

ARE THERE HARMS FROM BISPHENOL A PRODUCTS?

An evidence-based investigation

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ABSTRACT

This report presents an evidence-based investigation of the potential harms of bisphenol A products in dentistry. A survey of the literature was conducted through searches in four major databases. Initial background research led to the selection of hypersensitivity reactions to bisphenol A products as the focus of this study. A total of 42 articles were then identified from the databases, and they underwent a series of inclusion/exclusion stages, including critical appraisal according to a causation checklist. Twelve of these articles were deemed the most relevant and providing the strongest available evidence. All of the selected articles are case reports of allergic reactions in which bisphenol A or a related compound was the confirmed allergenic agent following patch testing. Eleven of the 12 articles received a Canadian Task Force (CTF) research design rating of Level III Evidence, and all 12 were rated Grade I in terms of the CTF recommendations grading system. Three of the studies controlled for potential confounding environmental triggers, and the majority of the 12 studies included negative patch tests for non-bisphenol A-related compounds to rule out irrelevant allergic reactions. The issue of cross reactivity among bisphenol A and related chemicals in triggering hypersensitivity reactions was also examined by several studies. They demonstrated the possibility of cross reactivity among certain compounds, suggesting that an allergic reaction to a particular product can occur without prior exposure to the product. Although this literature review found some evidence for the harms of bisphenol A products in terms of allergic reactions, there is currently insufficient evidence to recommend any clinical action. Furthermore, although suspected to be very low, an estimated prevalence of bisphenol A allergies is yet to be determined. Thus, this investigation has only revealed evidence that prompts further, more rigorous primary research on the harms of bisphenol A products in dentistry.

INTRODUCTION

The development of new dental materials is ongoing to meet the increasing demand by the public for aesthetic dentistry.¹ New materials bring novel benefits, but not without the risk of adverse reaction in both dental personnel who handle such materials, and patients who receive them in dental treatments.^{2,3} Adverse reactions to dental materials, most commonly allergic reactions, tend to occur near the site of material application, such as the dental pulp, gingiva and

oral mucosa.³ In contrast, systemic adverse responses to dental restorative treatment are very infrequent, and thus not well studied.⁴

Reports of allergy to resin materials which contain bisphenol A have been identified for the present study. Epoxy component bisphenol A has been shown to act as a strong sensitizer that can produce allergic contact dermatitis.⁵ Allergenic components of dental materials are released intraorally due to incomplete polymerization and degradation processes of the composite resin monomer. Specifically, the presence of bisphenol A has been demonstrated in saliva collected after the placement of dental fissure sealants.¹ Thus, allergic reactions to bisphenol A and bisphenol A-derived components are conceivable.

A survey of the literature has been conducted in order to formulate an evidence-based conclusion regarding the potential harms of bisphenol A products. Initial searches of current literature led to the selection of allergic, or hypersensitivity, reactions as the scope of this endeavour. This report presents the methods employed for the literature review, a summary of the evidence gathered, as well as implications and conclusions derived based on the available evidence.

BACKGROUND

Bisphenol A and related compounds

Figure 1 shows the chemical structure of bisphenol A and related compounds. Both Bisphenol A and F are classified as epoxy resins. Bisphenol A (BPA) is formed when two phenols react with one acetone. Bisphenol F is a variation on the bisphenol A structure. The only structural difference is the replacement of the propyl with a methyl group on the carbon backbone connecting the two phenol moieties in bisphenol F.

Bisphenol A is converted into diglycidylether bisphenol A (DGEBA) by reacting bisphenol A with epichlorohydrin. DGEBA is then reacted with methyl methacrylate to form Bis-GMA. The methacrylate groups are located on both ends of the monomer, to allow for polymerization. Bis-GMA, Bis-DMA and Bis-EMA are all classified as epoxy acrylates. Bis-DMA and Bis-EMA are modifications on the Bis-GMA structure. For example, Bis-EMA has an ethyl group separating the bisphenol group from the methacrylate group whereas Bis-GMA

contains an isopropyl group in place of the ethyl group. These slight modifications impart different chemical properties which can affect the conversion rate of polymerization, the relative hydrophobicity, and the degree of polymerization shrinkage in the resulting polymer. Since no polymerization reaction has 100% conversion, unreacted monomer is present in all polymerized products.

