

MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Di-, Tri-, and Glycerol-Methacrylates Safety Profile

Report Details

Date of Submission

August 26, 2021

Prepared For

U.S. FDA Center for Devices and Radiological Health

Submitted to

Ed Margerrison, PhD

Director, Office of Science and Engineering Laboratories (OSEL)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

ECRI Corporate Governance

Michael Argentieri, MS

Vice President, Technology and Safety

Phone: (610) 316-2766

Email: margentieri@ECRI.org

Dheerendra Kommala, MD

Chief Medical Officer, Executive Committee

Phone: (610) 825-6000 ext. 5090

Email: dkommala@ECRI.org

Project Manager

Christopher N. Schabowsky, PhD, CCE

Director, Accident and Forensic Investigations

Phone: (540) 272-2740

Email: cschabowsky@ECRI.org

If you have any questions or require additional information, please do not hesitate to call the Project Manager.



ECRI

The Most Trusted
Voice in Healthcare

Table of Contents

Executive Summary.....	3
Project Overview.....	4
Literature Search and Systematic Review Framework.....	5
ECRI Surveillance Search Strategy	6
Safety Profile - DMA, TMA and bis-GMA.....	8
Safety Brief - Systematic Review Results	8
ECRI Surveillance Data.....	15
Potential Gaps	15
Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria.....	17
Appendix B. Search Summary	18
Appendix C. Study Flow Diagram	24
Appendix D. Evidence Tables.....	25
Appendix E. References.....	58
Appendix F. Surveillance Event Reports - PSO and Accident Investigation.....	61
Appendix G. Regulatory and Manufacturer Safety Alerts	62

Table of Tables

Executive Summary

Key Points

1. Searches identified 833 citations; 41 articles were selected for inclusion
2. For DMA/TMA/bis-GMA as a material, low quality evidence suggests local allergic skin reactions in human studies and inflammatory responses to monomers in animal studies.
3. For four device categories (dental luting cement, dental bonding adhesive, dental restoration, and dental primer etching agent), low quality evidence suggests that the material causes inflammation (but only short-term inflammation for both dental luting cement and dental primer etching agent). Additional local responses for dental bonding adhesive include pulpitis and weak thin mineralized tissue.
4. For dental luting cement and dental bonding adhesive, low quality evidence suggests that there are no systemic effects. For dental restoration, low quality evidence suggests increased B-cell activation attributable to the material. For the other device categories, there were no included studies.
5. For dental restoration, one study followed patients for five years, and observed increased B-cell activation at both six months and one year, but not at five years (suggesting that the activation spontaneously resolved at some point between 1 and 5 years) (low quality evidence).
6. For dental sealants, low quality evidence suggests there are no local responses, and no studies investigated whether there are systemic effects.
7. There were no PSO data, accident investigations, or problem reports associated with DMA/TMA/bis-GMA.
8. There were 7 alerts; however, they were not related to biocompatibility. These manufacturer-issued alerts described problems with mislabeling, wrong product, wear, and product not to specifications.
9. Evidence gaps:
 - a. With the exception of the host response to dental sealants, the quality of evidence of host and systemic responses to all products was low or worse.
 - b. For four device categories (denture relining or rebasing, dental fabrication of crown/bridge appliance, dental self-cure activator, custom cranial implants), there were no included studies.
 - c. None of the 6 included studies that reported whether there were systemic effects also reported whether there were any patient-related or material-related factors associated with systemic adverse effects.

Overview - Di-, Tri-, and Glycerol-Methacrylates

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to dimethacrylates and trimethacrylates (EDMA, EGDMA, TEGDMA, PEGDMA), and Glycerol Methacrylate (bis-GMA). If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to these materials?

For DMA, TMA, or bis-GMA as a material, evidence suggests local allergic skin reactions in human studies and inflammatory responses to monomers in animal studies. For four device categories (dental luting cement, dental bonding adhesive, dental restoration, and dental primer etching agent), evidence suggests that the material causes inflammation (but only short-term inflammation for both dental luting cement and dental primer etching agent). Additional local responses for dental bonding adhesive include pulpitis and weak thin mineralized tissue. For dental sealants, there do not appear to be any local adverse events caused by the material. For four other device categories (denture relining or rebasing, dental fabrication of crown/bridge appliance, dental self-cure activator, custom cranial implants), there were no included studies.

- a. *Can that response vary by location or type of tissue the device is implanted in or near?*
 - i. Because all device categories were dental applications (i.e., oral), evidence does not indicate whether similar local reactions would be observed in other parts of the body.

- b. *Over what time course does this local host response appear?*
 - i. The 38 studies reporting whether there were local responses varied greatly in their length of follow-up, ranging from 3 days to 30 years (median 1.5 months), and 20/38 studies had a follow-up between 1 and 3 months.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

- a. *What evidence exists to suggest or support this?*

Six of the 41 included studies reported whether there were systemic effects (see the next sub-question for more details).
- b. *What are the likely systemic manifestations?*

For dental luting cement and dental bonding adhesive, evidence suggests that there are no systemic effects. For dental restoration, evidence suggests increased B-cell activation attributable to the material. For the other device categories, there were no included studies.
- c. *What is the observed timeline(s) for the systemic manifestations?*

For dental restoration, the study had followed patients for five years, and observed increased B-cell activation at both six months and one year, but not at five years (suggesting that the activation spontaneously resolved at some point between 1 and 5 years).
- d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*

Regarding increased B-cell activation were, the authors did not suggest a cellular/molecular mechanism.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

None of the 6 included studies that reported whether there were systemic effects also reported whether there were any patient-related factors associated with systemic adverse effects.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

None of the 6 included studies that reported whether there were systemic effects also reported whether there were any material-related factors associated with systemic adverse effects.

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

- a. With the exception of the host response to dental sealants, the quality of evidence of host and systemic responses to all products was low or worse.
- b. For four device categories (denture relining or rebasing, dental fabrication of crown/bridge appliance, dental self-cure activator, custom cranial implants), there were no included studies.
- c. None of the 6 included studies that reported whether there were systemic effects also reported whether there were any patient-related or material-related factors associated with systemic adverse effects.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. To date, in 2021, the following twelve topics were chosen:

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates
7. Correlations between complications with polypropylene mesh and surgical procedure/anatomical location and chemical/mechanical device properties
8. Dimethacrylates, Trimethacrylates (EDMA, EGDMA, TEGDMA, PEGDMA), and glycerol methacrylate (bis-GMA)
9. Polyethylene glycol (PEG)
10. Other Fluoropolymers (PFPE, PVDF, PVDF-HFP, PCTFE)
11. Silver
12. Small-Molecule Per- and polyfluoroalkyl substances (SM-PFAS)

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to DMAs, TMAs and bis-GMAs?
 - a. *Can that response vary by location or type of tissue the device is implanted in or near?*
 - b. *Over what time course does this local host response appear?*
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
 - a. *What evidence exists to suggest or support this?*
 - b. *What are the likely systemic manifestations?*
 - c. *What is the observed timeline(s) for the systemic manifestations?*
 - d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps exist and what research is needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2010 and 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- I. Material Response
 - a. Strength
 - b. Embrittlement
 - c. Degradation
 - d. Migration
 - e. Delamination
 - f. Leaching
- II. Host Response
 - a. Local
 - i. Inflammation
 - ii. Sensitization
 - iii. Irritation
 - iv. Scarring/fibrosis
 - 1. Keloid formation
 - 2. Contracture
 - v. Ingrowth
 - vi. Erosion
 - b. Systemic
 - i. Cancer
 - 1. Lymphoma
 - ii. Inflammation
 - iii. Immune Response
 - iv. Fatigue
 - v. Memory Loss
 - vi. Rash
 - vii. Joint Pain
 - viii. Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Text mining, logistic regression, and a search for “random” and “systematic” in titles and abstracts were used to prioritize only the top 35%-40% of the identified literature. This subset was screened against the inclusion criteria, first by title/abstract review, and then by full article review.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2021, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A: (No Error)

Circumstances or events that have the capacity to cause error.

Category B: (Error, No Harm)

An error occurred but the error did not reach the patient (An "error of omission" does reach the patient).

Category C: (Error, No Harm)

An error occurred that reached the patient but did not cause patient harm.

Category D: (Error, No Harm)

An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E: (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F: (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G: (Error, Harm)

An error occurred that may have contributed to or resulted in permanent patient harm

Category H: (Error, Harm)

An error occurred that required intervention necessary to sustain life.

Category I: (Error, Death)

An error occurred that may have contributed to or resulted in the patient's death.

Definitions:



Harm – Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring – To observe or record relevant physiological or psychological signs.

Intervention – May include change in therapy or active medical/surgical treatment.

Intervention Necessary to Sustain Life – Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - DMA, TMA and bis-GMA

Full Name: Dimethacrylates, Trimethacrylates, and bisphenol A-glycidyl methacrylate

CAS Registry Number: [97-90-5, 3290-92-4, 1565-94-2]

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Dimethacrylates, Trimethacrylates, and bisphenol A-glycidyl methacrylate (DMA, TMA and bis-GMA) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of DMA, TMA, and bis-GMA.

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of DMA/TMA/bis-GMA. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in

Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings appears in Table 1. After the table, we then turn to a detailed discussion of research on DMA/TMA/bis-GMA as a material as well as research on the five device categories. For the other four categories, no included studies addressed them (Denture relining or rebasing, Dental fabrication of crown/bridge appliance, Dental self-cure activator, Custom cranial implants).

Table 1: Summary of Primary Findings from our Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
DMA, TMA, or bis-GMA as a material	Local allergic skin reactions in human studies. Inflammatory responses to monomers in animal studies.	Low	No studies examined or reported systemic responses	None
Dental luting cement	Short-term inflammation	Low	No systemic toxicity	Low
Dental adhesive, bonding	Pulpitis Weak thin mineralized tissue Inflammation	Low	No systemic toxicity	Low
Dental restoration	Inflammation	Low	Increased B-cell activation	Very Low
Dental primer etching agent	Short-term inflammation	Low	No studies examined or reported systemic responses	None
Dental sealants	No local adverse events due to the material	Low	No studies examined or reported systemic responses	None

Dimethacrylates, Trimethacrylates, and bisphenol A-glycidyl methacrylate as a Material

2 human studies (2 studies comparing reactions in those with vs without dermatitis), 5 animal studies (2 RCTs, 3 non-randomized studies comparing exposures). For more information see Tables 1 and 2 in Appendix D.

Local Responses (human studies)

Two studies used patch tests to study local allergic reactions to methacrylates and other materials used in dentistry. Local reactions included erythema, infiltration, papules and vesicle formation. One study used a database analysis to examine patch test results for dental technicians with and without occupational contact dermatitis (OCD).¹ Individuals with OCD were more likely to react (37.6% versus 18.5%, a statistically significant difference). Positive reactions were most frequent for 2-

hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, methyl methacrylate, ethyl methacrylate, and ethylene glycol dimethacrylate.

The second study examined individuals with a clinical history of atopic dermatitis and other allergies and compared them with non-atopic individuals.² Individuals with atopic dermatitis were more likely to react but the difference was not statistically significant (67.5% versus 55%). Ten percent of individuals with atopic dermatitis reacted to Bis-GMA but no non-atopic individuals reacted to Bis-GMA. Atopic individuals were more likely to react to compounds with dimethacrylate.

Local Responses (animal studies)

One RCT examined the inflammatory effects of various monomer combinations of Bis-GMA, UDMA, TEGDMA, and HEMA implanted in Wistar rats.³ All implants contained 65% E-glass fibers plus some combination of the monomers. Severe inflammatory reactions with dense inflammatory infiltrate were present after 30 days around implants with 21% Bis-GMA, and 14% TEGDMA. Moderate inflammatory reactions were present around implants with 21% Bis-GMA, and 14% HEMA. Mild inflammatory reactions were present around implants with 3.5% Bis-GMA, 21% UDMA, and 10.5% TEGDMA and implants with 3.5% Bis-GMA, 21% UDMA, and 10.5% HEMA. Differences in inflammatory reactions were attributed to a greater production of monomers of Bis-GMA not converting to polymers compared with UDMA.

One RCT examined the inflammatory effects of implanted silorane-based composite resin and Bis-GMA and DMA-based composite resin (Filtek Supreme XT) in mice.⁴ Tissue reactions were compared with a sham control implanted with an empty tube. By 63 days healing had occurred in all mice and no differences were found in inflammatory infiltrate. The authors noted that Filtek Supreme XT is composed of nanoparticles and nanoclusters and reduced the amount of methacrylates released that were capable of connective tissue irritation.

A prospective nonrandomized comparison study examined the inflammatory effects of implanted Bis-GMA and DMA-based resin disks in Wistar rats.⁵ Intense inflammatory infiltrate was present at 7 days in all implants but gone by 14 days in the sham implants (surgery but no disk). The inflammatory response was prolonged (up to 28 days) in implants containing the largest amounts of Bis-GMA.

A prospective nonrandomized comparison study examined the inflammatory effects of implanted Bis-GMA plus methacrylate-based composite resin and Bis-GMA plus TEGDMA-based composite resin in rats.⁶ Tissue reactions were compared with a sham control implanted with an empty tube. At 2 months both resins had significantly more inflammatory infiltrate than controls with the Bis-GMA and TEGDMA-based composite resin being the least biocompatible. A persistent foreign body reaction (macrophages and giant cells engulfing resin particles) was reported for both resins. No foreign body reactions were reported in the controls.

A prospective nonrandomized comparison study examined the toxic effect of methacrylates in zebra fish embryos.⁷ Material prewashed with ethanol prior to embryo exposure resulted in a 90% survival rate compared with over 50% lethality when not prewashed. The authors believed the lethality was due to uncured monomers in the material samples which were reduced by the ethanol prewash.

Systemic Responses

No studies examined or reported systemic responses.

Overall Quality of Evidence

Two human studies using patch tests provide evidence of local allergic reactions to methacrylates used in dentistry. Dental technicians with OCD are more likely to have reactions than those without OCD. Although these two studies found consistent results, the studies were small (n = 350 and 80) and described specific patient populations, and therefore studies results may not be generalizable to other patients. Therefore, the quality of evidence is low.

The 5 animal studies included 3 using rats, 1 using mice, and 1 using zebra fish embryos. All studies consistently showed a local inflammatory response or toxicity when exposed to methacrylates and a dose response to Bis-GMA was seen in some studies. However the evidence base is small and therefore the quality of evidence is low.

Dental luting cement

One human study (an RCT), three animal studies (all RCTs). For more information see Tables 3 and 4 in Appendix D.

All four included studies were designed to determine whether devices containing DMA/TMA/bis-GMA cause toxicity, by having a control group that did not receive device(s) containing DMA/TMA/bis-GMA.

Local Responses/Device Events (human studies)

Marcondes et al. (2016)⁸ randomized the teeth of 10 patients to receive either a DMA cement (RelyX ARC conventional resin cement) or a non-DMA cement (self-adhesive resin cement RelyU100). There were no treatment-related complications (local or systemic) in either group of teeth.

Local Responses/Device Events (animal studies)

Mesquita et al. (2017)⁹ investigated five types of resin modified glass ionomer cement (two of them with both DMA and bis-GMA, and the other three without DMA or TMA or bis-GMA). At 7 days, there was statistically significantly greater inflammatory response in the two DMA/bis-GMA groups than in two of the three control groups. However, the difference was not statistically significant at either 15 days or 30 days.

Systemic Responses

Marcondes et al. (2016)⁸ randomized the teeth of 10 patients to receive either a DMA cement (RelyX ARC conventional resin cement) or a non-DMA cement (self-adhesive resin cement RelyU100). There were no treatment-related complications (local or systemic) in either group of teeth.

Two animal studies each found that oral administration of DMA/TMA/bis-GMA had no influence on the fertility of mice.^{10,11}

Overall Quality of Evidence

Of two studies investigating local toxicity, one animal study found short-term inflammation due to the device, and the other found no complications. We rated the quality of the evidence for short-term inflammation as Low due to the small amount of evidence and inconsistency. For systemic toxicity, two animal studies found no adverse fertility effects on mice, and one human study found no complications. We rated the evidence that there is no systemic toxicity due to DMA/TMA/bis-GMA as Low, due to the small amount of evidence.

Dental bonding adhesive

Four human studies (all randomized controlled trials), 4 animal studies (all non-randomized comparative studies). For more information see Tables 5 and 6 in Appendix D.

Of the eight included studies, four (two human studies and two animal studies) were designed to determine whether devices containing DMA/TMA/bis-GMA cause toxicity, by having a control group that did not receive device(s) containing DMA/TMA/bis-GMA. In the other four studies, all humans/animals received only devices containing DMA/TMA/bis-GMA, thus they were not designed to examine the causal effect of DMA/TMA/bis-GMA.

Local Host Responses (human studies)

Two RCTs reported whether devices containing DMA/TMA/bis-GMA cause local toxicity. Pinna et al. (2015)¹² stated that no patients reported adverse events in any group (regardless of the presence of DMA/TMA/bis-GMA). Nowicka et al. (2016)¹³ reported that on histological assessment of extracted teeth, Single Bond Universal exhibited non-statistically significantly increased histological signs of pulpitis and a statistically significantly weaker thin mineralized tissue layer compared with the calcium hydroxide group. No statistically significant difference in inflammatory response of the pulp between SBU and calcium hydroxide, however inflammatory markers were greater with SBU than in the no bonding group.

