed. The first two had no side effects, but she needed corticosteroids for a "severe asthma attack" that happened four hours after the pMMA denture was inserted.

Two instances of "hypersensitivity pneumonitis" in dental technician trainees "within the first weeks of exposure to MMA" were documented in a laboratory setting **by (Scherpereel et al 2004).**

Six months after the start of training, **Patient 1,** a 24-year-old woman, was admitted to the hospital six months after the start of the program because her severe dyspnea and coughing had gotten worse.On physical examination, there were diffuse bilateral crackles, arterial blood was hypoxemic (Pao2: 55mm Hg), Dlco was 45% of expected, and a computed tomography (CT) scan revealed a ground glass pattern.Her symptoms were alleviated by systemic corticosteroids. After going back to work for three days a month later, she needed to be hospitalized once more due to severe dyspnea.Her Pao2 was 58 mm Hg, indicating hypoxemia. The FEV was abnormal, and the FVC was predicted to be 50%. There was no PEFR, NSIC, or SIC performed.

A few weeks after training started, Patient 2, a 20-year-old woman, was admitted to the hospital with acute respiratory distress.Her bilateral ground glass patterns were visible on her chest X-ray, her arterial blood was hypoxemic (Pao2: 65 mm Hg), she coughed, and she had diffuse bilateral crackles. In addition, she experienced "major dyspnea." PEFR and NSIC were not conducted, and spirometry was abnormal (total lung capacity [TLC]: 67% of predicted).Corticosteroids administered systemically helped her symptoms.Treatment

Afterbeing exposed to "aerolized particles of MMA" while in a "glass cage," SIC was positive (indicating "moderated dyspnea," 20% fall in Tlco, 20% fall in Dlco, and 30% lymphocytes in bronchoalveolar lavage [BAL]).

Recommendation for use

Users need to be informed that materials used in dentistry, such as denture base resins, can have both local and systemic side effects in addition to having an impact on the environment. In order to reduce the negative effects of denture base resins, the authors would like to suggest the following actions:

a) Well-ventilated areas are strongly advised when using denture base resin materials in order to minimize the effects of residual monomer vaporizing.
b) It is recommended to wear safety glasses and aprons with impermeable gloves.
c) The substance needs to be kept in containers with tight closures.
d) If exposure occurred, the affected area has to be thoroughly cleaned with water, particularly if there was eye contact. It is best to remove contact lenses right away and give them a thorough wash.
e) Remove tight clothing to facilitate breathing and relocate to an area with fresh air if contact was established and ventilation was inadequate. If there is a spill, use the right cleaning supplies to give the area a thorough cleaning.f) Appropriate curing methods need to be used, and vacuum mixing is advised.

g) In case of any symptom appearing and if they persist, immediately seek medical advice.

conclusion

MMA should be anticipated to have a low sensitizing potential in comparison to other acrylates and methacrylates due to its relatively low electrophilicity and relatively high water solubility. Expectations that MMA would have relatively low sensitizing potential are further supported by experimental data showing that methyl substitution of an ester, such as MMA, reduces its reactivity compared to corresponding unsubstituted esters. Moreover, It is anticipated that MMA would exhibit a lower sensitizing potential compared to other acrylates and methacrylates, attributed to its comparatively reduced electrophilicity and higher solubility in water. This expectation of MMA's relatively low sensitizing potential is reinforced by empirical evidence demonstrating that the introduction of methyl substitution, as in the case of MMA, diminishes its reactivity when compared to analogous unsubstituted esters. Studies on structure-activity relationships (SAR) indicated that esters typically exhibit minimal or negligible effects as respiratory sensitizers. Additionally, there is minimal risk of respiratory sensitization from low molecular weight (LMW) compounds like MMA, which possess only one reactive functional group. Furthermore, SAR analyses concluded that MMA was "inactive" according to a model with a reported specificity of 99% for respiratory sensitizers. Taken together, these findings offer robust evidence suggesting that respiratory sensitization is an unlikely adverse effect of MMA. The examination of MMA's sensitization potency in vitro has been infrequent. Cellular response assays demonstrated that MMA did not trigger lymphocyte transformation but rather induced a mild, temporary, and predominantly nonspecific enhancement in cytokine production. Despite the constraints of these studies, their findings contradict the anticipation of MMA causing respiratory sensitization. Although thorough in vivo animal testing has assessed MMA's potential for contact skin sensitization, these studies have not provided substantial insights into its ability to induce

respiratory sensitization. Although LLNA has been used, direct testing for inhalation sensitization in mice and guinea pigs has not been documented.

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