Applications of bisphenol A and related products

Bisphenol A (BPA) is a compound primarily used in the synthesis of epoxy resins and polycarbonate plastics.⁶ BPA-based epoxy resins compose products such as dental resins, inner coating of food and beverage cans, plastic bottles, jugs, and baby bottle.^{6,7} In the industry of polyvinyl chloride (PVC) plastics, BPA serves as an antioxidant and an inhibitor of end polymerization in PVC, which is frequently used in the production of gloves for the general public as well as dental personnel.⁸ The other, perhaps more widespread, use of BPA in dentistry is the resin monomer BIS-GMA, the reaction product of diglycidyl ether of BPA (DGEBA) and methyl methacrylate.⁷ The precursors of current composite restorative materials can be traced back 150 years, when acrylic resin was first developed for the use of denture-base material in Germany. Shortly after, poly(methylmethacrylate) resin came into use as indirect fillings, and then in the 1930's, the use of direct restorative materials was seen. Before the Bis-GMA composite systems were introduced by Bowen and Marjenhoff, the prior resins presented toxicity effects and chronic pulpitis, which still can be seen with the Bis-GMA systems, but to a much lesser extent.⁴

Allergic contact dermatitis and stomatitis

Allergic contact dermatitis is now the most frequently reported occupational disease.⁴ Common symptoms of allergic contact dermatitis include local inflammation of the skin and symptoms include pain, redness, swelling, itching, and blisters on the skin.⁹ Allergic contact stomatitis is the most common adverse reaction to dental materials in the dental patient, and is the localized form of allergic contact dermatitis in the oral mucosa. Symptoms include erythema, erosions, ulcerations, leukoplakia-like lesions, lichenoid reactions, swelling, burning, and peri-oral rash.^{4,10}

Allergic contact dermatitis in the workplace develops in stages. The outer layer of the skin acts as a protective layer which consists of fats, oils, and water. An agent causes a reaction by first eliminating the protective action of the skin by removing the fats, oils, and water, thereby facilitating its penetration into the body. This initial penetration results in sensitization to the allergenic agent. It is common not to see any signs of damage to the skin at this point. Once the substance has fully penetrated, natural skin proteins combine with the allergenic substance, and the complex is then carried throughout the body by lymphocytes. Upon re-exposure, in sensitized individuals, lymphocytes immediately recognize and react with the allergen, triggering a release of tissue-damaging chemicals called lymphokines. These lymphokines are the cause of symptoms that appear during allergic contact dermatitis.⁹ In the mouth, these allergens can be released into the saliva where they will diffuse to the oral or the gastrointestinal mucosa and cause a reaction. Allergens in the saliva can also enter the connective tissue of the pulp by diffusing through the dentin and trigger a reaction.³ Despite this, allergic contact stomatitis is not seen frequently due the natural state of the oral mucosa that helps protect against such reactions. Normally, saliva dilutes and washes away antigens before they are able to penetrate the mucosa; the high vascularization of oral mucosa quickly removes allergens that penetrate before an allergic response can take place; finally, the oral mucosa is not heavily keratinized, so there are limited proteins available for the binding of the allergen to trigger a reaction.^{4,11}