For the two RCTs that did not investigate the effect of the material, Gresnigt et al. (2012)¹⁴ found low rates in both DMA groups for tooth failure due to severe discoloration, secondary caries, endodontic complications, minor surface roughness, and marginal discoloration. Patil et al. (2015)¹⁵ reported that there were no adverse events in any of the three groups (all received DMA-containing devices).

Local Host Responses (animal studies)

Nowicka et al. (2012)¹⁶ found that both groups receiving DMA-containing devices had low-grade inflammatory response, whereas the control group (no DMA) had no moderately-intense inflammation or total tissue disorganization. By contrast, dos

Santos et al. (2014)¹⁷ found that both DMA groups and non-DMA groups had a small amount of inflammatory infiltrate, circulatory alterations (edema), and granulation tissue at all experimental time intervals, showing gradual reduction with time, without statistically significant differences among them.

Regarding the two animal studies comparing different DMA devices, Taira et al. (2011)¹⁸ found no difference between a DMA-containing primer and a non-DMA primer with respect to pulp tissue disorganization or inflammatory cell infiltration. However, all animals were restored with a DMA-containing resin composite. By 28 days no animals showed severe pulp inflammation. Suzuki et al. (2016)¹⁹ reported normal pulpal tissue morphology in almost all the specimens, and no long-term differences between groups in pulp tissue disorganization or inflammatory cell infiltration.

Systemic Responses

Two of the human RCTs reported whether there were systemic responses (Nowicka et al. (2016)¹³ and Patil et al. (2015)¹⁵), and both reported that no systemic effects were observed in any groups.

None of the four animal studies reported whether there were systemic effects.

Overall Quality of Evidence

For local toxicity, evidence existed on three studies comparing DMA to non-DMA (two human RCTs and one animal non-randomized comparative study), but evidence was conflicting. One of the human RCTs reported pulpitis and weaker thin mineralized tissue layer in patients receiving devices with DMA. We rated the evidence as Low for all of these events. For systemic toxicity, only two of the human studies addressed it, and both reported that there were no systemic effects; none of the four animal studies reported whether there were systemic effects. We rated the evidence as Low.

Dental restoration

22 human studies (14 RCTs, 5 prospective nonrandomized comparison studies, 2 randomized, split-mouth clinical studies, and 1 prospective single-arm study), 6 animal studies (all prospective non-randomized comparative studies). For more information see Tables 7 and 8 in Appendix D.

Of the 28 included studies, 18 (12 human studies and 6 animal studies) were designed to determine whether restorations containing DMA/TMA/bis-GMA cause toxicity, by having a control group that did not receive restoration(s) containing DMA/TMA/bis-GMA. In the other 10 studies, all humans/animals received only restorations containing DMA/TMA/bis-GMA, thus they were not designed to examine the causal effect of DMA/TMA/bis-GMA.

Local Host Responses (human studies)

Six RCTs and five prospective nonrandomized comparison studies reported whether restorations containing DMA/TMA/bis-GMA cause local toxicity.

Five RCTs examined post-operative sensitivity (POS)/hypersensitivity of various dental restorations. Pallesen et al. (2015)²⁰ found that the control, no DMA composite groups and the DMA-containing resin composite group had no POS at 3, 5, 10, 20, and 30 year recalls. Similarly, Popoff et al. (2014)²¹ found that the control, no DMA restoration group and DMA restoration group had no POS at 6 month, 1 year and 2 year recalls. Corral et al. (2016)²² found that the control, no DMA restoration groups and DMA restoration groups had similar mean reductions in tactile and evaporative visual analog scale (VAS) scores at 360 days.

van Dijken et al. (2017)²³ reported that four molar teeth (1 in the control group, and 3 in the DMA adhesive group) had POS during the first 3 weeks of the 6-year follow up period. Askari et al. (2019)²⁴ found that the control, no DMA adhesive groups and DMA adhesive group had similar mean reductions in dentin hypersensitivity at 90 days, but in the DMA adhesive group, mild pain was reported by 53% of patients in response to tactile stimulus and 30% of patients in response to air stimulus.

One RCT examined inflammatory cytokine concentrations in rinsing solutions of cavities treated with control, no DMA restorations and DMA-containing restorations. Schmidt et al. (2021)²⁵ found that the control and DMA restoration groups had statistically significantly lower IL-1 β concentrations at 8 weeks, but only the groups without DMA had statistically significantly lower concentrations of IL-6 and C-reactive protein (CRP) at eight weeks.

Three prospective nonrandomized comparison studies examined inflammatory cytokine concentrations in gingival crevicular fluid (GCF) in control, no DMA restoration groups and DMA-containing restoration groups. Celik et al. (2017)²⁶ found that GCF volume and IL-8 concentration were statistically significantly higher in the amalgam (no DMA) group and DMA restoration

groups compared to the untreated negative control (NC) group at 21 days. Stefanovi et al. (2016)²⁷ found that patients in the DMA restoration groups had higher average IL-9 concentrations in GCF compared to the no DMA restoration groups at 30 days. Sakallio et al. (2015)²⁸ found that GCF volume were significantly higher in the DMA resin composite group and no DMA restoration groups compared to NC at four weeks ($p < 0.05$), but median GCF concentrations of IL-1 α , IL-1 β , calcitonin-gene related peptide, and prostaglandin E₂ were not significantly different between DMA resin composite, no DMA restoration, and NC groups ($p > 0.05$).

One prospective nonrandomized comparison study examined inflammatory response in a control, no DMA resin composite group and a DMA resin composite group. Chandwani et al. (2014)²⁹ found that the DMA resin composite group had a statistically significantly higher inflammatory response compared to the no DMA group at seven days. Another prospective nonrandomized comparison study examined dentin thickness and reparative dentin formation in control, no DMA restoration groups and DMA-containing restoration groups. Nowicka et al. (2015)³⁰ found that one of the DMA restoration groups had statistically significantly less dentin thickness and reparative dentin formation than the other groups at six weeks.

Seven RCTs, two randomized split-mouth clinical studies and one prospective single-arm study did not investigate the effect of DMA/TMA/bis-GMA on local host responses because all groups had DMA/TMA/bis-GMA-containing dental restorations.

Six RCTs examined POS/hypersensitivity of various DMA-containing dental restorations. Marcondes et al. (2016)⁸ found no reports of POS in two DMA restoration groups at 12 months; Beck et al. (2014)³¹ found no reports of POS in two DMA restoration groups at one year. Rocha Gomes Torres et al. (2014)³² found no statistically significant difference in POS between conventional and high-viscosity DMA restoration groups at two years. Similarly, Strober et al. (2013)³³ found no statistically significant difference in dentin hypersensitivity between two DMA restoration groups at four weeks and Ghavamnasiri et al. (2012)³⁴ found no statistically significant difference in POS between two DMA restoration groups at 12 months. By contrast, Patil et al. (2015)¹⁵ found that two DMA groups, Gluma sealant and Gluma sealant plus adhesive, had a statistically significantly greater reduction in dentin hypersensitivity than the DMA-containing Single Bond Universal adhesive group at six weeks.

One RCT examined the inflammatory response of groups with DMA-containing restorations. Ergin et al. (2018)³⁵ found that gingival inflammation was not statistically significantly different between two DMA restoration groups at 4 years.

Two randomized, split-mouth clinical studies examined POS of various DMA-containing dental restorations. Gresnigt et al. (2012)¹⁴ found no reports of POS in two DMA restoration groups at approximately 41.3 months. By contrast, Perdigao et al. (2012)³⁶ reported POS in all four DMA restoration groups studied at 18 months: 7.7% of teeth in the Easy Bond group, 9.1% of teeth in the Scotchbond SE group, 9.1% of teeth in the Scotchbond Multi-Purpose group, and 8.3% of teeth in the Single Bond Plus group.

One prospective single-arm study examined POS, blood cell extravasation, and pulp tissue inflammation in a DMA restoration group. Silva et al. (2013)³⁷ found no reports of POS, but blood cell extravasation and multinucleated giant cells were identified along the DMA adhesive layer at 30 days.

Local Host Responses (animal studies)

Six prospective nonrandomized comparison studies reported whether devices containing DMA/TMA/bis-GMA cause local toxicity in animals. Suzuki et al. (2016)¹⁹ found no specimens with inflammatory cell infiltration or pulp tissue disorganization in two DMA bond groups and a control (no DMA) primer group at 112 days. Similarly, Taira et al. (2011)¹⁸ found no specimens with inflammatory cell infiltration, pulp tissue disorganization, or bacterial penetration in a control (no DMA) primer group and DMA primer group at 28 days. Da Silva et al. (2018)³⁸ found no statistically significant difference in pulp tissue inflammation, soft tissue organization, or transforming growth factor- β 1 expression between control (no DMA) and DMA restoration groups at 15 days.

By contrast, Ruiz-de-Castañeda et al. (2013)³⁹ found periapical and pulpal inflammatory response in 20% of teeth in the DMA restoration group and a combined 6.6% of teeth in two no DMA restoration groups at 90 days. Rendjova et al. (2012)⁴⁰ found that pulp tissue inflammation was slightly elevated in the Prime&Bond DMA adhesive group compared to control no DMA cement (Fuji IX), DMA cement (Fuji Lining LC) and DMA adhesive (G Bond) groups without inflammation at 30 days. Similarly, Nowicka et al. (2012)¹⁶ found a combined 62.5% of teeth had low inflammatory pulp responses in two DMA restoration groups compared to 25% of teeth in a no DMA group with low inflammatory pulp responses at 40 days.

Systemic Responses

One RCT reported whether dental restorations containing DMA/TMA/bis-GMA cause systemic toxicity. The RCT examined white blood cell (WBC) distribution, activation of T-cells and B-cells, CD4 and CD8 expression, and monocyte and neutrophil function in patient samples from a control, no DMA restoration group and three DMA-containing restoration groups. Maserejian et al. (2014)⁴¹ reported that DMA restorations were associated with increased B-cell activation at six months and one year, but not at the five year follow-up. The cellular mechanisms for increased B-cell activation were not reported.

None of the six animal studies reported whether there were systemic effects.

Overall Quality of Evidence

For local toxicity, there is some evidence for inflammatory reactions to DMA/TMA/bis-GMA, but effects were not consistent, and some studies were not randomized, so the quality of the evidence is low. For systemic toxicity, only one of 28 included studies investigated it, and the study found that DMA-containing restorations had increased B-cell activation. Because it was only a single study, the quality of the evidence is Very Low.

Dental primer etching agent

No human studies, one animal study (observational study). For more information see Tables 9 and 10 in Appendix D.

Local Host Responses (human studies)

No studies

Local Host Responses (animal studies)

Taira et al. (2011)¹⁸ found no difference between a DMA-containing primer and a non-DMA primer with respect to pulp tissue disorganization or inflammatory cell infiltration. However, all animals were restored with a DMA-containing resin composite. By 28 days no animals showed severe pulp inflammation.

Systemic Responses

No studies.

Overall Quality of Evidence

The evidence base contains only one study and therefore the quality of evidence is very low.

Dental sealants

Two human studies (2 RCTs), no animal studies. For more information see Tables 11 and 12 in Appendix D.

Local Host Responses (human studies)

Two RCTs, Patil et al. (2015)¹⁵ and Pinna et al. (2015),¹² with a total of 66 patients (170 teeth) examined dental sealants and their effect on teeth hypersensitivity. In both studies patients reported no adverse reactions to treatment. Patil et al. examined materials that contained HEMA and other methacrylates. Pinna et al. compared dental products with and without HEMA and dimethacrylates.

Local Host Responses (animal studies)

No studies

Systemic Responses

No reports of systemic responses

Overall Quality of Evidence

Both studies were small RCTs and the specific study goals were not related to identifying adverse reactions to dental materials, therefore the quality of the evidence is low.

ECRI Surveillance Data

DMA/TMA/bis-GMA are primarily used in dental products which are often not captured in ECRI's databases. Accordingly, there were no identified PSO data, accident investigations, or problem reports associated with DMA/TMA/bis-GMA. There were 7 alerts; however, they were not related to biocompatibility. These manufacturer-issued alerts described problems with mislabeling, wrong product, wear, and product not to specifications.

Refer to Appendix F for a list of devices that guided our searches of ECRI Surveillance Data.

Patient Safety Organization

Search Results:

ECRI PSO identified 359 reports that occurred between 9/2015 and 12/2020 and contained the keyword search utilized for DMAs, TMAs and bis-GMAs; however, none of these involved complications with devices made from DMA/TMA/bis-GMA.

Accident Investigations

Search Results: No accident investigations involving devices made from DMA/TMA/bis-GMA were identified in the surveillance search.

ECRI Problem Reports

Search Results: The search returned 0 reports submitted by ECRI members.

Healthcare Technology Alerts

Search Results: The search returned 7 manufacturer-issued alerts describing problems with mislabeling, wrong product, wear, and product not to specifications, summarized in **Error! Reference source not found..**

Table 7: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
Dental Cement	7 Manufacturer-Issued	<ul style="list-style-type: none">• Increased wear during use• Wrong product included• Mislabeling• Contains plastic particulate• Product not to specified standard

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of DMA/TMA/bis-GMA. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

With the exception of the host response to dental sealants, the quality of evidence of host and systemic responses to DMA/TMA/bis-GMA as materials and all products composed of these materials were low or worse. This indicates an overall gap of evidence from biocompatibility studies investigating these materials.

Further, for four of the identified device categories (denture relining or rebasing, dental fabrication of crown/bridge appliance, dental self-cure activator, custom cranial implants), there were no included studies.

None of the 6 included studies that reported whether there were systemic effects also reported whether there were any patient-related or material-related factors associated with systemic adverse effects.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

- I. Inclusion Criteria
 - 1. English Language publication.
 - 2. Published between 1/1/2011 and 3/11/2021.
 - 3. Human and animal studies.
 - 4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series.
 - 5. Studies that evaluate toxicity/biocompatibility of Dimethacrylates, Trimethacrylates, and bisphenol A-glycidyl methacrylate or priority devices that include this material.
- II. Exclusion Criteria
 - 1. Foreign language publication.
 - 2. Published before January 2011.
 - 3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial).
 - 4. Off-topic study.
 - 5. On-topic study that does not address a key question.
 - 6. No device or material of interest.
 - 7. No relevant outcomes (adverse events or biocompatibility not reported).
 - 8. Study is superseded by more recent or more comprehensive systematic review.
- III. Quality of Evidence Criteria
 - 1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
 - 2. **Quantity of data** – number of systematic reviews and individual studies providing relevant data.
 - 3. **Consistency of data** – are the findings consistent across studies that report relevant data?
 - 4. **Magnitude of effect** – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
 - 5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
 - 6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI’s medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from Emtree. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called “major” headings. This “major” concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. “Exploding” in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n=174) and their associated entry terms (lexical variants and synonyms) to the strategy using an “OR” without the searcher having to type them in. That’s one of the major advantages to searching using controlled vocabularies. We don’t rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That’s why we also include free text words in our strategies.