Clinical tests of hypersensitivity reactions

Patch testing

Patch testing was first developed by Jadassohn in 1895 and to date it remains as the only practical method for testing a true cell mediated contact allergy.¹² This test is done by placing the materials to be tested in wells which are on scanpore tape. The scanpore tape is then fixed to the patient's upper back and left on for two days. Upon removal, the area of skin under each well is read and recorded. Four days after the test was initiated, the areas are read again since some patients react later than others. The time of onset may also be dependant on the type of material tested. For example, a reaction to gold salts can take between 2 to 4 weeks to occur.¹² The biologic mechanism of a true contact allergy, and the basis of patch testing, is the type IV (cell-mediated) hypersensitivity reaction. While patch testing is the gold standard for clinical testing of allergic contact dermatitis, it should be noted that it is not without flaws. The biggest

pitfall of patch testing is differentiating between irritant reactions and allergic reactions.¹² Despite this problem and others, the specificity and sensitivity of patch testing nears 70-80%.¹³ Therefore, patch testing remains the best method available for identifying contact sensitivity.¹⁴

Prick Testing

Urticaria to proteins or chemicals may or may not be due to an IgE mediated allergic response.¹² In order to distinguish a true Type 1 (IgE mediated) hypersensitivity from non-immunological reactions, a prick test should be conducted. A prick test uses commercially prepared solutions that are placed on the forearm and pricked into the skin. In contrast to patch test results, prick test results are available in 15 minutes. A wheal of 4 mm or greater represents a positive test. According to Gawkrödger¹², prick tests are not always completely reliable.

METHODS

A systematic approach was used to identify and select relevant studies to be critically appraised.

Search Strategy

An initial search in PubMed using ‘bisphenol A *and* adverse effects’ as search terms was conducted to reveal the scope of studies currently available on this topic. The majority of studies fell under one of three categories: cytotoxicity, estrogenic effects and hypersensitivity reactions. Background research on bisphenol A indicated that both the FDA and EPA consider daily exposures up to 50 ppb bisphenol A to be safe. Fung *et al.*⁷ noted that BPA was not detectable in a patient’s saliva 3 hours after dental sealant placement. Thus, the studies on cytotoxicity and estrogenic effects were excluded from this paper since these experiments used exposure levels which were significantly higher than levels that a dental patient would experience. Also, these studies were typically conducted on either tissue cultures or rodents. Both of these experimental systems may not react the same way to BPA as a live human would, and the tissue cultures do not have the benefit of an immune response which otherwise could be successful in neutralizing this foreign chemical. This furthered this paper’s resolve to focus on hypersensitivity reactions, as these reactions can occur at the minute amounts of allergen to which the human dental patient would be exposed *in vivo*.

Four databases were used to include the maximum amount of literature possible. They included PubMed, Web of Science, Ovid and Medline. The initial search term was 'bisphenol A'. The amount of hits was refined by then including 'adverse effects' to the search term. The results were then limited to those in the English language, and conducted on humans. These results were further limited to allerg* (to cover all forms of the word such as allergy, allergies, allergic, allergenic, etc.) and then to dent* (to cover dentistry, dental, etc.). See Table 1 for search result numbers. After removing duplicate studies, 42 potential articles remained.

Determination of Relevance

The 42 article yield from the electronic search underwent further scrutiny. To be relevant to this paper, the studies had to:

- 1) investigate the hypersensitivity potential of bisphenol A on humans;
- 2) confirm that exposure to BPA was through dental related products;
- 3) use a patch test to confirm that BPA or a BPA-based product was the allergen.

Despite the use of the search term 'dent*', many articles referred to BPA in dental resins, but in fact described industrial-related occupational contact dermatitis from BPA hypersensitivity. These materials are very different from dental BPA materials and were thus excluded from this study. The patch test was an inclusion requirement in order to ensure that the reactions reported were indeed from BPA and not from another component in the dental material, an oral hygiene product or the general environment. Using these criteria, articles were rejected at the title, abstract, or first reading stage (at which point it was definitively determined whether or not a patch test was used). This produced 18 articles, 6 of which were deemed useful for background information, and 12 primary articles which were to be critically read and scored (See Figure 2).

Expert opinions

Dr. P.A. Watson and Dr. J.P. Santerre were approached for their expert opinions on bisphenol A and its role in dentistry. Both are Biomaterials professors at the Faculty of Dentistry, University of Toronto. Discussions centred around the chemistry of BPA and epoxy acrylates, BPA's degradation byproducts and the possible adverse effects of BPA materials in a dental

context. During these discussions, it was noted that the incidence of BPA hypersensitivity in the general population is indiscernible at present time, since it is so rare. Four articles were recommended, and they joined the 6 which have not been excluded but were not chosen as primary articles, to make a total of 10 articles useful for background information on dental applications of BPA.

Critical appraisal

The 12 articles were scored using the 'Checklist for assessing causation', developed by Dr. J.L. Leake¹⁵ (See Table 2). Since bisphenol A is not an infectious organism, the test for causation of non-infectious agents was used. Thus, the highest possible score was 13. The strength of study design (Grade I – III) and level of evidence (A to I) was also assigned as outlined by the Canadian Task Force on Preventive Health Care.

RESULTS

The 12 articles selected report on varying presentations of allergic contact dermatitis, as documented in case studies by dental clinicians around the world. (Tables 3 and 4) The relative strength of the articles was determined by the score attained on the causation checklist (Table 2). No article received a score higher than eight out of the maximum thirteen; therefore none of the articles were considered to present strong evidence. Three of the studies controlled for potential confounding environmental triggers.^{8,16,17} The majority of the studies conducted patch tests for ingredients of the allergenic material other than BPA or the BPA-based molecule, in order to confirm the role of BPA as the allergenic agent. One of the studies included a patch test only for the ingredient found in the allergenic resin that was suspected to have triggered the dermatitis; no other components of that resin were tested, thereby decreasing the study's validity.¹⁸ One report of rashes, hives, and an asthmatic reaction to a fissure sealant showed no positive test results to the patch testing and prick testing done. However, the reactions subsided upon removal of the fissure sealant, demonstrating reversibility of the reaction.¹⁹ Since the reaction could not be validly measured, no allergic reaction could be proven in this study.

Four of the twelve studies included patch testing for both epoxy resins, such as BPA, and epoxy acrylates, such as Bis-GMA. Three of the studies concluded that no cross-reactivity between the two compounds was found in the patients.^{20,21,22} A study conducted by Björkner²³

reported eight patients who patch tested positive to epoxy resins (e.g. BPA), six of whom also patch tested positive to Bis-GMA, an epoxy acrylate, yielding a 75% cross reactivity between the compounds.

The study conducted by Lee *et al.*²¹ reported complete cross-reactivity between bisphenol A and bisphenol F products, no cross reactivity between aliphatic acrylates and either epoxy resins or epoxy acrylates, and a 19.5% rate of cross-reactivity between BPA and at least one epoxy acrylate.

DISCUSSION

Implications of current evidence

Based on this review of the literature, the evidence on harms caused by bisphenol A is insufficient to make recommendations on clinical preventive action. All of the studies investigated included case reports on individuals who were sensitized to a BPA-containing material, underwent a dermatitis reaction, and were assessed by patch testing to determine the presence of a true allergy. The corresponding evaluation of eleven of the twelve articles according to the guidelines set out by the Canadian Task Force (CTF) was Grade I, Level III. The twelfth article reports a multi-centre study of forty-one cases who all tested positive for BPA following sensitization and dermatitis reactions, in order to examine the cross reactivity among a variety of materials, including bisphenol F, epoxy acrylates and aliphatic acrylates. This study by Lee *et al.*²¹ was given a rating of Grade I, Level II-iii according to the CTF guidelines.

Cross-reactivity was a significant factor investigated in many of the studies. The results showed that the more similarity existed between two compounds, the more cross- reactivity was likely to occur. Bisphenol F and bisphenol A are similar chemically; the only difference is the exchange of the propyl group in bisphenol A with a methyl group in bisphenol F. Epoxy acrylates have a greater amount of structural variation relative to BPA and consequently a lower level of cross-reactivity. Aliphatic acrylates do not contain epoxy rings in their chemical structure; this major structural variation accounts for their complete lack of cross-reactivity with either epoxy resins or epoxy acrylates. Kanerva, Jolanki and Estlander²⁴ reference a study done by Bjorkner²³, which reports 75% cross reactivity between epoxy resin and epoxy acrylates. Kanerva *et al.*²⁴ proposed the possibility that epoxy resin impurities were present in the initial

sensitizing epoxy acrylate material (in amounts below the detectable level), such that cross reactivity appeared to have occurred, when in reality the patients were actually sensitized to both materials, from the initial sensitization. In all, evidence of allergenic cross reactivity of various compounds with BPA and BPA-based molecules suggests the possibility of an allergic reaction to BPA products occurring at initial exposure, without prior sensitization by the same product.