Literature Search for Dimethacrylates and Trimethacrylates (DMA, TMA)

Set Number	Concept	Search Statement
Material		
1.	Dimethacrylates and trimethacrylates (DMA, TMA)	'bisphenol a bis(2 hydroxypropyl) ether dimethacrylate'/exp OR 'ethylene glycol dimethacrylate'/exp OR 'triethylene glycol dimethacrylate'/exp OR 'bisphenol a diglycidyl methacrylate*' OR 'bisphenol a diglycidyl ether methacrylate*' OR 'bowen s resin' OR 'ethylene glycol dimethacrylate*' OR 'triethyleneglycol dimethacrylate*' OR 'triethylene glycol dimethacrylate*' OR 'polyethylene glycol dimethacrylate*' OR 'glycerolate dimethacrylate*' OR 'ethylene dimethacrylate*' OR ethylenedimethacrylate* OR 'diurethane dimethacrylate*' OR 'urethane dimethacrylate*' OR 'decamethylene dimethacrylate*' OR 'glycerol 1,3-dimethacrylate*' OR 'trimethylolpropane trimethacrylate*' OR 'trimethylol propane trimethacrylate*' dimethacrylate* OR 'di-methacrylate*' OR trimethacrylate* OR 'tri-methacrylate*'
2.		dimethacrylate* OR 'di-methacrylate*' OR trimethacrylate* OR 'tri-methacrylate*'
3.		bisema OR 'bis-ema' OR bisdma OR 'bis-dma' OR bisgma OR 'bis-gma' OR egdma OR 'eg-dma' OR 'egdm' OR 'udma' OR 'dudma' OR 'edma' OR tegdma OR 'teg-dma' OR ppgdma OR 'ppg-dma' OR pegdma OR 'peg-dma' OR pegdm OR 'peg-dm' OR pegma OR 'peg-ma' OR 'tmptma'
4.		ethyleneglycoldimethacrylate* OR ethylenglycoldimethacrylate* OR triethyleneglycoldimethacrylate* OR triethylenglycoldimethacrylate* OR urethandimethacrylate* OR urethanedimethacrylate* OR

		diurethandimethacrylate* OR diurethanedimethacrylate* OR glycoldimethacrylate*
5.	DMA materials and dental devices	('dental material'/exp OR 'adhesive agent'/exp OR 'resin'/exp OR 'resin cement'/exp OR 'denture material'/exp OR 'dental bonding'/exp/mj OR 'tooth filling'/exp/mj OR 'dental restoration'/exp/mj OR 'dental device'/dv OR 'denture'/dv OR 'tooth crown'/dv OR 'tooth prosthesis'/dv) AND (#1 OR #2 OR #3 OR #4)
6.	DMA product names	'adhere' OR 'adper single bond' OR 'adper scotchbond' OR 'all-bond universal' OR 'allbond universal' OR 'ambar universal' OR 'clearfil photo*' OR 'clearfil se' OR 'clearfil universal' OR 'protect bond' OR 'futurabond*' OR 'gluma solid bond' OR 'gradia direct' OR 'one-step plus' OR 'one-up bond' OR 'optibond all-in-one' OR 'optibond extra universal' OR 'optibond fl' OR 'optibondfl' OR 'optibond s' OR 'optibond solo' OR 'optibond universal' OR 'optibond xtr' OR 'prime & bond' OR 'prime and bond' OR 'scotchbond multipurpose' OR 'scotchbond multipurpose' OR 'scotchbond universal' OR 'single bond universal' OR 'surefil' OR 'syntac' OR 'tetric' OR 'tokuyama bond force' OR 'tph spectra' OR 'vertise flow' OR 'xeno iv' OR 'xenoiv' OR 'xeno ix' OR 'xenoix' OR 'calibra' OR 'calibra ceram' OR 'ceram x spectra st' OR 'ceram x universal' OR 'ceram x duo' OR 'dyract' OR 'esthetx hd' OR 'fluorocore' OR 'prisma universal bond' OR 'probond' OR 'heliobond' OR 'estecem' OR 'estelite' OR 'peak universal bond' OR 'filtek bulk fill' OR 'filtek one' OR 'filtek p60' OR 'filtek supreme' OR 'filtek ultimate' OR 'filtek universal' OR 'filtek z100' OR 'filtek z250' OR 'filtek z350' OR 'filtek z500' OR 'espe bulk fill' OR 'espe one' OR 'espe p60' OR 'espe supreme' OR 'espe ultimate' OR 'espe universal' OR 'espe z100' OR 'espe z250' OR 'espe z350' OR 'espe z500' OR '3m bulk fill' OR '3m one' OR '3m p60' OR '3m supreme' OR '3m ultimate' OR '3m universal' OR '3m z100' OR '3m z250' OR '3m z350' OR '3m z500' OR (('rebase*' OR 'bond force') AND 'tokuyama*')
7.	Combine and Limit by language and publication date	(#1 OR #2 OR #3 OR #4 OR #6) AND [english]/lim AND [2011-2021]/py
8.	Limit by publication type	#7 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

9.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation' OR 'biological* acceptab**'
10.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence OR leakage* OR microleakage*
11.		leachable* OR extractable* OR 'degree of conversion' OR (incomplete NEAR/2 polymeri?ation) OR unpolymeri?ed OR ((residual OR unreacted OR retained) NEAR/2 monomer*)
12.		shrink*:ti,ab OR contract*:ti,ab OR stretch*:ti,ab OR retract*:ti,ab OR extension:ti,ab OR deform*:ti,ab OR creep:ti,ab OR plasticity:ti,ab OR disintegrat*:ti,ab OR fail*:ti,ab OR fragment*:ti,ab OR debond*:ti,ab OR migrat*:ti,ab OR leak*:ti,ab OR microleak*:ti,ab OR compression:ti,ab
13.		'mechanics'/exp
14.		'device material'/exp/mj

15.		'Biomedical and dental materials'/exp/mj
16.	Combine sets	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17.	DMA/TMA + Material Response	#8 AND #16

Host Response

18.		(host OR tissue OR pulpal OR pulp OR tooth) NEAR/3 (reaction* OR response* OR damage)
19.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
20.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj OR 'pruritus'/exp OR 'pruritus' OR 'skin irritation'/exp OR itch*:ti,ab
21.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluoresc*:ti
22.		'inflammation'/exp OR inflamm*:ti,ab OR 'tongue swelling'/exp OR 'burning mouth syndrome'/exp OR 'burn'/exp OR edema:ti,ab OR anaphylac*:ti,ab OR swell*:ti,ab
23.		'foreign body' OR granuloma* OR 'foreign body'/exp
24.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'fibrosis'/exp OR 'necrosis'/exp OR necrosis OR (pulp NEAR/2 (death OR expos*))
25.		protrude* OR protrus* OR perforat* OR deminerali?ation
26.	Combine sets	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27.	Combine sets DMA/TMA + Material Response+ Host Response	#17 AND #26
28.	DMA/TMA devices + Host response	#8 AND (#5 OR #6) AND #26
29.	Combine sets	#27 OR #28
30.	DMA/TMA systematic reviews	#8 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
31.	Final set	#29 OR #30

Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
 - Bladder compliance
 - Blood vessel compliance
 - Artery compliance
 - Vein compliance
 - Heart muscle compliance
 - Heart left ventricle compliance

- Heart ventricle compliance
 - Lung compliance
 - Compressive strength
 - Dynamics
 - Compression
 - Computational fluid dynamics
 - Decompression
 - Explosive decompression
 - Rapid decompression
 - Slow decompression
 - Gravity
 - Gravitational stress
 - Microgravity
 - Weight
 - Body weight
 - Birth weight
 - High birth weight
 - Low birth weight
 - Small for date infant
 - Very low birth weight
 - Extremely low birth weight
 - Body weight change
 - Body weight fluctuation
 - Body weight gain
 - Gestational weight gain
 - Body weight loss
 - Emaciation
 - Body weight control
 - Fetus weight
 - Ideal body weight
 - Lean body weight
 - Live weight gain
 - Dry weight
 - Fresh weight
 - Molecular weight
 - Organ weight
 - Brain weight
 - Ear weight
 - Heart weight
 - Liver weight
 - Lung weight
 - Placenta weight
 - Spleen weight
 - Testis weight
 - Thyroid weight
 - Uterus weight
 - Seed weight
 - Tablet weight
 - Thrombus weight
 - Weightlessness
 - Hydrodynamics
 - Hypertonic solution
 - Hypotonic solution
 - Isotonic solution

- Osmolality
 - Hyperosmolality
 - Hypoosmolality
 - Plasma osmolality
 - Serum osmolality
 - Urine osmolality
 - Osmolarity
 - Blood osmolarity
 - Hyperosmolarity
 - Hypoosmolarity
 - Plasma osmolarity
 - Serum osmolarity
 - Tear osmolarity
 - Urine osmolarity
 - Osmosis
 - Electroosmotic
 - Osmotic stress
 - Hyperosmotic stress
 - Hypoosmotic stress
 - Photodynamics
 - Photoactivation
 - Photoreactivation
 - Photodegradation
 - Photoreactivity
 - Photocytotoxicity
 - Photosensitivity
 - Photosensitization
 - Phototaxis
 - Phototoxicity
 - Photostimulation
 - Proton motive force
 - Shock wave
 - High-energy shock wave
 - Stress strain relationship
 - Thermodynamics
 - Adiabaticity
 - Enthalpy
 - Entropy
- Elasticity
 - Viscoelasticity
 - Young modulus
- Force
- Friction
 - Orthodontic friction
- Hardness
- Kinetics
 - Adsorption kinetics
 - Flow kinetics
 - Electroosmotic flow
 - Flow rate
 - Gas flow
 - Laminar airflow
 - Laminar flow
 - Powder flow

- Angle of repose
 - Hausner ration
 - Pulsatile flow
 - Shear flow
 - Thixotropy
 - Tube flow
 - Turbulent flow
 - Vortex motion
 - Water flow
- Motion
 - Coriolis phenomenon
 - Rotation
 - Vibration
 - Hand arm vibration
 - High frequency oscillation
 - Oscillation
 - Oscillatory potential
 - Whole body vibration
- Velocity
 - Acceleration
 - Deceleration
 - Processing speed
 - Wind speed
- Mass
 - Biomass
 - Fungal biomass
 - Immobilized biomass
 - Microbial biomass
 - Body mass
 - Bone mass
 - Dry mass
 - Fat free mass
 - Fat mass
 - Heart left ventricle mass
 - Kidney mass
- Materials testing
- Mechanical stress
 - Contact stress
 - Contraction stress
 - Shear stress
 - Surface stress
 - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
 - Quantum theory
- Rigidity
- Torque
- Viscosity
 - Blood viscosity
 - Plasma viscosity
 - Gelatinization

- Shear rate
- Shear strength
- Shear mass
- Sputum viscosity
- Viscoelasticity

Appendix C. Study Flow Diagram

- I. 833 citations identified by searches, of which
 - i. **475 citations not screened manually due to likely irrelevance** (based on text mining, logistic regression, etc.) and
 - ii. 358 articles selected for title/abstract screening: 250 selected by text mining in Distiller (30%), 42 by logistic regression (5%), 66 for including “random” or “systematic” in the title or abstract, of which:
 1. **291 citations excluded at the title/abstract level** – Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest and
 2. 67 full-length citations reviewed, of which
 - a. **26 citations excluded at the full article level** – Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest
 - b. 41 citations reviewed for evidence prioritization, of which
 - i. **0 citations excluded at the prioritization level** – Because there were already fewer than 50 articles, we did not apply the evidence prioritization scheme
 - ii. 41 citations included

Appendix D. Evidence Tables

Table 2: DMA/TMA as a Material - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Heratizadeh et al. (2018)¹

Study Design: Retrospective case series (database analysis)

Device or Material: Patch test: 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, methyl methacrylate, ethyl methacrylate, and/or ethylene glycol dimethacrylate

Contact Duration: 72 hours

Dose: NR

Frequency/Duration: Single administration

Response: Positive reactions: erythema, infiltration, papules, and/or (coalescing) vesicles

Patient characteristics (gender, mean age): DT with OCD: 46.5% male, 52% over 40 years old. DT without OCD: 31.5% male, 52% over 40 years old.

Number per group: 226 DTs with OCD compared with 124 DTs without OCD.

Observed adverse effects: Individuals with OCD were more likely to react (37.6% versus 18.5%; $p=0.0002$). Positive reactions were most frequently observed to methacrylates and/or acrylates. 61 patients showed positive reactions to at least one of the five most frequent allergens in this group, namely 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, methyl methacrylate, ethyl methacrylate, and/or ethylene glycol dimethacrylate.

Timing of adverse effects: 72 hours

Factors that predict response: "Methacrylates and acrylates, which are used in the manufacture and repair of dental prostheses, were identified as the main cause of allergic OCD in DTs. ..According to our data, they still represent the most important occupational sensitizers in DTs. In our study, approximately one-third of the DTs with OCD reacted to methacrylates and/or acrylates."

Source Citation: Rojas-Alcayaga et al. (2012)²

Study Design: Case series

Device or Material: Numerous materials used in patch test

Contact Duration: 72 hours

Dose: NR

Frequency/Duration: Single administration

Response: Delayed-type sensitization

Patient characteristics (gender, mean age): Atopic patients: a clinical history of atopic dermatitis, allergic rhinitis, allergic asthma, or food allergies; 28 women and 12 men, with an average age of 34.6 years. Non-atopic patients: defined as those that did not present signs or symptoms of immediate allergies at the taking of the history; 30 women and 10 men, with an average age of 41.87 years.

Number per group: 40 atopic and 40 non-atopic

Observed adverse effects: Patch test: Of the entire group of patients (n=80), 61.25% presented sensitization to at least one of a battery of dental materials, with palladium chloride (21.25%), ammoniated mercury (20%), benzoyl peroxide (12.5%) and amalgam (10%) being the most frequent. The frequency of sensitization was 67.5% in the group of atopic patients, compared to 55% in the non-atopic group ($p>0.05$). For atopic patients, ammoniated mercury (25%), benzoyl peroxide (22.5%), palladium chloride (22.5%), amalgam (17.5%) and Bis-GMA (10%). Reaction to Bis-GMA was not seen in non-atopic patients. Atopic individuals were more likely to react to compounds with dimethacrylate.

Timing of adverse effects: 48 and 72 hours

Factors that predict response:

Bis-GMA = bisphenol A-glycidyl methacrylate; DT = dental technician; NA – not applicable; NR = not reported; Obs – observational; OCD – occupational contact dermatitis; Retro = retrospective; R = reliable, Dose = mg/kg/day

Table 3: DMA/TMA as a Material - Health Effects (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Barreto Giro et al. (2020)⁵

Study Design: Prospective nonrandomized comparison study

Device or Material: 3M, Ivoclar and Kerr bulk fill (BF) Bis-GMA and DMA-based resin disks (Filtek Bulk Fill One, Sonic Fill, Tetric N-Ceram Bulk Fill) versus 3M, Ivoclar and Kerr non-BF Bis-GMA and DMA-based resin disks (Filtek Z-350, Herculite Classic, Tetric N-Ceram)

Route: Subcutaneous dorsal implants

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory infiltrate (inflammatory cells per field) Gomes-Filho scores

Species (strain): Rat (Wistar)

Gender: Female, 4 months old

Number per group: 3M: n=18 each received no disk (sham), one Filtek Z-350 disk, one superficial Filtek Bulk Fill One disk, and one deep Filtek Bulk Fill One disk. Ivoclar: n=18 each received no disk (sham), one Tetric N-Ceram disk, one superficial Tetric N-Ceram Bulk Fill disk, and one deep Tetric N-Ceram Bulk Fill disk. Kerr: n=18 each received no disk (sham), one Herculite Classic disk, one superficial SonicFill disk, and one deep SonicFill disk.

Observed adverse effects: "At day 7, all samples from all sites showed intense inflammatory infiltrate. At day 14, there was a significant reduction in the intensity of inflammatory infiltrate in all sham sites ($p < 0.05$)". In the 3M group at 28 days, "there was no difference between the intensity of the inflammatory infiltrate in the surgical sites of the sham group, control resin, and superficial or deep BF resins ($p = 0.099$ ". "In the Ivoclar group, all sites submitted to resins presented intense inflammatory infiltrate after 14 days, with values significantly higher than those of the sham group ($p = 0.036$). On day 28, all sites had mild or absent inflammation ($p = 0.163$ ". "In the Kerr group, on day 14 and day 28, the inflammatory infiltrate intensity scores were significantly higher in both the superficial and deep BF-treated groups than those in the sham group ($p = 0.028$ and $p = 0.031$, respectively".

Timing of adverse effects: 7, 14 and 28 days

Factors that predict response: "The degree of conversion of a composite is crucial for determining its biocompatibility." "Despite the BF resins allowing application in a single increment, there is a gradual decrease in DC [degree of conversion] in the deeper layers of the material, thus we suggest caution in the use of BF resin with a large concentration of bis-GMA in very deep cavities ($> 2\text{mm}$)." "Fibroblasts are more sensitive to monomer toxicity. The exposition of connective tissue of the rats treated with Kerr BF resin disks showed a high bis-GMA proportion and prolonged the inflammatory process. Despite blood cell cultures not being influenced by monomeric Bis-GMA, this monomer leads to overexpression of proinflammatory cytokines due to cell toxicity...as shown in our study." "Another critical factor affecting the leaching of residual monomers is the nature and molecular size of the monomers in the resin." "TEDGMA is a low-molecular weight monomer that exhibits greater mobility and is eluted faster than large molecules, such as Bis-GMA...which may justify the prolonged inflammatory response observed in this study in resins with high Bis-GMA (Kerr) concentration."

Source Citation: Alifui-Segbaya et al. (2018)⁷

Study Design: Prospective nonrandomized comparison study

Device or Material: E-Denture (ED), E-Guard (EG) and Dental SG (DSG) methacrylates

Route: Material samples were placed in petri dishes along with embryos. The samples were tested in ethanol-treated (Tx) and non-treated (nTx) conditions.

Dose: See below

Frequency/Duration: Up to 120 hours

Response: Lethal endpoints: embryo coagulation, absence of somite formation, nondetachment of tail-bud and absence of heartbeat; Sublethal endpoints

Species (strain): Zebra fish embryo model

Gender: NR

Number per group: 40

Observed adverse effects: ED is a Class IIa acrylic material for 3DP of denture bases containing >60% Ethoxylated bis-phenol A dimethacrylate (Bis-EMA), 15–25% Proprietary methacrylic oligomer and <2.5% Phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide. nTx ED in E3 medium resulted in 100% lethality after 3 days. No lethal endpoint was observed in bioassays containing Tx ED. EG is a Class I material (>70% Proprietary methacrylic oligomer, <20% glycol methacrylate, <5% Pentamethyl-piperidyl sebacate and <2,5% Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide)). At 2 days nTX EG resulted in greater than 50% lethality. At 120 hours, bioassays containing Tx EG had a 90% survival rate with no indicators of lethality but some larvae showed reduced melanophores and minor pericardial edema. DSG is a Class I material (≥75% Bis-EMA, 30–50% Diurethane dimethacrylate, mixture of isomers and <10%phenyl bis (2,4,6-trimethylbenzoyl)-phosphine oxide)). Extracts from aSb and nTx DSG samples elicited a 100% lethality (embryonic mortality) in bioassays within 24 h.