Nine of the twelve studies patch tested for all of the components that may have been in the irritating material, as well as any other possible surrounding irritants (e.g. latex, local anaesthetic) to ensure accurate isolation of the specific allergenic component.^{8,16,17,20,22,24-27} The specific allergen was found to be an epoxy acrylate, most commonly Bis-GMA, in five of the cases, and bisphenol A in five of the cases. Bis-GMA was found to have a high rate of cross reactivity with other epoxy acrylates, such as Bis-EMA and Bis-GA. The isolation of either epoxy acrylate or bisphenol A in the majority of cases as the allergenic agent strengthens the evidence that allergic contact dermatitis is a potential harm caused by bisphenol A products.

Limitations

The case report descriptive study is inherently weak in design. The study depends partly on the patient's awareness of symptoms and the patient's decision to report those symptoms to the dentist, and partly on the dentist's reporting of the symptoms and the results of any further investigations. This process is vulnerable to recall bias that lowers a study's validity. The dentist must also recall accurately the specific material used in the case which caused the dermatitis reaction; this will enable the dermatologist to perform patch tests using the exact components of the irritating material. Because clinicians tend to use a variety of dental composite resin products, it is likely that the dentist will not accurately recall the exact materials used. Moreover, case reports are studies that are reported by different dentists from different countries across the world, and there is no way to standardize completely these reports among dentists. It cannot be established with certainty that clinicians are using the same criteria to define a contact dermatitis reaction, for example. This, too, compromises the validity of case report comparisons.

Another potential source of inconsistency among reports is patient variability. While some studies did attempt to control for environmental factors when performing patch tests, there is no way to control for the variation between patients' own immunologic responses to allergens.

A patient who is hypersensitive to many things may respond to two different materials, producing a false positive with regard to cross-reactivity.

A further problem associated with case reports is the inability to determine the prevalence of a disease within a population, and the inability to generalize the prevalence of the disease in other populations. Despite the vast amount of research carried out, the prevalence of harms caused by bisphenol A cannot be established, or even predicted. It may be of significance that no cases of non-allergic contact dermatitis (i.e. dermatitis with a negative patch test result) are reported. This makes it impossible to calculate any pre-test probabilities, which could attempt to determine the likelihood of a patient experiencing a true allergy when the patient presents with contact dermatitis prior to patch testing.

Future directions

Possible future research may include a case-control study with a large sample size, which would provide a higher level of evidence and potentially would be able to determine an estimated prevalence. Such a case-control study could compare between epoxy resin and epoxy acrylates used in dental composite resins, as well as bisphenol A- containing disposable gloves and bisphenol A-free disposable gloves, etc. The study should include a demonstration of reversibility to increase its ranking on the causation checklist; as reversibility was demonstrated in only four of the studies in this review.^{20-22,27} Where possible, all patient factors should be controlled for, although it remains difficult to obtain accurately information such as history of prior exposure to various BPA-related materials. Finally, there may be ethical issues associated with certain aspects of the proposed studies, which would need to be first assessed and approved.

CONCLUSION

Based on this review of the literature, the evidence on harms caused by bisphenol A is insufficient to make recommendations on clinical preventive action. According to the guidelines set out by the Canadian Task Force, 11 of the 12 articles were evaluated as Grade I, Level III, and the twelfth article as Grade I, Level II-iii. The inherent weakness of case reports accounts for these weak study design evaluations. In order to enhance the strength of the evidence, future studies should include stronger designs including prospective and case-control studies which demonstrate reversibility and greater levels of control.

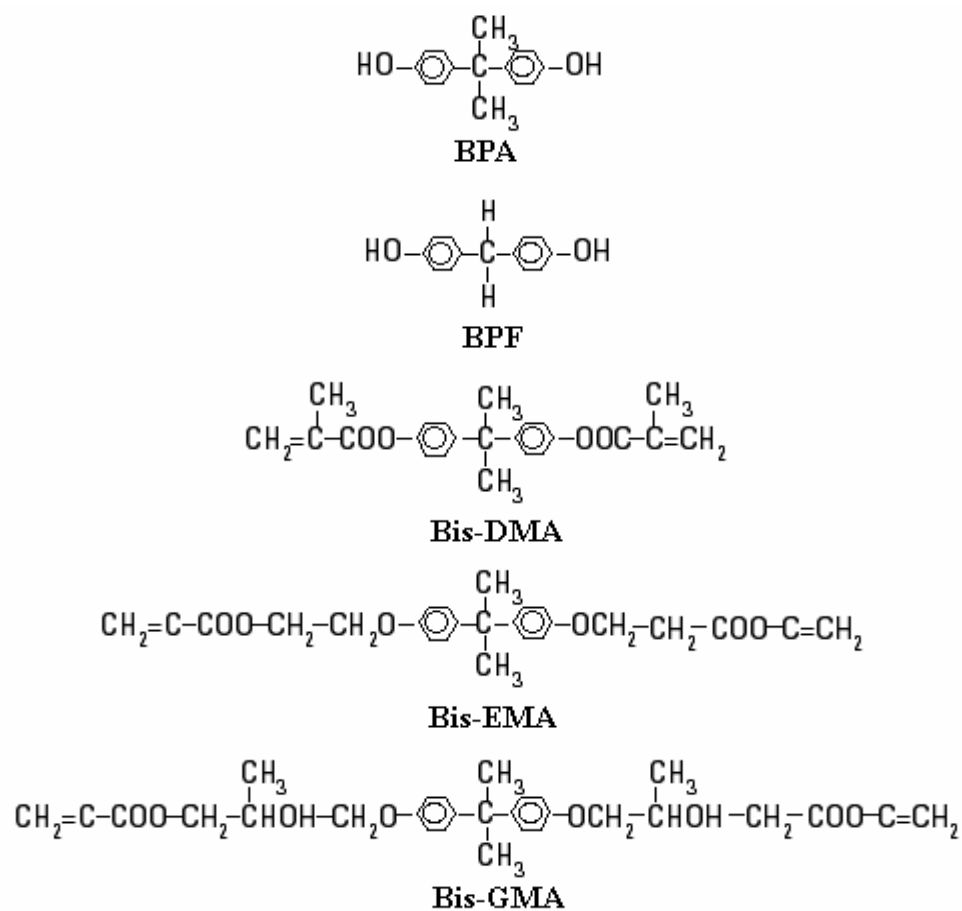


Figure 1. Bisphenol A (BPA) and bisphenol F (BPF) are very similar chemically. Bis-DMA, Bis-EMA, and Bis-GMA are all modifications of bisphenol A, which are known as epoxy acrylates. Based on figure from Pulgar *et al.*²⁸

Table 1: Search Term Table. Numbers represent yield from each search engine.

Search Term	PubMed	Web of Science	Ovid	Medline
Bisphenol A	4132	7833	3985	7516
Bisphenol A, adverse effects	741	114	62	59
Limit to: human, English	381	47	25	59
Allerg*	43	8	41	28
Dent*	31	4	5	17