Timing of adverse effects: As early as 24 hours

Factors that predict response: "The observed level of toxicity in the methacrylates can probably be explained by uncured monomers. This class of materials has high cytotoxicity due to Michael addition of the methacrylate group with amino or thiol groups of DNA or proteins in the human body. Similarly, hydrolysis of non-reacted groups forms unwanted methacrylic acid, decreasing pH locally, which may produce adverse biological effects on the surrounding tissue." "For this study, we observed 'detoxicant' effects of ethanol treatment. Immersion of dental acrylics in pure ethanol solution reduces residual compounds. Likewise, ethanol-water solutions lower residual monomer contents in acrylic resins, depending on concentration and temperature."

Source Citation: Lazar et al. (2016)³

Study Design: RCT

Device or Material: Combinations of monomers bisphenol A glycidylmethacrylate [bis-GMA], urethane dimethacrylate [UDMA], triethylene glycol dimethacrylate [TEGDMA], hydroxyethyl methacrylate [HEMA] and E-glass fibers

Route: Subcutaneous dorsal implants

Dose: See below

Frequency/Duration: Single administration/30 days

Response: Inflammatory reaction; tissue repair status; presence of the capsule

Species (strain): 40 Wistar rats

Gender: male

Number per group: 10

Observed adverse effects: Tissue surrounding the implant made of FRC1 (21% Bis-GMA, 14% TEGDMA, 65% E-glass fibers) showed severe inflammatory reaction, with dense inflammatory infiltrate (numerous macrophages, lymphocytes, and neutrophils), vasodilatation, and edema. Tissue in the proximity of the implant made of FRC2 (21% Bis-GMA, 14% HEMA, 65% E-glass fibers) showed moderate, chronic,

inflammatory reaction. Intensity of the inflammatory reaction was milder in case of FRC3 (3.5% Bis-GMA, 21% UDMA, 10.5% TEGDMA, 65% E-glass fibers) compared with the previous groups. The repair process was advanced, and the capsule was well organized and completely formed. In case of the FRC4 (3.5% Bis-GMA, 21% UDMA, 10.5% HEMA, 65% E-glass fibers), the inflammatory reaction was mild. The surrounding tissue exhibited a moderate repair process. In the scores of inflammation, FRC1 had highest scores and followed by FRC2, FRC4, and FRC3.

Timing of adverse effects: Within 30 days

Factors that predict response: "Due to the lower viscosity of UDMA compared with the Bis-GMA oligomers and a longer gel time, a greater number of methacrylic groups can react and convert to polymer. Monomers of FRC3 have a higher conversion rate and, consequently, a lower residual monomer, that ultimately lead to a good biological behavior." Bis-GMA produces more monomers leading to a greater inflammatory reaction. "According to our studies, FRC3 based on UDMA monomer is the best formulation in regards to the biological behavior."

Source Citation: Castañeda et al. (2011)⁴

Study Design: RCT

Device or Material: Polyethylene tubes filled with Filtek Silorane (silorane-based resin composite), Filtek Silorane adhesive bond, Filtek Silorane primer, Filtek Supreme XT (Bis-GMA and DMA-based composite resin)

Route: Dorsal implants

Dose: NR

Frequency/Duration: Single administration

Response: Collagen fiber formation; Inflammatory infiltrate

Species (strain): Mice (Isogenic BALB/c)

Gender: Male, 6-8 weeks old, 15-20 grams

Number per group: Filtek Silorane group: n=30, Filtek Silorane adhesive bond group: n=30, Filtek Silorane primer group: n=30, Filtek Supreme XT group: n=30, Control group (empty tubes): n=15.

Observed adverse effects: At 21 days, "In one specimen of group V (Filtek Silorane adhesive bond) there was a well organized foreign body granuloma surrounding a material fragment that extruded to the circumjacent tissue." At 63 days, "In the semi-quantitative microscopic analysis there was no statistically significant difference ($p > 0.05$) among the groups at any of the periods according to the mean scores values obtained after analysis of collagen fiber formation and inflammatory infiltrate".

Timing of adverse effects: 7, 21, and 63 days

Factors that predict response: "Filtek Supreme XT is composed of nanoparticles and nanoclusters...which may reduce the interstitial space and, consequently, the amount of organic matrix capable of releasing methacrylates, thus causing less tissue irritation than conventional methacrylate-based resins. The biological response to dental restorative polymer composites is mediated by the release of uncured residual monomers. Methacrylate-free resin composite formulations have claimed to reduce unpolymerized residual mass." In the present in vivo study, this resin [Filtek Silorane] and its components alone (primer and adhesive bond) induced low-intensity connective tissue reactions. These responses were similar to those triggered by the empty tube (control) at all evaluation periods, demonstrating the low capacity of this material inducing unfavorable tissue reactions".

Source Citation: Hammad et al. (2011)⁶

Study Design: Prospective nonrandomized comparison study

Device or Material: Silicone tubes filled with Geristore Syringeable (Bis-GMA and methacrylate-based composite resin, includes HEMA), Grey mineral trioxide aggregate (GMTA), Retroplast (Bis-GMA and TEGDMA-based composite resin)

Route: Subcutaneous dorsal implants

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory infiltrate

Species (strain): Rat (Wistar, Albino)

Gender: Male, 3-4 months old, 300-350 grams

Number per group: n=30 each received an empty tube (control), one Geristore Syringeable-filled silicone tube, one GMTA-filled silicone tube, and one Retroplast-filled silicone tube.

Observed adverse effects: At 1 month, "Tukey's multiple comparisons test revealed a significant difference [in inflammatory infiltrates] between the control group and each of the other groups, the difference being most significant from Retroplast, followed by GMTA, then Geristore ($p < 0.05$ ". At 2 months, "Tukey's multiple comparisons test revealed a significant difference [in inflammatory infiltrates] between the control group and each of the other groups, the difference being most significant from Retroplast, followed by GMTA, then Geristore ($p < 0.05$ ". Retroplast was the least biocompatible of the three tested materials at 2 months, followed by Geristore then GMTA.

Timing of adverse effects: 1 week, 1 month and 2 months

Factors that predict response: "The initially severe inflammatory response to GMTA is most likely multifactorial...The factors include high pH and heat generated during the setting reaction; because the calcium oxide component, when mixed with water, generates calcium hydroxide in an exothermic reaction. Generation of inflammatory cytokines such as interleukin-1 and interleukin-6 contributes to the process." "Leaching of TEGDMA into the nearby humid connective tissue environment may explain the higher incidence of necrosis with Retroplast, especially at the initial assessment period, with the effects becoming milder as the toxic material is neutralised and removed by local lymphatic drainage." "The cytotoxicity of HEMA was found to be much less than that of TEGDMA, which in turn was less cytotoxic than Bis-GMA...This explains the relatively milder reaction to Geristore compared with Retroplast in this study." "All tested materials caused a persistent foreign body reaction with the macrophages and/or giant cells observed engulfing particles released from the implanted materials."

BF = bulk fill; Bis-EMA = Ethoxylated bisphenol A glycol dimethacrylate; Bis-GMA = Bisphenol A-glycidyl methacrylate; DMA = Dimethacrylate; HEMA = hydroxyethyl methacrylate; TEGDMA = Triethylene glycol dimethacrylate; UDMA = Dimethacrylate urethane; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Tx = treated; nTx = non-treated; Dose = mg/kg/day

Table 4: Dental Luting Cement - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Marcondes et al. (2016)⁸

Study Design: RCT: teeth were randomly assigned to cement

Device or Material: RelyX ARC conventional resin cement and self-adhesive resin cement RelyU100. Filtek Supreme XT composite resin used for restoration.

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response: Sensitivity; Complications

Patient characteristics (gender, mean age): 6 women with mean age of 47 years and 4 men with mean age of 46 years.

Number per group: 10 patients with 24 composite resin restorations with 12 restorations for each cement.

Observed adverse effects: No sensitivity or complications reported for either cement.

Timing of adverse effects:

Factors that predict response: A polymerization protocol using LED along with heat and pressure increased conversion of composite resins and improved composite properties.

LED = light-emitting diodes; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 5: Dental Luting Cement - Health Effects (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Mesquita et al. (2017)⁹

Study Design: Animal Study

Device or Material: 5 types of resin modified glass ionomer cement: Group CK (Crosslink Orthodontic Band Cement); Group RS (Resilience Light Cure Band Cement) Group RMO (RMO Band Cement), Group TP (Transbond Plus Light Cure Band), and Group C (Control-polyethylene). Of these, only RS and RMO have Bisphenol A glycerolate dimethacrylate (bis-GMA). TP does 2-hydroxy-1,3-dimethacryloxypropane.

Route: Subcutaneous

Dose: NR

Frequency/Duration: One implantation; data captured at 7, 15, or 30 days after implantation (5 rats per cement per timepoint, 5x5x3=75 total rats)

Response: At 7 days, three cements (RS, RMO and TP) had statistically significantly greater histopathological inflammatory response than the other two cements. However, the difference was not statistically significant at either 15 days or 30 days.

Species (strain): Rats, adult male Wistar

Gender: 75M

Number per group: 5

Observed adverse effects: inflammation response

Timing of adverse effects: 7 days

Factors that predict response: NR

Systemic Toxicity

Source Citation: Moilanen et al. (2014)¹⁰

Study Design: Animal Study

Device or Material: Triethylene glycol dimethacrylate (TEGDMA). Mice exposed were mated with mice unexposed.

Route: Oral

Dose: 0 or 0.01 or 0.1 or 1 mg/kg/day

Frequency/Duration: Daily dosage, 42 days for males, and 45-59 days for females

Response: No adverse fertility effects for males or females at any dose

Species (strain): CrI:CD1(ICR) mice

Gender: 100F, 100M

Number per group: 50

Observed adverse effects: None

Timing of adverse effects: NA

Factors that predict response: NR

Source Citation: Moilanen et al. (2013)¹¹

Study Design: Animal Study
Device or Material: bisphenol A glycidyl methacrylate (BisGMA)
Route: Oral
Dose: 0 or 0.008 or 0.08 or 0.8 mg/kg/day
Frequency/Duration: Daily dosage, 42 days for males, and 45-59 days for females
Response: No adverse fertility effects for males or females at any dose
Species (strain): Crl:CD1(ICR) mice
Gender: 100F, 100M
Number per group: 50
Observed adverse effects: None
Timing of adverse effects: NA
Factors that predict response: NR

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 6: Dental Adhesive, Bonding - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Gresnigt et al. (2012)¹⁴

Study Design: Randomized, split-mouth clinical study
Device or Material: Enamel Plus HFO (DMA) vs Miris2 (DMA)
Contact Duration: Mean observation period was 41.3 months.
Dose: After photo-polymerization of this layer for 40 seconds, a second increment of enamel shade was applied at the incisal area and photo-polymerized
Frequency/Duration: Mean 41 months
Response: Tooth failure due to severe discoloration in 1/48 for Miris2 and 0/48 for Enamel Plus HFO. No occurrence of secondary caries or endodontic complications in either group. Minor surface roughness in 2/45 for Miris2 and 1/39 for Enamel Plus HFO. Marginal discoloration in 1/45 for Miris2 and 0/39 for Enamel Plus HFO.
Patient characteristics (gender, mean age): 23 patients, mean age 52.4 years, 6 male, 17 female
Number per group: Ena-Bond-Enamel HFO: 48 teeth, Clearfil SE Bond-Miris2: 48 teeth).
Observed adverse effects: No endodontic complications were observed during the study (maximum 45.7 months). "Six teeth showed slight post-operative sensitivity (Enamel Plus HFO: n=2; Miris2: n=4) that disappeared after 1 week."
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Pinna et al. (2015)¹²

Study Design: Split-mouth RCT

Device or Material: Vertise Flow compared to Universal Dentine Sealant, Clearfil Protect Bond, and Flor-Opal Varnish.

Contact Duration: 12 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Hypersensitivity; Adverse events

Patient characteristics (gender, mean age): 46 patients with 116 hypersensitive teeth, 27 females and 19 males

Number per group: Number of treated teeth: Vertise Flow = 28, Universal Dentine Sealant = 27, Clearfil Protect Bond = 30, Flor-Opal Varnish = 31

Observed adverse effects: All materials reduced hypersensitivity but hypersensitivity increased in Vertise Flow treated patients by 12 weeks. Patients reported no adverse reactions to treatment.

Timing of adverse effects:

Factors that predict response: "Compared with the baseline, [Vertise Flow] showed the ability to significantly reduce the sensitivity immediately after the application, however lowering its efficiency within the 12-week post-treatments, as a possible loss of the resin sealing in dentine under oral fluids exposure." ... "A significant increase was observed in scores within the 12-week controls as a possible consequence of deterioration of the physical-mechanical properties of the resin cover in dentine."

Source Citation: Nowicka et al. (2016)¹³

Study Design: RCT (DMA vs no DMA)

Device or Material: Single Bond Universal (SBU) (has DMA)

Contact Duration: Single Bond Universal was applied to the exposed pulp and cavity walls for 20 s and light-cured for 10 s.

Dose: NR

Frequency/Duration: One-time

Response: On histological assessment of extracted teeth, the universal adhesive system exhibited nonsignificantly increased histological signs of pulpitis ($p > 0.05$) and a significantly weaker thin mineralized tissue layer ($p < 0.001$) compared with the calcium hydroxide group. No statistically significant difference in inflammatory response of the pulp between SBU and calcium hydroxide, however inflammatory markers were greater with SBU than in the no bonding group.

Patient characteristics (gender, mean age): N=17, age 19-30, gender NR

Number per group: 11 teeth in the adhesive group, 11 teeth in the calcium hydroxide, and 6 teeth in the control group

Observed adverse effects: Pulpitis, thinning of mineralized tissue layer, inflammation

Timing of adverse effects: Effects observed in extracted teeth 6 weeks after material application

Factors that predict response: NR

Source Citation: Patil et al. (2015)¹⁵

Study Design: RCT (all groups received DMA)

Device or Material: Group A-Gluma Desensitizer (GD)(has DMA), vs Group B-Gluma Comfort Bond + Desensitizer (GCBD) (has DMA) vs Group C-Single Bond Universal (SBU) (has DMA)

Contact Duration:

Dose: NR

Frequency/Duration: 3 weeks and 6 weeks after treatment

Response: "No adverse effects were observed in any of the subjects enrolled in the study"

Patient characteristics (gender, mean age): N=20, age 18-35, 12F and 8M

Number per group: 18 teeth

Observed adverse effects: None

Timing of adverse effects: NA

Factors that predict response: NA

Systemic Response/Toxicity

Source Citation: Nowicka et al. (2016)¹³

Study Design: RCT (DMA vs no DMA)

Device or Material: Single Bond Universal (SBU) (has DMA)

Contact Duration: Single Bond Universal was applied to the exposed pulp and cavity walls for 20 s and light-cured for 10 s.

Dose: NR

Frequency/Duration: One time

Response: "None of the patients in the SBU group reported any particular symptoms during the experimental time period"

Patient characteristics (gender, mean age): N=17, age 19-30, gender NR

Number per group: 11 teeth in the adhesive group, 11 teeth in the calcium hydroxide, and 6 teeth in the control group

Observed adverse effects: None

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Patil et al. (2015)¹⁵

Study Design: RCT (all groups received DMA)

Device or Material: Group A-Gluma Desensitizer (GD)(has DMA), vs Group B-Gluma Comfort Bond + Desensitizer (GCBD) (has DMA) vs Group C-Single Bond Universal (SBU) (has DMA)

Contact Duration:

Dose: NR

Frequency/Duration: 3 weeks and 6 weeks after treatment

Response: "No adverse effects were observed in any of the subjects enrolled in the study"

Patient characteristics (gender, mean age): N=20, age 18-35, 12F and 8M

Number per group: 18 teeth
Observed adverse effects: None
Timing of adverse effects: NA
Factors that predict response: NA

Bis-GMA = bisphenol A-glycidyl methacrylate; NA = not applicable; NR = not reported; Obs = observational; RCT = randomized controlled trial; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 7: Dental Adhesive, Bonding - Health Effects (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Nowicka et al. (2012)¹⁶

Study Design: Nonrandomized comparative study (three groups: two received DMA, and one did not)
Device or Material: AdheSE adhesive + Tetric Ceram restoration (the ASE group), or Adper Prompt L-Pop adhesive + Filtek Supreme restoration (the APLP group). Dycal liner +Amalgam control group
Route: Applied to prepared cavities in separate teeth, pulp capping
Dose: NR
Frequency/Duration: Single administration/40 days
Response: Histological assessment of teeth
Species (strain): 38 teeth from 3 health felines
Gender:
Number per group: 12 teeth per experimental group, 8 teeth for control group, plus 6 intact teeth
Observed adverse effects (brief): ASE: A majority of the specimens presented low-grade inflammatory pulp responses with tissue disorganization. One moderate inflammatory response. APLP: Pulp displayed lowgrade to moderate chronic inflammatory responses. Control: No moderately-intense inflammation or total tissue disorganization.
Timing of adverse effects: Seen at 40 days
Factors that predict response:

Source Citation: Taira et al. (2011)¹⁸

Study Design: Nonrandomized comparative study (six groups: all received DMA)
Device or Material: Clearfil SE Bond primer and CSE bond (dental adhesive, bonding), Dycal calcium hydroxide preparation used as a control. All teeth restored with Clearfil AP-X A3 resin composite
Route: direct pulp capping
Dose: NR
Frequency/Duration: Single administration/up to 112 days
Responses: pulp tissue disorganization; inflammatory cell infiltration; reparative dentin formation
Species (strain): Sprague Dawley rats

Gender: Male

Number per group: 62 total, 5 teeth assigned to each of 6 experimental groups.