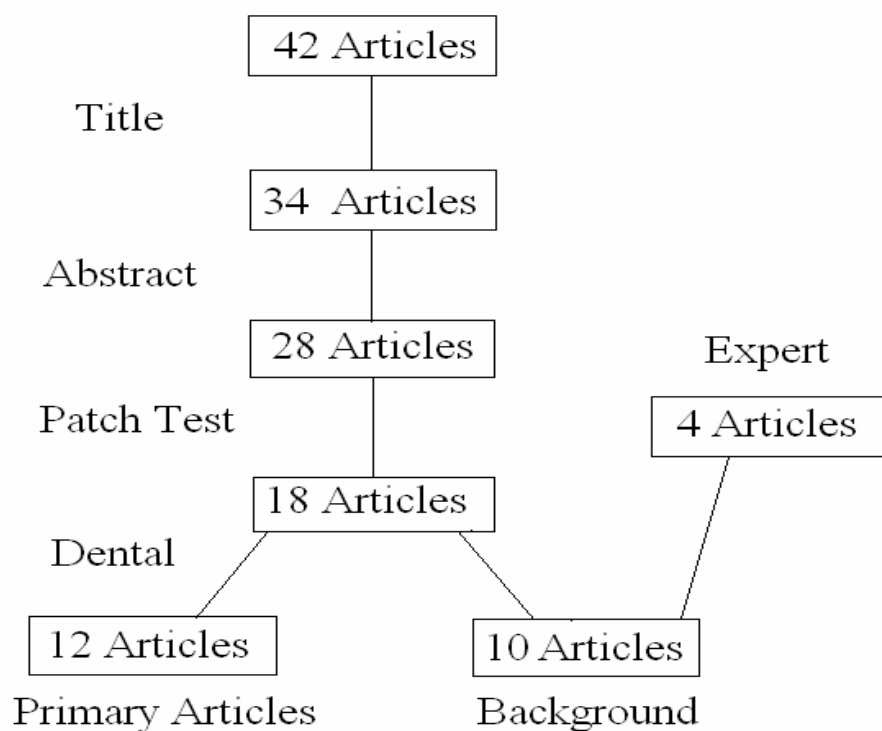


Figure 2: Exclusion/Inclusion Flowchart

Table 2: Checklist for assessing causation¹⁵

<ol style="list-style-type: none">1. Was the study ethical?2. Was a strong design used to assess causation or risk?3. Were cases defined validly and reliably measured?4. Were the risks validly and reliably measured?5. For diseases with multi-factorial risks, were the risks assessed controlling for other factors and was the model's prediction power strong6. Do the findings meet the tests for causation? (Use test below)
<p><u>Test for causation of non-infectious agents</u></p> <ol style="list-style-type: none">1. Did the "cause" precede the effect?2. Was the estimate of risk beyond chance, and large?3. Was there a dose-response relationship?4. Was reversibility demonstrated?5. Is the "cause" consistently observed in different times, places?6. Is the "cause" biologically plausible?7. Is the "cause" specific to that disease?8. Is the "cause" analogous to another established disease/exposure?

Table 3. Evidence for bisphenol A allergic reactions in dental patients.

Author, date	Population	Treatment	Outcome	Critical appraisal comments/strength of study/Conclusions
Connolly <i>et al.</i> , 2006	2; U.K.; 13 y.o. and 14 y.o. female orthodontic patients	Cases of contact dermatitis following orthodontic bracket placement. Both cases were patch tested.	Both cases test positive for epoxy resin, 1% and Bis-GMA 2%. Both tested negative for nickel and latex.	Case report Level III Grade I CC (causation checklist) 8/13 Bis-GMA may have caused the reactions; uncertain since no other ingredients of resins were tested
Carmichael, Gibson, Walls, 1997	1; England; 46-yr old woman with 5-yr history of recurrent episodes of perioral erythema, occurring within 2 hours of dental restoration placement.	Referred for dermatological patch testing	Positive patch test to epoxy resin, Bis-GMA, and Benzoyl peroxide. Negative patch test to Bisphenol A (BPA) and Urethane dimethacrylate.	Case report Level III Grade I CC 8/13 Allergic contact dermatitis episode is likely attributed to Bis-GMA, a component of the resin used for the patient's restorations. (no cross-reactivity found between Bis-GMA and BPA)
Kanerva, Alanko, Estlander, 1999	1; Finland; 48 y.o female dental patient with gingivitis, stomatitis, perioral dermatitis from temp crown made of "proacrylate, tricyclate, urethane methacrylate"	Referred for dermatological patch testing	Positive patch test for epoxy dimethacrylates, Bis-GMA. Negative patch test to "urethane methacrylate," and no details on the "tricyclic methacrylate"	Case report Level III Grade I CC 8/13 Reaction was likely caused by the Bis-GMA found in the material used for the temporary crown.