Observed adverse effects (brief): Pulp tissue disorganization: no difference between experimental and control at 14 days. Inflammatory cell infiltration: no difference between experimental and control at 14 days. By 28 days, "histopathological evaluation of all groups at each observation period showed that no specimen exhibited severe inflammation of the pulp."

Timing of adverse effects:

Factors that predict response: "Severe pulp tissue disorganization and inflammatory cell infiltration observed in some specimens might result from the insufficient control of exudation of tissue fluid due to a large exposure site, inadequate polymerization of the bonding agents and severe irritation from cavity preparation. It has been reported that the unpolymerized components of adhesive resin systems showed more cytotoxicity to pulp cells than polymerized ones." Lack of these responses implies good polymerization of these compounds.

Source Citation: Suzuki et al. (2016)¹⁹

Study Design: Nonrandomized comparative study (four groups: all received DMA)

Device or Material: Clearfil SE Bond/Primer (CSP), Clearfil SE Bond/Bond (CSB), Dycal control; Clearfil AP-X restorative resin composite used on all teeth

Route: Direct pulp capping

Dose: NR

Frequency/Duration: Single administration/up to 112 days

Responses: pulp tissue disorganization; inflammatory cell infiltration

Species (strain): Sprague Dawley rats

Gender: Male

Number per group: 80 noncarious, upper (maxillary) first molars were treated with direct pulp capping

Observed adverse effects (brief): Normal pulpal tissue morphology was observed in almost all the specimens. In the specimens that showed formation of dentin bridges, a reorganized odontoblastic layer was seen beneath the reparative dentin. After day 14, three specimens (one in Group 1 [Clearfil SE Bond1/Primer] and two in control group) exhibited mild-to-moderate [pulp tissue disorganization and inflammatory cell infiltration]. However, after days 56 and 112, none of the specimens exhibited [pulp tissue disorganization and inflammatory cell infiltration]."

Timing of adverse effects: 14 days

Factors that predict response: "Although it is well-known that un-polymerized resin monomer can cause pulpal inflammation; however, polymerized resin monomers do not cause irritation of the pulp tissue. Therefore, we speculate that the soft-tissue hybrid layer functions as a protective membrane for the pulp tissue."

Source Citation: dos Santos et al. (2014)¹⁷

Study Design: Nonrandomized comparative study (four groups: 3 received DMA and 1 did not)

Device or Material: 4 types of material: C (polyethylene), TCC (Transbond Color Change), QS (Quick-Cure), and EB (Eagle Bond). The latter 3 all have both bis-GMA and TEG_DMA (chemicals/materials of interest)

Route: Subcutaneous

Dose: NR

Frequency/Duration: One implantation; data captured at 7, 15, or 30 days after implantation (2 rats per cement per timepoint, 2x4x3=24 total rats)

Response: "All the groups presented a small amount of inflammatory infiltrate, circulatory alterations (edema), and granulation tissue at all experimental time intervals, showing gradual reduction with time, without statistically significant differences among them."

Species (strain): Rats, adult male Wistar

Gender: 24M

Number per group: 6

Observed adverse effects: Inflammatory infiltrate, circulatory alterations (edema), and granulation tissue

Timing of adverse effects: Reduction in effects between 7 and 30 days

Factors that predict response: NR

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 8: Dental Restoration - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Schmidt et al. (2021)²⁵

Study Design: RCT

Device or Material: Guttapercha (GP); Biodentine (BD); Clearfil Protect Bond (PB); Clearfil SE Bond 2 (SE)

Contact Duration: 8 weeks

Dose: NR

Frequency/Duration: Single administration

Response: IL-1 β ; IL-6; CRP; IFN- γ ; TIMP-2; TIMP-1; MMP-8

Patient characteristics (gender, mean age): GP and BD: 8 male, 3 female median age 26 years; PB and SE 7 male, 3 female, median age 23.5 years. Each study participant presented two posterior teeth with deep primary carious lesions

Number per group: GP and BD n = 11, PB and SE n = 10. 42 teeth total

Observed adverse effects: Pro-inflammatory cytokine and tissue homeostasis proteins were measured in cavity rinsing solutions at baseline and at 8 weeks after treatment. For each intervention group (GP, BD, PB, SE) the changes remained significant in all groups for IL-1 β ($p < 0.05$), whereas for IL-6 and CRP concentrations at visits 1 and 2 were significantly reduced in GP and BD (IL-6; CRP $p < 0.05$), but were not significantly different with PB and SE (IL-6, $p \geq 0.068$; CRP $p \geq 0.09$). MMP-8 (a tissue hemostasis protein) showed a significant increase in concentration in visit 2 compared to visit 1 in all intervention groups.

Timing of adverse effects: Pro-inflammatory cytokines were reduced after treatment indicating these materials did not initiate a local inflammatory response after treatment.

Factors that predict response: "The decrease in the concentration of CRP, IL-1 β , and IL-6 between visit 1 and visit 2 can be interpreted as a decline in inflammation after the reduction of the microbial challenge by [selective caries therapy]."

Source Citation: Askari et al. (2019)²⁴

Study Design: RCT

Device or Material: Single Bond Universal dentin bonding agent compared with bee glue and distilled water placebo

Contact Duration: 90 days

Dose: NR

Frequency/Duration: Single administration

Response: Dentin hypersensitivity (DH)

Patient characteristics (gender, mean age): Bonding agent: 49 years, 15 female, 8 male; 10% bee glue: 47 years, 19 female, 8 male; 30% bee glue: 46 years, 16 female, 6 male; placebo: 46 years, 17 female, 7 male.

Number per group: Bonding agent n = 23, 10% bee glue n = 27, 30% bee glue n = 22, placebo n = 24.

Observed adverse effects: "At 60 days, there was no significant difference between the application of Single Bond Universal and 10% and 30% propolis [bee glue] ($p > .05$)." "At 90 days, approximately half of the [Bonding agent group] patients (53%) had mild pain while 47% had no pain" in response to tactile stimulus. At 90 days, mean reduction in DH was 77.0% for 10% bee glue, 84.0% for 30% bee glue, 80.5% for Bonding agent, and 31.0% for placebo groups.

Timing of adverse effects: 1 day, 7 days, 14 days, 21 days, 60 days, and 90 days

Factors that predict response: Shrinkage of methacrylate-based composite resins may be responsible for dentin hypersensitivity.

Source Citation: Ergin et al. (2018)³⁵

Study Design: RCT

Device or Material: Adper Single Bond 2 etch and rinse adhesive + Filtek-Z550 resin composite compared with Gluma2 Bond etch and rinse adhesive + Charisma-Diamond resin composite

Contact Duration: Mean 43.4 months (range 37-48 months)

Dose: NR

Frequency/Duration: Single administration

Response: Periodontal response

Patient characteristics (gender, mean age): 6 male and 17 female with a maxillar anterior midline or multidiastema problem. Mean age 31.27 years.

Number per group: Filtek-Z550 group: n=10 (37 teeth), Charisma-Diamond group: n=13 (39 teeth)

Observed adverse effects: "At 4 years recall, little plaque accumulation without gingival inflammation and pocket development were observed on 4 Filtek-Z550 and three Charisma-Diamond restorations... no significant differences were observed between [the] two groups during 4 years ($p > 0.05$)."

Timing of adverse effects: 1 year, 2 years, 3 years, and 4 years

Factors that predict response: "Plaque accumulation on composite resin surfaces is greater than other esthetic restorative materials. In this study, although the margins of the restorations were placed slightly below the gingival crest to obtain a natural appearance, accurate application of composite resin material and polishing of all composite surfaces might reduce their impact on adjacent oral tissues."

Source Citation: van Dijken et al. (2017)²³

Study Design: RCT

Device or Material: els resin composite + cmf etch and rinse adhesive compared with els resin composite + AdheSE One F self-etching adhesive

Contact Duration: 6 years

Dose: NR

Frequency/Duration: Single administration

Response: POS; Caries formation

Patient characteristics (gender, mean age): 34 male and 33 female with class II carious lesions. Mean age 53 years, range 29-82 years.

Number per group: cmf group: n=67 (72 teeth), ASE group: n=67 (67 teeth)

Observed adverse effects: "Three molar teeth (1 cmf, 3 ASE) showed post-operative sensitivity during the first 3 weeks for temperature changes and occlusal forces." "Five of seven caries lesions were observed in high caries risk participants and eight of eleven fractures (cusp and material) occurred in bruxing participants."

Timing of adverse effects: 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years

Factors that predict response: "The clinical handling characteristics, estimated as rather poor during the placement of the restorations, may have resulted in an inferior wetting of the cavity explaining partly the higher failure rate. Also an aging effect of the interfacial adhesive bond may have influenced the outcome."

Source Citation: Celik et al. (2017)²⁶

Study Design: Prospective nonrandomized split-mouth comparison study

Device or Material: Filtek TM Z250 resin composite + Clearfil SE bond, Dyract XP compomer resin + Prime & Bond NT bond, Fuji IX GP capsule GIC, Cavex Avalloy amalgam

Contact Duration: 21 days

Dose: NR

Frequency/Duration: Single administration

Response: IL-6 concentration; IL-8 concentration; TNF- α concentration; GCF volume; Loe and Silness GI; Loe and Silness PI

Patient characteristics (gender, mean age): 21 male and 39 female with a class V carious lesion associated with gingiva. Range 25-40 years.

Number per group: Composite group: n=15, Compomer group: n=15, Cement group: n=15, Amalgam group: n=15. Split-mouth control (contralateral tooth intact enamel surface): n=15 in all groups.

Observed adverse effects: At 21 days, GI was significantly higher in the composite group compared to control ($p<0.05$). GCF volume was significantly higher in composite, compomer and amalgam groups compared to control at 21 days ($p<0.05$). IL-6 concentration was significantly higher in compomer, cement, and amalgam groups compared to control at 21 days ($p<0.05$). IL-8 concentration was significantly higher in the composite, compomer, and amalgam groups compared to control at 21 days ($p<0.05$). At 21 days, TNF- α concentration was significantly higher in the Compomer and Cement groups ($p<0.05$).

Timing of adverse effects: 7 days and 21 days

Factors that predict response: "Release of inflammatory mediators in GCF might be caused not only to the bacterial plaque but also compounds released from the materials." "Difference in the surface characteristics of GIC and its acidic character might have affected the TNF- α level."

Source Citation: Corral et al. (2016)²²

Study Design: RCT: Single-center, split-mouth, placebo-controlled triple blinded

Device or Material: Adper Single Bond 2 etch-and-rinse adhesive + Filtek Z250 resin composite, Adper Silorane self-etch adhesive + Filtek Silorane P90 resin composite, Adper Single Bond 2 + Filtek Z250 + OA desensitizing agent, Adper Silorane adhesive + Filtek Silorane P90 + OA desensitizing agent

Contact Duration: 360 days

Dose: NR

Frequency/Duration: Single administration

Response: Dentin hypersensitivity to tactile stimuli; Dentin hypersensitivity to evaporative stimuli

Patient characteristics (gender, mean age): 15 male and 16 female with noncarious cervical lesions and moderate to severe dentin hypersensitivity (VAS score > 40 mm). Mean age 46.8 years, range 24-66 years.

Number per group: 31 patients total. Z250 group: NR (31 teeth), P90 group: NR (31 teeth), Z250+OA group: NR (31 teeth), P90+OA group: NR (31 teeth)

Observed adverse effects: "After the intervention, all treatment groups showed a reduction in their [tactile and evaporative] VAS scores." At 360 days, mean tactile VAS scores were significantly lower in Z250+OA (1.16) and P90+OA (0.75) groups compared to Z250 (2.97) and P90 (2.90) groups ($p < 0.001$). At 360 days, mean evaporative VAS scores were significantly lower in Z250+OA (0.94) and P90+OA (0.55) groups compared to Z250 (2.61) and P90 (2.88) groups ($p < 0.001$).

Timing of adverse effects: 30, 60, 90, 180, and 360 days

Factors that predict response: "The enhanced reduction in dentin hypersensitivity produced by the desensitizing agent in terms of intensity and absolute risk could be explained by the mechanisms of action of the different components of this desensitizing agent. The agent contained potassium oxalate 0.5%, potassium nitrate 4%, and potassium fluoride 4%, which in acidic pH medium would raise the local calcium ion concentration, resulting in the precipitation of calcium oxalate and calcium fluoride crystals. Both types of mineral deposits could occlude exposed dentinal tubules."

Source Citation: Marcondes et al. (2016)⁸

Study Design: RCT: teeth were randomly assigned to cement

Device or Material: RelyX ARC conventional resin cement + Filtek Supreme XT resin composite compared with RelyU100 self-adhesive resin cement + Filtek Supreme XT resin composite

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response: POS; Complications

Patient characteristics (gender, mean age): 6 women with mean age of 47 years. 4 men with mean age of 46 years.

Number per group: 10 patients with 24 composite resin restorations with 12 restorations for each cement.

Observed adverse effects: No sensitivity or complications reported for either cement.

Timing of adverse effects: 12 months

Factors that predict response: A polymerization protocol using LED along with heat and pressure increased conversion of composite resins and improved composite properties.

Source Citation: Stefanovi et al. (2016)²⁷

Study Design: Prospective nonrandomized comparison study

Device or Material: GC Fuji Plus GIC, Cegal NV zinc phosphate cement, Harvard zinc polycarboxylate cement, Extracap D caps amalgam, Beautifil restorative, Tetric EvoCeram resin composite

Contact Duration: 30 Days

Dose: NR

Frequency/Duration: Single administration

Response: IL-9 concentration

Patient characteristics (gender, mean age): 90 patients with approximal caries on frontal and side teeth. Gender NR, age range 18-70 years.

Number per group: Light weight group (fillings less than 0.50 grams): n=30, Medium weight group (0.50–1.00 gram fillings): n=30, and Heavy weight group (fillings greater than 1.00 grams): n=30.

Observed adverse effects: At 30 days, the Light weight group had a higher average IL-9 concentration in GCF (47) compared to the Medium weight (21) and Heavy weight (17) groups (p value NR). At 30 days, patients that received Tetric EvoCeram fillings had the highest average IL-9 concentration in GCF (117), followed by Beautifil (78), GC Fuji Plus (40), Cegal NV (30), Extracap D caps (18), and Harvard (3) fillings. At 30 days, the only significant difference in the average IL-9 concentration was between the Tetric EvoCeram fillings and Harvard fillings ($p < 0.01$).

Timing of adverse effects: 15 and 30 days

Factors that predict response: NR

Source Citation: Sakallio et al. (2015)²⁸

Study Design: Prospective nonrandomized split-mouth comparison study

Device or Material: VMK 95 ceramic, Wiron 99 metal alloy, Filtek Z250 resin composite, Filtek Z250 amalgam

Contact Duration: 4 weeks

Dose: NR

Frequency/Duration: Single administration

Response: IL-1 α , IL-1 β , Substance P (SP) n, Neurokinin A (NKA), Calcitonin-gene related peptide (CGRP), Prostaglandin E2 (PGE2), GCF volume, Loe and Silness GI, Loe and Silness PI, Probing pocket depth (PPD)

Patient characteristics (gender, mean age): 14 male each with 1 molar tooth suitable for metal-ceramic crown restoration, 2 premolar teeth with mesioocclusal or disto-occlusal caries suitable for composite and amalgam restorations, and 1 tooth without dental caries or any endodontic problem. Age range 35-45 years.

Number per group: Ceramic group: n=14, Metal group: n=14, Composite group: n=14, Composite control (unrestored enamel surface) group: n=14, Amalgam group: n=14, Amalgam control (unrestored enamel surface) group: n=14, NC group (unrestored enamel surface): n=14

Observed adverse effects: Four weeks following restorations, there were no significant differences in median values of PI, GI, and PPD between the 7 groups ($p > 0.05$). Also at 4 weeks, median GCF concentrations of IL-1 α , IL-1 β , CGRP, and PGE2 were not significantly different between groups ($p > 0.05$). Median GCF volume was significantly different between the NC group (29.0) and the six other groups, with the Amalgam group (146.5) having the highest GCF volume, followed by Amalgam control (72.50), Composite (72.50), Ceramic (70.50), Metal (56.50), Composite control (45.0) groups. "Of the neuropeptides, SP and NKA demonstrated statistically significant differences among the study groups ($p = 0.000$). SP levels of the ceramic, amalgam and composite groups were higher than that of the enamel [NC] group ($p < 0.05$)". "NKA was higher in the ceramic, composite and amalgam groups than in the enamel [NC] group ($p < 0.05$)".

Timing of adverse effects: 4 weeks

Factors that predict response: "these study results suggest that ceramic, composite and amalgam materials may trigger local neuropeptide production in periodontium even in the absence of plaque-induced reactions. In this respect, they may also increase susceptibility to periodontal inflammatory reactions by stimulating periodontal neurogenic inflammation."

Source Citation: Nowicka et al. (2015)³⁰

Study Design: Prospective nonrandomized comparison study

Device or Material: Calcipast calcium hydroxide paste + Life calcium hydroxide cavity liner + Single Bond Universal adhesive + Filtec Ultimate resin composite, ProRoot White MTA + Ketac, Molar GIC, Biodentine, Single Bond Universal adhesive + Filtec Ultimate resin composite

Contact Duration: 6 weeks

Dose: NR

Frequency/Duration: Single administration for groups with resin composite. MTA and Biodentine groups had additional restoration 7 days after initial treatment.

Response: Dentin thickness, Reparative dentin formation

Patient characteristics (gender, mean age): 21 patients with scheduled extraction of caries-free, intact, maxillary and mandibular third molars for orthodontic or surgical purposes. Gender NR, mean age 26 years, range 19-32 years.

Number per group: Calcipast group: NR (11 teeth), MTA group: NR (11 teeth), Biodentine group: NR (11 teeth), Filtec group: NR (11 teeth).

Observed adverse effects: At 6 weeks, the Calcipast, MTA, and Biodentine groups "actively initiated the formation of reparative dentin in each tooth [whereas the Filtec group] was significantly less active and induced the formation of" four small dentin bridges. At 6 weeks, dentin thickness in the Calcipast, MTA, and Biodentine groups was significantly greater than in the Filtec group; dentin thickness was not significantly different between the Calcipast, MTA, and Biodentine groups.

Timing of adverse effects: 6 weeks

Factors that predict response: "Therefore, in consideration of the fact that bonding of resins to the underlying tissue deteriorates over time in the absence of a dentin bridge, which increases the risk of pulp infection, the use of these preparations [directly] on exposed pulp should be carefully considered."

Source Citation: Pallesen et al. (2015)²⁰

Study Design: RCT

Device or Material: Dycal calcium hydroxide cement + Scotchbond adhesive + Concise Enamel Bond + P10 resin composite, Dycal calcium hydroxide cement + Scotchbond adhesive + Concise Enamel Bond + P30 resin composite, Dycal calcium hydroxide cement + Scotchbond adhesive + Concise Enamel Bond + Miradapt resin composite

Contact Duration: 30 years

Dose: NR

Frequency/Duration: Single administration

Response: Pain, POS

Patient characteristics (gender, mean age): 30 patients with class II carious lesions in 99 teeth. 9 male (30 teeth) and 21 female (69 teeth). Mean age 29.6 years, range 20-43 years.

Number per group: P10 group: NR (33 teeth), P30 group: NR (33 teeth), Miradapt group: NR (33 teeth)

Observed adverse effects: "Two restorations [in the P30 group]...in a male and female participant, were replaced after 7 and 11 months, respectively, because of persisting nonacceptable pain symptoms, caused by occlusal forces and in lesser degree by temperature changes. One of these restorations was replaced by amalgam after which the symptoms disappeared, while the other tooth received an endodontic treatment." "Most of the [POS] symptoms disappeared after 3-4 weeks, for two teeth the symptoms disappeared after 2-3 months, while after two years 3 participants reported still mild, but acceptable for the participants, symptoms of 4 teeth (2 P10, 1 P30, 1 Miradapt). No remaining POS was reported at the following recalls."

Timing of adverse effects: 2, 3, 5, 10, 20, and 30 years

Factors that predict response: "Postoperative [sensitivity] symptoms can occur partly by insufficient sealing of the dentin and restoration margins or by too effective adhesive bonding to enamel and dentin." "A high frequency

of the included cavities had a proximal cervical marginal adaption localized in dentin. An insufficient cervical adaptation may therefore, partly explain the POS frequency.”

Source Citation: Patil et al. (2015)¹⁵

Study Design: Double-blind RCT

Device or Material: Gluma Desensitizer sealant (GD) glutaraldehyde and hydroxyl ethyl methacrylate [HEMA] primer), Gluma Comfort Bond adhesive + GD (GCBD), Single Bond Universal adhesive (SBU)

Contact Duration: 6 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Dentin hypersensitivity to tactile stimuli, Dentin hypersensitivity to evaporative stimuli, Dentin hypersensitivity to thermal stimuli

Patient characteristics (gender, mean age): 54 teeth in 20 patients in the age range of 18-35 years (12 females, 8 males). Patients had a chief complaint of dentinal hypersensitivity and seeking treatment.

Number per group: 18 teeth in each group

Observed adverse effects: All three groups showed a significant reduction in dentinal hypersensitivity ($P < 0.05$) compared to baseline at all time intervals. Statistically, significant differences were noted between GD and SBU; between GCBD and SBU in all testing parameters. Between GD and GCBD no significant difference was noted

Timing of adverse effects: 3 and 6 weeks

Factors that predict response: “The one-bottle self-etching adhesive (SBU) tested in the current study did not perform better than GD and GCBD. This might be due to the fact that single-bottle self-etching adhesives contain mixtures of hydrophilic and less hydrophobic monomers and thus, are permeable to water after application to the dentinal surface and thus may not penetrate deeper into the dentinal tubules.”

Source Citation: Chandwani et al. (2014)²⁹

Study Design: Prospective nonrandomized comparison study

Device or Material: DeTrey Conditioner 36 etch and rinse adhesive + Prime & Bond NT bond + Dispersalloy amalgam compared with DeTrey Conditioner 36 etch and rinse adhesive + Prime & Bond NT bond + SureFil resin composite

Contact Duration: 7 days

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory response (Inflammatory infiltrate, necrosis), Fibrosis

Patient characteristics (gender, mean age): 30 patients with scheduled extraction of 100 caries-free, intact, maxillary and mandibular premolars for orthodontic treatment. Gender NR, age range 14-25 years.

Number per group: 24 hr Amalgam group: NR (25 teeth), 24 hr Composite group: NR (25 teeth), 7 day Amalgam group: NR (25 teeth), 7 day Composite group: NR (25 teeth)

Observed adverse effects: There was not a significant difference in inflammatory response between 24 hr Amalgam and Composite groups ($p = 1.00$). For the 7 day Amalgam group, 15 teeth (60%) had a mild inflammatory response and 10 teeth (40%) showed moderate to severe inflammatory responses; fibrosis was seen in 8 teeth and necrosis was observed in 3 teeth. For the 7 day Composite group, 7 teeth (28%) had a mild inflammatory response, 12 teeth (48%) showed a moderate inflammatory response, and 6 teeth (24%) had a severe inflammatory response; necrosis was seen in 8 teeth and fibrosis was not observed.

Timing of adverse effects: 24 hours, 7 days

Factors that predict response: "The evidence of fibrosis in 32% of teeth restored with amalgam is a proof that the healing potential of the pulp was increased, which could be attributed to the inertness of amalgam and its better sealing properties". "However, no such evidence of healing was evident in any tooth restored with composite...This can be attributed to the marginal leakage which is the result of polymerization shrinkage of composite resin, bacterial penetration beneath composite restoration, its dimensional instability in the oral environment, curing method, restoration technique, and to some extent cell death through the seepage of uncured monomer in the pulp, and to their sealing and adhesion characteristics with cavity walls as well."

Source Citation: Rocha Gomes Torres et al. (2014)³²

Study Design: RCT: Single-center, split-mouth, double-blinded

Device or Material: Futurabond M UDMA-based self-etching adhesive + GrandioSO BisGMA and TEGDMA-based resin composite compared with Futurabond M self-etching adhesive + GrandioSO Heavy Flow BisGMA and TEGDMA-based resin composite

Contact Duration: 2 years

Dose: NR

Frequency/Duration: Single administration

Response: POS

Patient characteristics (gender, mean age): 47 patients with carious lesions, fractures, or cosmetic class II restorations of first, second, or permanent molars. Gender and age NR.

Number per group: Conventional group: n=47 (47 teeth), Heavy Flow group: n=47 (47 teeth)

Observed adverse effects: "Chi-square test was...performed in order to compare the two materials [Conventional and Heavy Flow groups] in relation to the different parameters analysed after 6, 12 and 24 months and no significant differences were observed between the two materials for all parameters analysed at each recall."

Timing of adverse effects: 6 months, 1 year and 2 years

Factors that predict response: "Polymerization shrinkage can cause flaws in the tooth-restoration interface, leading to microleakage, marginal discolouration, recurrent caries, postoperative sensitivity and enamel fractures."

Source Citation: Beck et al. (2014)³¹

Study Design: RCT: Single-center, single-blinded

Device or Material: Dycal calcium hydroxide paste + Conditioner 36 etch and rinse adhesive + Prime & Bond NT bond + Ceram X mono resin composite compared with Dycal calcium hydroxide paste + Conditioner 36 etch and rinse adhesive + OptiBond Solo Plus bond + Tetric Ceram resin composite

Contact Duration: 1 year

Dose: NR

Frequency/Duration: Single administration

Response: Pain, POS

Patient characteristics (gender, mean age): 198 male, 255 female and 3 sex-unknown patients with class I or II carious lesions. Mean age 33.96 years, median age 30.47 years.

Number per group: Ceram X group: n=226, Tetric Ceram group: n=230

Observed adverse effects: At 1 year, patient sensitivity/pain was not reported in the Ceram X or Tetric Ceram groups.

Timing of adverse effects: 1 year

Factors that predict response: NR

Source Citation: Popoff et al. (2014)²¹

Study Design: RCT: Single-center, single-blinded

Device or Material: Magic Acid Gel + Adper SE Plus Self-Etch Adhesive + DMA-based Filtek P60 Posterior Restorative resin composite + Enhance System Polish compared with Magic Acid Gel + P90 System Adhesive Self-Etch Primer + P90 System Adhesive Bond + Silorane-based Filtek P90 Low Shrink Posterior Restorative + Enhance System Polish

Contact Duration: 2 years

Dose: NR

Frequency/Duration: Single administration

Response: POS

Patient characteristics (gender, mean age): 34 patients with 100 defective class I or II methacrylate-based composite resin restorations on premolars and molars. Age range 18–56 years.

Number per group: DMA group: NR (50 teeth), Silorane group: NR (50 teeth)

Observed adverse effects: post-operative sensitivity was not reported at any recall (6 months, 1 year, and 2 years) for both DMA and Silorane groups.

Timing of adverse effects: 6 months, 1 years, and 2 years

Factors that predict response: "At 2-year follow-up, the same good performance was observed for all composites, possibly because resin-based agents may provide pulp protection as long as the dentin is sealed by hydrophilic resins."

Source Citation: Silva et al. (2013)³⁷

Study Design: Prospective single-arm study

Device or Material: 37% phosphoric acid gel + Single Bond adhesive system + Charisma resin composite

Contact Duration: 30 days

Dose: NR

Frequency/Duration: Single administration

Response: Blood cell extravasation, Multinucleated giant cell presence, POS

Patient characteristics (gender, mean age): Patients with scheduled extraction of caries-free, intact, first premolars for orthodontic purposes. Gender NR, mean age NR.

Number per group: 1 day group: NR (6 teeth), 30 day group: NR (6 teeth)

Observed adverse effects: "All patients were asymptomatic postoperatively (1–30 days)." On day 1, there was "acute inflammation of the pulp tissue underlying the capping and by disorganization of the odontoblast layer near the exposure site". "Failures in adhesion between the layers of the adhesive system were observed in samples at 30 days. In these cases, red blood cells and plasma extravasated between the layers of the adhesive system or the first layer of adhesive applied to pulp tissue multinucleated giant cells were frequent along the adhesive layer".

Timing of adverse effects: 1 day and 30 days

Factors that predict response: "in the case of direct pulp exposure, the appropriate or more biocompatible material would be the one that, in addition to meeting the general requirements prescribed for dental materials, has a minimum level of waste release and is easily degraded by local defense cells. Thus, the risk of introducing

chemical compounds or by-products into the bloodstream should be considered in cases of dental pulp exposure.”

Source Citation: Strober et al. (2013)³³

Study Design: RCT

Device or Material: Clearfil SE Bond self-etching dentin bonding agent + Herculite Ultra resin composite compared with Vitrebond Light Cure Glass Ionomer Liner/Base + Clearfil SE Bond self-etching dentin bonding agent + Herculite Ultra-resin composite

Contact Duration: 4 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Air-stimulated hypersensitivity, Cold-stimulated hypersensitivity, Patient-reported hypersensitivity

Patient characteristics (gender, mean age): 339 patients with one or more unrestored posterior teeth with class I or II carious lesions. Gender “1.5 female-to-male ratio”, Age range 15–60 years.

Number per group: Liner group: n=168, No liner group: n=171

Observed adverse effects: At 1 week, there was no significant difference in cold-stimulated hypersensitivity, air-stimulated hypersensitivity, or patient-reported hypersensitivity between liner and no liner groups. At 4 weeks, there was no significant difference in cold-stimulated hypersensitivity, air-stimulated hypersensitivity, or patient-reported hypersensitivity between liner and no liner groups.

Timing of adverse effects: 1 week and 4 weeks

Factors that predict response: “Our results led to the conclusion that...the 341 restorations (333 participants at four weeks), there was no evidence to support the use of an RMGI liner in moderate-depth lesions (mean greatest depth, 3.9 mm).”

Source Citation: Ghavamnasiri et al. (2012)³⁴

Study Design: RCT

Device or Material: 35% phosphoric acid etch and rinse primer + Prime & Bond NT adhesive + Clearfil AP-X resin composite compared with Clearfil SE self-etching primer + Clearfil SE Bond adhesive + Clearfil AP-X resin composite

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response: Air-stimulated POS

Patient characteristics (gender, mean age): 23 patients with 76 class V carious lesions located in maxillary and mandibular premolars. Age range 25–55 years.

Number per group: Prime & Bond group: NR (38 teeth), Clearfil group: NR (38 teeth)

Observed adverse effects: At 2 days, post-operative sensitivity in the Prime & Bond (38.5%) and Clearfil (29.7%) groups were not significantly different ($p=0.426$). At 7 days, post-operative sensitivity in the Prime & Bond (43.6%) and Clearfil (27.0%) groups were not significantly different ($p=0.134$). At 14 days, post-operative sensitivity in the Prime & Bond (43.6%) and Clearfil (24.3%) groups were not significantly different ($p=0.079$). At 30 days, post-operative sensitivity in the Prime & Bond (48.7%) and Clearfil (27.0%) groups were significantly different ($p=0.049$). At 3 months, post-operative sensitivity in the Prime & Bond (30.8%) and Clearfil (20.0%) groups were not significantly different ($p=0.293$). At 6 months, post-operative sensitivity in the Prime & Bond (20.5%) and Clearfil (18.2%) groups were not significantly different ($p=0.805$). At 12

months, post-operative sensitivity in the Prime & Bond (15.4%) and Clearfil (20.0%) groups were not significantly different ($p=0.619$).

Timing of adverse effects: 2 days, 7 days, 14 days, 30 days, 3 months, 6 months, and 12 months

Factors that predict response: "post-operative sensitivity associated with removal of the smear layer and smear plugs is reduced when non-rinsing adhesives are used".

Source Citation: Gresniqt et al. (2012)¹⁴

Study Design: Randomized, split-mouth clinical study

Device or Material: Ena-Bond adhesive + Enamel Plus HFO micro-hybrid composite compared with Clearfil SE Bond adhesive and Miris2 micro-hybrid composite. The micro-hybrid composites and Clearfil SE Bond contain bis-GMA

Contact Duration: Mean observation period was 41.3 months.

Dose: NR

Frequency/Duration: Single administration

Response: Complications, POS

Patient characteristics (gender, mean age): 23 patients, mean age 52.4 years, 6 male, 17 female

Number per group: Ena-Bond-Enamel HFO: 48 teeth, Clearfil SE Bond-Miris2: 48 teeth.

Observed adverse effects: No endodontic complications were observed during the study (maximum 45.7 months). "Six teeth showed slight post-operative sensitivity (Enamel Plus HFO: $n=2$; Miris2: $n=4$) that disappeared after 1 week."

Timing of adverse effects: Mean observation period was 41.3 months.

Factors that predict response: NR

Source Citation: Perdigao et al. (2012)³⁶

Study Design: Randomized, split-mouth clinical study

Device or Material: Adper Easy Bond self-etch adhesive + Filtek, Supreme Plus resin composite, Adper Scotchbond SE self-etch adhesive + Filtek, Supreme Plus resin composite, Adper Scotchbond Multi-Purpose etch and rinse adhesive + Filtek, Supreme Plus resin composite, Adper Single Bond Plus etch and rinse adhesive + Filtek, Supreme Plus resin composite

Contact Duration: 18 months

Dose: NR

Frequency/Duration: Single administration

Response: POS

Patient characteristics (gender, mean age): 39 patients with 125 class V noncarious cervical lesions without undercuts. Mean age 47.6 years, range 22–78 years.

Number per group: Easy Bond group: NR (34 teeth), Multi-Purpose group: NR (29 teeth), Scotchbond SE group: NR (30 teeth), Single Bond group: NR (32 teeth).

Observed adverse effects: At 1 week, post-operative sensitivity was reported in 0/34 teeth in the Easy Bond group, 0/30 teeth in the Scotchbond SE group, 0/29 teeth in the Multi-Purpose group, and 0/32 teeth in the Single Bond group. At 6 months, post-operative sensitivity was reported in 1/28 teeth (3.6%) in the Easy Bond group, 1/26 teeth (3.8%) in the Scotchbond SE group, 1/26 teeth (3.8%) in the Multi-Purpose group, and 1/27 teeth (3.7%) in the Single Bond group. At 18 months, post-operative sensitivity was reported in 2/26

teeth (7.7%) in the Easy Bond group, 2/22 teeth (9.1%) in the Scotchbond SE group, 2/22 teeth (9.1%) in the Multi-Purpose group, and 2/24 teeth (8.3%) in the Single Bond group.

Timing of adverse effects: 1 week, 6 months, and 18 months

Factors that predict response: NR

Source Citation: Maserejian et al. (2014)⁴¹

Study Design: RCT

Device or Material: Dispersalloy amalgam, Revolution BisGMA-based resin composite and/or Ultraseal XT BisGMA and UDMA sealant, Dyract AP TMA and UDMA-based compomer resin, Z100 Composite BisGMA and TEGDMA-based resin composite

Contact Duration: 5 years

Dose: NR

Frequency/Duration: Single administration

Response: WBC distribution, T-cell activation, B-cell activation, Neutrophil function, Monocyte function, CD4 expression, CD8 expression

Patient characteristics (gender, mean age): 59 patients with preventive, primary, or permanent teeth restorations. Gender NR, age range 6-10 years.

Number per group: 29 total patients in Amalgam groups: Amalgam primary teeth and Amalgam permanent teeth groups. Revolution preventive group: n=43-53, Dyract primary teeth group: n=43-53, Z100 permanent teeth group: n=43-53

Observed adverse effects: "Using repeated measures of immune function over the entire 5-year follow-up in a multivariable model, associations between the present number of resin-composite surfaces and immune function changes were generally of negligible magnitude". At 5 years, the Amalgam permanent teeth group showed a significant decrease in B-cell activation compared to baseline values (%CD69 $\beta=-2.1$, 95% CI:-3.8,-0.4; %CD23 $\beta=-3.8$, 95% CI:-6.2,-1.4). At 5 years, there were no significant difference in assessed parameters for the Amalgam primary teeth group. At 5 years, the Revolution preventive group showed a significant increase in total WBC count ($\beta=0.2$, 95% CI:0.03,0.3) and decrease in neutrophil function ($\beta=-0.2$, 95% CI:-0.4,-0.04) compared to baseline values ($p=0.02$). For the Dyract primary teeth group, there was a significant increase in monocyte function ($\beta=1.1$, 95% CI:0.1,2.0) at 5 years compared to baseline ($p=0.02$). At 5 years, the Z100 permanent teeth group showed a significant increase in B-cell activation compared to baseline values (%CD69 $\beta=1.7$, 95% CI:0.6,2.7; %CD23 $\beta=2.2$, 95% CI:0.5,4.0). "Overall, results of this exploratory investigation showed no overt immune function alterations associated with resin-composites."

Timing of adverse effects: 6 months, 12 months, 18 months, and 5 years

Factors that predict response: NR

Bis-GMA = Bisphenol A-glycidyl methacrylate; CD = cluster of differentiation; CRP = C-reactive protein; DMA = Dimethacrylate; Dose = mg/kg/day; GCF = Gingival crevicular fluid; GI = Gingival index; GIC = Glass ionomer cement; IFN = Interferon; IL = Interleukin; MTA = Mineral trioxide aggregate; MMP = matrix metalloproteinase; NA = not applicable; NC = negative control; NR = not reported; Obs = observational; OA = oxalic acid; PI = Plaque index; POS = Post-operative sensitivity; R = reliable; RCT = randomized controlled trial; Retro = retrospective; TEGDMA = Triethylene glycol dimethacrylate; TIMP = tissue inhibitor of metalloproteinases; TMA = trimethacrylate; TNF = tumor necrosis factor; UDMA = urethane dimethacrylate; VAS = visual analog scale; WBC = White blood cell

Table 9: Dental Restoration - Health Effects (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Da Silva et al. (2018)³⁸

Study Design: Prospective nonrandomized comparison study

Device or Material: IRM (zinc and eugenol-based cement) compared with Clearfil SE Bond + Filtek Supreme (DMA-based self-etch adhesive system and resin composite, respectively)

Route: Oral, restoration of mandibular left first molars (MLFMs) with induced caries lesions

Dose: NR

Frequency/Duration: Single administration

Response: Pulp tissue inflammation, Thickness of physiological dentin, Soft-tissue organization, Osteonectin expression, Transforming growth factor- β 1 expression

Species (strain): Rat (Wistar, specific pathogen-free)

Gender: Male

Number per Group: NC is untreated group: n=20, DMA group: n=20, Non-DMA group: n=20, PC group (mandibular right first molars (MRFMs) with untreated induced caries lesions): n=20 in both DMA and Non-DMA groups.

Observed adverse effects: "Only at 15 days post-treatment, was a lower level of inflammation found between restored teeth [DMA and Non-DMA groups]...when compared with their respective PCs (unrestored teeth) ($p < 0.05$ and that there was no difference in pulp inflammation between restored teeth" groups at either time point. The thickness of physiological dentin was not significantly different between DMA and Non-DMA groups at either time point. Between DMA and Non-DMA groups, "no disorganization of the odontoblastic layer was observed at either time ($p > 0.05$). The NC presented normal pulp tissue at both times". "at 15 days post-treatment, the OSN [Osteonectin] expression differed between restored versus the unrestored teeth since the unrestored teeth showed more intense expression than both restored groups, especially, in the central pulp zone". At 15 days, the DMA and Non-DMA groups "exhibited [transforming growth factor- β 1] immunostaining patterns similar to each other since the expression was limited to pre-dentin."

Timing of adverse effects: 3 and 15 days

Factors that predict response: "The good performance of... [DMA group] at 15 days can be related to this material being capable of more effectively sealing the cavity margins in a short period of time (up to 15 days)." "Another positive factor for the [DMA group] was that at the 15 days post-treatment analysis, the antimicrobial action produced by acidic monomers could interfere in the pulp response."

Source Citation: Ruiz-de-Castañeda et al. (2013)³⁹

Study Design: Prospective nonrandomized comparison study

Device or Material: Scotchbond Etchant + Adper Single Bond 2 Plus Adhesive + Filtek Supreme XT DMA-based composite resin, Filtek Silorane self-etch primer + Filtek Silorane adhesive bond + Filtek Silorane resin composite, Caulk IRM Intermediate Restorative Material zinc oxide and eugenol-based cement

Route: Oral, restoration of maxillary and mandibular premolars with induced deep cavities

Dose: NR

Frequency/Duration: Single administration

Response: Periapical and pulpal inflammatory response

Species (strain): Dog (mongrel)

Gender: Dog (mongrel)

Number per Group: Five dogs. 10 day Silorane group: NR (10 teeth), 90 day Silorane group: NR (10 teeth), 10 day DMA group: NR (10 teeth), 90 day DMA group: NR (10 teeth), 10 day Cement group: NR (5 teeth), 90 day Cement group: NR (5 teeth).

Observed adverse effects: At 10 days, periapical and pulpal inflammatory response was absent in all 10 teeth of the Silorane and DMA groups. Periapical and pulpal inflammatory response was mild in all 5 teeth of the 10 day Cement group. At 90 days, periapical and pulpal inflammatory response was absent in 9 teeth of the Silorane group, 8 teeth of the DMA group, and all 5 teeth of the Cement group.

Timing of adverse effects: 10 days and 90 days

Factors that predict response: "Several factors such as air drying of exposed dentin, heat generation by continuous cutting during cavity preparation, or inadequate water cooling, among others, have been considered as responsible for eliciting pulp damage." "In the present study, there was good pulpal and periapical response to the placement of this material [Filtek Supreme XT] in deep cavities. This possibly occurred because Filtek Supreme XT is composed of nanoparticles and nanoclusters which may reduce the interstitial space and, consequently, the amount of organic matrix capable of releasing methacrylates, thus causing less tissue irritation than conventional methacrylate-based resins."

Source Citation: Rendjova et al. (2012)⁴⁰

Study Design: Prospective nonrandomized comparison study

Device or Material: Fuji Lining LC DMA-based cement + resin composite, Fuji IX carboxylic acid-based cement + resin composite, Prime&Bond DMA-based adhesive + resin composite, G Bond DMA-based adhesive + resin composite

Route: Oral, restoration of first upper molars with induced, 1-millimeter-deep cavities

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory infiltrate, Tissue organization, Hard tissue formation, Reactive dentin formation

Species (strain): Rat (Wistar)

Gender: NR, 12 weeks old, 250-260 grams

Number per Group: Fuji Lining LC: n=6 (12 teeth), Fuji IX: n=6 (12 teeth), Prime&Bond: n=6 (12 teeth), G Bond: n=6 (12 teeth)

Observed adverse effects: "Over a period of 30 days slight changes were noticed in the odontoblast layer in one sample from the G Bond group and in one from the P&B Group. In rest of the specimens the odontoblast layer was unchanged." "Over a period of 30 days all [o]f the tested specimens resulted in reparation of pulp tissue, with lack of inflammatory response, except in the Prime&Bond group where a persistent slight inflammatory reaction was observed in one of the specimens." "The occurrence of reparative dentinogenesis was seen in all specimens after a 30-day period. The ANOVA test showed that there was no statistically significant difference in reactive dentine formation between the groups."

Timing of adverse effects: 7 and 30 days

Factors that predict response: "There are two main reasons for the pulp response, the toxic effect of the material and bacterial microleakage. The age of the patient, method of applying the material and remaining dentine thickness also play an important role in the intensity of pulp response and deposition of reparative dentine." "Any unpolymerized monomer in the composite is a potential biological liability if it leaches from the composite toward the pulp of the tooth." "In our research there was an inflammatory pulp response of different intensity without the presence of bacteria. This leads to the fact that the reason for pulp reaction is the toxicity of the material." "The results observed in the G Bond group showed slight inflammatory changes of pulp tissue and odontoblast layer. Considering the fact that in our research dental materials were applied on dentine in cavities with approximately the same depth, we can conclude that differences in the pulp response are due to

the toxicity of the material and the technique of application.” “Based on the histological findings observed in the present study, glass ionomer cements seem to be more biocompatible with pulp tissue than dentine adhesives, without a significant difference in pulp reaction between conventional and resin-modified glass ionomer cement.” “The other reasons that explain the biological tolerance of the pulp to the glass ionomer cements is considered to be a good adhesion to cavity walls and capability to prevent microleakage.”

Source Citation: Nowicka et al. (2012)¹⁶

Study Design: Prospective nonrandomized comparison study

Device or Material: AdheSE adhesive + Tetric Ceram restoration (the ASE group), or Adper Prompt L-Pop adhesive + Filtek Supreme restoration (the APLP group). Dycal liner +Amalgam control group

Route: Applied to prepared cavities in separate teeth, pulp capping

Dose: NR

Frequency/Duration: Single administration

Response: Histological assessment of teeth

Species (strain): 38 teeth from 3 health felines

Gender: NR

Number per Group: 12 teeth per experimental group, 8 teeth for control group, plus 6 intact teeth

Observed adverse effects: ASE: A majority of the specimens presented low-grade inflammatory pulp responses with tissue disorganization. One moderate inflammatory response. APLP: Pulp displayed lowgrade to moderate chronic inflammatory responses.

Control: No moderately intense inflammation or total tissue disorganization.

Timing of adverse effects: 40 days

Factors that predict response: “From the available data, it may be inferred that pulp inflammation and necrosis was primarily induced by the toxicity of the adhesive system composition. Indeed, the absence of dentin bridge formation may result in degenerative pulp alterations by all components of dentin-bonding systems and resin composites. ASE and APLP consist of monomers such as dimethacrylate, phosphonic acid acrylate, HEMA, and Bis-GMA, any of which may be toxic to pulp cells.

Source Citation: Taira et al. (2011)¹⁸

Study Design: Prospective nonrandomized comparison study

Device or Material: Clearfil SE Bond primer and CSE bond (dental adhesive, bonding), Dycal calcium hydroxide preparation used as a control. All teeth restored with Clearfil AP-X A3 resin composite

Route: direct pulp capping

Dose: NR

Frequency/Duration: Single administration

Response: pulp tissue disorganization, inflammatory cell infiltration (ICI), reparative dentin formation

Species (strain): Sprague Dawley rats

Gender: Male

Number per Group: 62 total, 5 teeth assigned to each of 6 experimental groups.

Observed adverse effects: Pulp tissue disorganization: no difference between experimental and control at 14 days.
Inflammatory cell infiltration: no difference between experimental and control at 14 days. By 28 days, “histopathological evaluation of all groups at each observation period showed that no specimen exhibited severe inflammation of the pulp.”

Timing of adverse effects: 14 and 28 days

Factors that predict response: "Severe pulp tissue disorganization and inflammatory cell infiltration observed in some specimens might result from the insufficient control of exudation of tissue fluid due to a large exposure site, inadequate polymerization of the bonding agents and severe irritation from cavity preparation. It has been reported that the unpolymerized components of adhesive resin systems showed more cytotoxicity to pulp cells than polymerized ones." Lack of these responses implies good polymerization of these compounds.

Source Citation: Suzuki et al. (2016)¹⁹

Study Design: Prospective nonrandomized comparison study

Device or Material: Clearfil SE Bond/Primer (CSP), Clearfil SE Bond/Bond (CSB), Dycal control; Clearfil AP-X restorative resin composite used on all teeth

Route: Direct pulp capping

Dose: NR

Frequency/Duration: Single administration

Response: pulp tissue disorganization, inflammatory cell infiltration

Species (strain): Sprague Dawley rats

Gender: male

Number per Group: 80 noncarious, upper (maxillary) first molars were treated with direct pulp capping

Observed adverse effects: Normal pulpal tissue morphology was observed in almost all the specimens. In the specimens that showed formation of dentin bridges, a reorganized odontoblastic layer was seen beneath the reparative dentin. After day 14, three specimens (one in Group 1 [Clearfil SE Bond1/Primer] and two in control group) exhibited mild-to-moderate [pulp tissue disorganization and inflammatory cell infiltration]. However, after days 56 and 112, none of the specimens exhibited [pulp tissue disorganization and inflammatory cell infiltration]."

Timing of adverse effects: 14, 56, and 112 days

Factors that predict response: "Although it is well-known that un-polymerized resin monomer can cause pulpal inflammation: however, polymerized resin monomers do not cause irritation of the pulp tissue. Therefore, we speculate that the soft-tissue hybrid layer functions as a protective membrane for the pulp tissue."

DMA = dimethacrylate; NA = not applicable; NC = negative control; NR = not reported; PC = positive control; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 10: Dental Primer Etching Agent - Health Effects (In Vivo) Animal Studies

Source Citation: Taira et al. (2011)¹⁸

Study Design: Nonrandomized comparative study (six groups: all received DMA)

Device or Material: Clearfil SE Bond primer and CSE bond (dental adhesive, bonding), Dycal calcium hydroxide preparation used as a control. All teeth restored with Clearfil AP-X A3 resin composite

Route: direct pulp capping

Dose: NR

Frequency/Duration: Single administration / 14 and 28 days

Response: pulp tissue disorganization, inflammatory cell infiltration, reparative dentin formation

Species (strain): Sprague Dawley rats

Gender: Male

Number per Group: 62 total, 5 teeth assigned to each of 6 experimental groups.

Observed adverse effects: Pulp tissue disorganization: no difference between experimental and control at 14 days.

Inflammatory cell infiltration: no difference between experimental and control at 14 days. By 28 days, "histopathological evaluation of all groups at each observation period showed that no specimen exhibited severe inflammation of the pulp."

Timing of adverse effects:

Factors that predict response: "Severe pulp tissue disorganization and inflammatory cell infiltration observed in some specimens might result from the insufficient control of exudation of tissue fluid due to a large exposure site, inadequate polymerization of the bonding agents and severe irritation from cavity preparation. It has been reported that the unpolymerized components of adhesive resin systems showed more cytotoxicity to pulp cells than polymerized ones." Lack of these responses implies good polymerization of these compounds.

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 11: Dental Sealants - Health Effect (In Vivo) Human Studies

Source Citation: Patil et al. (2015)¹⁵

Study Design: Double-blind RCT

Device or Material: Gluma Desensitizer sealant (GD, glutaraldehyde and hydroxyl ethyl methacrylate [HEMA] primer), Gluma Comfort Bond adhesive + GD, Single Bond Universal adhesive (SBU)

Contact Duration: 3 and 6 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Sensitivity

Patient characteristics (gender, mean age): 54 teeth in 20 patients in the age range of 18-35 years (12 females, 8 males). Patients had a chief complaint of dentinal hypersensitivity and were seeking treatment.

Number per Group: 18 teeth in each group

Observed adverse effects: All three groups showed a significant reduction in dentinal hypersensitivity ($P < 0.05$) compared to baseline at all time intervals. Statistically, significant differences were noted between GD and SBU; between GCBD and SBU in all testing parameters. Between GD and GCBD no significant difference was noted. "No adverse effects were observed in any of the subjects enrolled in the study." All materials contained HEMA and other methacrylates.

Timing of adverse effects:

Factors that predict response: "The one-bottle self-etching adhesive (SBU) tested in the current study did not perform better than GD and GCBD. This might be due to the fact that single-bottle self-etching adhesives contain mixtures of hydrophilic and less hydrophobic monomers and thus, are permeable to water after application to the dentinal surface and thus may not penetrate deeper into the dentinal tubules."

Source Citation: Pinna et al. (2015)¹²

Study Design: Split-mouth RCT

Device or Material: Vertise Flow compared to Universal Dentine Sealant, Clearfil Protect Bond, and Flor-Opal Varnish.

Contact Duration: 12 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Hypersensitivity, adverse events

Patient characteristics (gender, mean age): 46 patients with 116 hypersensitive teeth, 27 females and 19 males

Number per Group: Number of treated teeth: Vertise Flow = 28, Universal Dentine Sealant = 27, Clearfil Protect Bond = 30, Flor-Opal Varnish = 31

Observed adverse effects: All materials reduced hypersensitivity but hypersensitivity increased in Vertise Flow treated patients by 12 weeks. Patients reported no adverse reactions to treatment.

Timing of adverse effects:

Factors that predict response: "Compared with the baseline, [Vertise Flow] showed the ability to significantly reduce the sensitivity immediately after the application, however lowering its efficiency within the 12-week post-

treatments, as a possible loss of the resin sealing in dentine under oral fluids exposure." ... "A significant increase was observed in scores within the 12-week controls as a possible consequence of deterioration of the physical-mechanical properties of the resin cover in dentine."

HEMA = hydroxyl ethyl methacrylate; NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 12: Dental Sealants - Health Effects (In Vivo) Animal Studies

Source Citation: No animal studies

Study Design:

Device or Material:

Route:

Dose:

Frequency/Duration:

Response:

Species (strain):

Gender:

Number per Group:

Observed adverse effects:

Timing of adverse effects:

Factors that predict response:

Appendix E. References

1. Heratizadeh A, Werfel T, Schubert S, Geier J, IVDK Collaborators. Contact sensitization in dental technicians with occupational contact dermatitis. Data of the Information Network of Departments of Dermatology (IVDK) 2001-2015. Contact Dermatitis. 2018 Apr;78(4):266-73. Also available: <http://dx.doi.org/10.1111/cod.12943>. PMID: 29327359.
2. Rojas-Alcayaga G, Carrasco-Labra A, Danús P, Guzmán MA, Morales-Bozo I, Urzúa B, Ortega-Pinto A. Determination of susceptibility to sensitization to dental materials in atopic and non-atopic patients. Med Oral Patol Oral Cir Bucal. 2012 Mar;17(2):320-4. Also available: <http://dx.doi.org/10.4317/medoral.17424>. PMID: 22143693.
3. Lazar MA, Rotaru H, Baldea I, Bosca AB, Berce CP, Prejmerean C, Prodan D, Campian RS. Evaluation of the biocompatibility of new fiber-reinforced composite materials for craniofacial bone reconstruction. J Craniofac Surg. 2016 Oct;27(7):1694-9. Also available: <https://doi.org/10.1097/scs.0000000000002925>. PMID: 27763970.
4. Castañeda ER, Silva LA, Gatón-Hernández P, Consolaro A, Rodríguez EG, Silva RA, Queiroz AM, Nelson-Filho P. Filtek™ Silorane and Filtek™ Supreme XT resins: tissue reaction after subcutaneous implantation in isogenic mice. Braz Dent J. 2011;22(2):105-10. PMID: 21537582.
5. Barreto Girão L, Ohana de Lima Martins J, Lemos JVM, Pinto MR, Rolim JPML, Alves E Silva FCF, Saboia VDP, Bitu Sousa F, de Barros Silva PG. Influence of the degree of conversion and Bis-GMA residues of bulk fill resins on tissue toxicity in an subcutaneous model in rats. J Appl Biomater Funct Mater. 2020;18 Also available: <http://dx.doi.org/10.1177/2280800020947330>. PMID: 33151768.
6. Hammad HM, Hamadah MA, Al-Omari WM. Histological evaluation of rat tissue response to GMTA, Retroplast, and Geristore retrograde filling materials. Aust Endod J. 2011 Apr;37(1):18-25. Also available: <http://dx.doi.org/10.1111/j.1747-4477.2009.00195.x>. PMID: 21418410.
7. Alifui-Segbaya F, Bowman J, White AR, Varma S, Lieschke GJ, George R. Toxicological assessment of additively manufactured methacrylates for medical devices in dentistry. Acta Biomater. 2018 Sep 15;78:64-77. Also available: <http://dx.doi.org/10.1016/j.actbio.2018.08.007>. PMID: 30099197.
8. Marcondes M, Souza N, Manfroi FB, Burnett LH, Spohr AM. Clinical evaluation of indirect composite resin restorations cemented with different resin cements. J Adhes Dent. 2016;18(1):59-67. Also available: <http://dx.doi.org/10.3290/j.jad.a35519>. PMID: 26814319.
9. Almeida Mesquita J, Lacerda-Santos R, Pina Godoy G, Francisco Weege Nonaka C, Muniz Alves P. Morphological and immunohistochemical analysis of the biocompatibility of resin-modified cements. Microsc Res Tech. 2017 May;80(5):504-10. Also available: <http://dx.doi.org/10.1002/jemt.22822>. PMID: 28029189.
10. Moilanen LH, Dahms JK, Hoberman AM. Reproductive toxicity evaluation of the dental resin monomer triethylene glycol dimethacrylate (CASRN 109-16-0) in mice. Int J Toxicol. 2014 Mar-Apr;33(2):106-15. Also available: <http://dx.doi.org/10.1177/1091581813513909>. PMID: 24345749.
11. Moilanen LH, Dahms JK, Hoberman AM. Reproductive toxicity evaluation of the dental resin monomer bisphenol a glycidyl methacrylate (CAS 1565-94-2) in mice. Int J Toxicol. 2013 Nov-Dec;32(6):415-25. Also available: <http://dx.doi.org/10.1177/1091581813511995>. PMID: 24231940.
12. Pinna R, Bortone A, Sotgiu G, Dore S, Usai P, Milia E. Clinical evaluation of the efficacy of one self-adhesive composite in dental hypersensitivity. Clin Oral Investig. 2015 Sep;19(7):1663-72. Also available: <http://dx.doi.org/10.1007/s00784-014-1390-3>. PMID: 25609032.
13. Nowicka A, Lagocka R, Lipski M, Parafiniuk M, Grocholewicz K, Sobolewska E, Witek A, Buczkowska-Radlinska J. Clinical and histological evaluation of direct pulp capping on human pulp tissue using a dentin adhesive system. Biomed Res Int. 2016;2016:2591273. Also available: <http://dx.doi.org/10.1155/2016/2591273>. PMID: 27803922.
14. Gresnigt MMM, Kalk W, Ozcan M. Randomized controlled split-mouth clinical trial of direct laminate veneers with two micro-hybrid resin composites. J Dent. 2012 Sep;40(9):766-75. Also available: <http://dx.doi.org/10.1016/j.jdent.2012.05.010>. PMID: 22664565.
15. Patil SA, Naik BD, Suma R. Evaluation of three different agents for in-office treatment of dentinal hypersensitivity: a controlled clinical study. Indian J Dent Res. 2015 Jan;26(1):38-42. Also available: <http://dx.doi.org/10.4103/0970-9290.156796>. PMID: 25961613.

16. Nowicka A, Parafiniuk M, Lipski M, Lichota D, Buczkowska-Radlinska J. Pulpo-dentin complex response after direct capping with self-etch adhesive systems. *Folia Histochem Cytobiol.* 2012;50(4):565-73. Also available: <http://dx.doi.org/10.5603/FHC.2012.0079>. PMID: 23264220.
17. dos Santos RL, de Sampaio GA, de Carvalho FG, Pithon MM, Guênes GM, Alves PM. Influence of degree of conversion on the biocompatibility of different composites in vivo. *J Adhes Dent.* 2014 Feb;16(1):15-20. PMID: 23678480.
18. Taira Y, Shinkai K, Suzuki M, Kato C, Katoh Y. Direct pulp capping effect with experimentally developed adhesive resin systems containing reparative dentin-promoting agents on rat pulp: mixed amounts of additives and their effect on wound healing. *Odontology.* 2011 Jul;99(2):135-47. Also available: <http://dx.doi.org/10.1007/s10266-011-0006-5>. PMID: 21516293.
19. Suzuki M, Taira Y, Kato C, Shinkai K, Katoh Y. Histological evaluation of direct pulp capping of rat pulp with experimentally developed low-viscosity adhesives containing reparative dentin-promoting agents. *J Dent.* 2016 Jan;44:27-36. Also available: <http://dx.doi.org/10.1016/j.jdent.2015.11.005>. PMID: 26620099.
20. Pallesen U, van Dijken JW. A randomized controlled 30 years follow up of three conventional resin composites in Class II restorations. *Dent Mater.* 2015 Oct;31(10):1232-44. Also available: <http://dx.doi.org/10.1016/j.dental.2015.08.146>. PMID: 26321155.
21. Popoff DA, de Magalhães CS, de Freitas Oliveira W, Soares LA, de Almeida Santa Rosa TT, Ferreira RC, Moreira AN, Mjör IA. Two-year clinical performance of dimethacrylatebased composite restorations repaired with a silorane-based composite. *J Adhes Dent.* 2014 Dec;16(6):575-83. Also available: <http://dx.doi.org/10.3290/j.jad.a33196>. PMID: 25516879.
22. Corral C, Grez PV, Letelier M, Dos Campos EA, Dourado AL, Fernández GE. Effect of oxalic acid-based desensitizing agent on cervical restorations on hypersensitive teeth: a triple-blind randomized controlled clinical trial. *J Oral Facial Pain Headache.* 2016 Aug;30(4):330-7. Also available: <http://dx.doi.org/10.11607/ofph.1676>. PMID: 27792801.
23. van Dijken JWV, Pallesen U. Durability of a low shrinkage TEGDMA/HEMA-free resin composite system in Class II restorations. A 6-year follow up. *Dent Mater.* 2017 Aug;33(8):944-53. Also available: <http://dx.doi.org/10.1016/j.dental.2017.04.021>. PMID: 28545657.
24. Askari M, Yazdani R. Comparison of two desensitizing agents for decreasing dentin hypersensitivity following periodontal surgeries: a randomized clinical trial. *Quintessence Int.* 2019;50(4):320-9. Also available: <http://dx.doi.org/10.3290/j.qi.a42096>. PMID: 30887965.
25. Schmidt J, Hübler C, Krohn S, Schmalz G, Schneider H, Berg T, Haak R, Ziebolz D. Detection of inflammatory and homeostasis biomarkers after selective removal of carious dentin--an in vivo feasibility study. *J Clin Med.* 2021 Mar;10(5):1-12. Also available: <http://dx.doi.org/10.3390/jcm10051003>. PMID: 33801317.
26. Celik N, Askin S, Gul MA, Seven N. The effect of restorative materials on cytokines in gingival crevicular fluid. *Arch Oral Biol.* 2017 Dec;84:139-44. Also available: <http://dx.doi.org/10.1016/j.archoralbio.2017.09.026>. PMID: 28992599.
27. Stefanovic V, Taso E, Petkovic-Curcin A, Dukic M, Gardasevic M, Rakic M, Xavier S, Jovic M, Miller K, Stanojevic I, Vojvodic D. Influence of dental filling material type on the concentration of interleukin 9 in the samples of gingival crevicular fluid. *Vojnosanit Pregl.* 2016 Aug;73(8):728-34. Also available: <http://dx.doi.org/10.2298/VSP140227054S>. PMID: 29328596.
28. Sakallioğlu EE, Lütfioğlu M, Sakallioğlu U, Ceylan GK, Pamuk F, Dede FÖ, Dede D. Gingival crevicular fluid levels of neuropeptides following dental restorations. *J Appl Biomater Funct Mater.* 2015 Apr;13(2):e186-e193. Also available: <http://dx.doi.org/10.5301/JABFM.5000197>. PMID: 24980682.
29. Chandwani ND, Pawar MG, Tupkari JV, Yuwanati M. Histological evaluation to study the effects of dental amalgam and composite restoration on human dental pulp: an in vivo study. *Med Princ Pract.* 2014;23(1):40-4. Also available: <http://dx.doi.org/10.1159/000355607>. PMID: 24217468.
30. Nowicka A, Wilk G, Lipski M, Koecki J, Buczkowska-Radliska J. Tomographic evaluation of reparative dentin formation after direct pulp capping with Ca(OH)₂, MTA, biodentine, and dentin bonding system in human teeth. *J Endod.* 2015 Aug;41(8):1234-40. Also available: <http://dx.doi.org/10.1016/j.joen.2015.03.017>. PMID: 26031301.
31. Beck F, Dumitrescu N, König F, Graf A, Bauer P, Sperr W, Moritz A, Schedle A. One-year evaluation of two hybrid composites placed in a randomized-controlled clinical trial. *Dent Mater.* 2014 Aug;30(8):824-38. Also available: <http://dx.doi.org/10.1016/j.dental.2014.05.006>. PMID: 24946982.

32. Rocha Gomes Torres C, Rêgo HM, Perote LC, Santos LF, Kamoziaki MB, Gutierrez NC, Di Nicolás R, Borges AB. A split-mouth randomized clinical trial of conventional and heavy flowable composites in class II restorations. *J Dent*. 2014 Jul;42(7):793-9. Also available: <http://dx.doi.org/10.1016/j.jdent.2014.04.009>. PMID: 24769385.
33. Strober B, Veitz-Keenan A, Barna JA, Matthews AG, Vena D, Craig RG, Curro FA, Thompson VP. Effectiveness of a resin-modified glass ionomer liner in reducing hypersensitivity in posterior restorations: a study from the practitioners engaged in applied research and learning network. *J Am Dent Assoc*. 2013 Aug;144(8):886-97. Also available: <https://doi.org/10.14219/jada.archive.2013.0206>. PMID: 23904575.
34. Ghavamnasiri M, Ameri H, Chasteen JE, Mofrad AH, Hashemi B. Correlation between dental arch location and clinical success rate of total etch and self-etch adhesives in ClassV composite restorations. *Eur J Prosthodont Restor Dent*. 2012 Mar;20(1):26-30. PMID: 22474933.
35. Ergin E, Kutuk ZB, Cakir FY, Gurgan S. Comparison of two different composite resins used for tooth reshaping and diastema closure in a 4-year follow-up. *Niger J Clin Pract*. 2018 Sep;21(9):1098-106. Also available: http://dx.doi.org/10.4103/njcp.njcp_36_18. PMID: 30156192.
36. Perdigão J, Dutra-Corrêa M, Saraceni CHC, Ciaramicoli MT, Kiyan VH, Queiroz CS. Randomized clinical trial of four adhesion strategies: 18-month results. *Oper Dent*. 2012 Jan-Feb;37(1):3-11. Also available: <http://dx.doi.org/10.2341/11-222-C>. PMID: 21942235.
37. Silva GAB, Gava E, Lanza LD, Estrela C, Alves JB. Subclinical failures of direct pulp capping of human teeth by using a dentin bonding system. *J Endod*. 2013 Feb;39(2):182-9. Also available: <http://dx.doi.org/10.1016/j.joen.2012.09.022>. PMID: 23321228.
38. Da Silva AF, Marques MR, Da Rosa WLO, Tarquinio SBC, Rosalen PL, Barros SP. Biological response to self-etch adhesive after partial caries removal in rats. *Clin Oral Investig*. 2018 Jul;22(6):2161-73. Also available: <http://dx.doi.org/10.1007/s00784-017-2303-z>. PMID: 29380132.
39. Ruiz-de-Castañeda E, Gatón-Hernández P, Rodríguez EG, Silva RA, Nelson-Filho P, Silva LA. Pulpal and periapical response after restoration of deep cavities in dogs' teeth with Filtek Silorane and Filtek Supreme XT systems. *Oper Dent*. 2013 Jan-Feb;38(1):73-81. Also available: <http://dx.doi.org/10.2341/11-341-L>. PMID: 22770433.
40. Rendjova V, Gjorgoski I, Ristoski T, Apostolska S. In vivo study of pulp reaction to glass ionomer cements and dentin adhesives. *Prilozi*. 2012;33(1):265-77. PMID: 22983105.
41. Maserejian NN, Shrader P, Brown OA, Trachtenberg FL, Soncini J, Hauser R, Shenker BJ. Dental sealants and composite restorations and longitudinal changes in immune function markers in children. *Int J Paediatr Dent*. 2014 May;24(3):215-25. Also available: <http://dx.doi.org/10.1111/jpd.12064>. PMID: 24033362.

Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Specific search terms are provided here. The associated alerts are provided with this report as a separate PDF.