Lee <i>et al.</i> , 2002	41; USA; 41 patients with history of hypersensitivity reactions to BPA-related dental work and all have had positive patch test to Bisphenol A epoxy resin.	Patch tests to: Bisphenol A epoxy resins, Bisphenol F epoxy resins, and epoxy acrylates.	Positive patch tests: 100%- Bis-A 100%-Bis-F 19.5%- at least one epoxy acrylate 17%-Bis-GMA 10%-Bis-EMA 0%-Bis-MA High concordance b/w Bis-GMA and epoxy methacrylate	Multi-centre case series Level II-iii Grade I CC 8/13 There is strong cross-reactivity between Bisphenol A and F resins; There is little cross reactivity between BPA epoxy resins and epoxy acrylates. No dental symptoms reported from epoxy acrylates.
Dutree-Meulenberg, R., Kozel, M., van Joost, Th., 1992.	22; Netherlands; 19 female, 3 male, (mean age=56) patients classified with BMS. 13 wore Complete dentures; 7 had removable partial dentures; 2 had resin fillings only.	Dentures remade to exclude any mechanical irritants. Supplements used to correct nutritional deficiencies. Patch tests with routine, acrylate, dental metal, and food spice series. Prick tests done for various environmental factors.	10 pts had dental sensitivities: -2 →own denture material -4 →AuCl -9 →metal crowns/fillings -7→ food spice -2 pts diagnosed with Sjogren's syndrome. NO sensitivities to any bisphenol products tested (including acrylates)	Case Report Level III Grade I CC 8/13 Not all pts were tested using material from their denture or dental inlays. But, well controlled: a) hematologic and nutritional variation corrected for b) prick test used to exclude environmental triggers. BPA products are not involved with hypersensitivity-related BMS.

<p>Van Joost, Th., van Ulsen, J., van Loon, L. 1988.</p>	<p>4; Netherlands; 4 female denture-wearing patients present with BMS.</p>	<p>Patch tests with standard series and selected test materials. 8 controls (undefined) who were negative to all tests.</p>	<p>(1,2)Positive to own denture material; negative to all patch test agents, including MMA. (3) diagnosed with Sjogren's syndrome. (4) positive to epoxy resin.</p>	<p>Case Report Level III Grade I CC 7/13 (4) tested for BPA → positive Role of BPA in allergy-related BMS is questionable.</p>
<p>Hallstrom, 1993</p>	<p>1; 6-yr old female with an allergic reaction consisting of asthmatic reaction, severe urticaria with rashes and swelling after placement of fissure sealant.</p>	<p>- prescribed with Betapred 0.5mg x 4 days - removal of fissure sealant - Referred for dermatological testing [open, closed, prick, and 48-hr] of BHT, formaldehyde, Bis-GMA, benzoylperoxide. - Freshly mixed resin applied as closed and 48-hr test. TEGDMA was applied as a 48-hr test</p>	<p>No allergic reaction could be proven.</p>	<p>Case Report Level III Grade I CC 7/13 The patient's reaction/symptoms to the fissure sealant disappeared after removal of the sealant. No method exists to chart the origin of urticaria → lack of proof of allergic reactions in the case was not unexpected</p>
<p>Kanerva and Zwanenburg, 2000</p>	<p>1; Finland; 48 y.o. female dental patient with temporary crown, using ProTemp presented with contact dermatitis</p>	<p>Referred for dermatological patch testing.</p>	<p>Positive patch test for BIS-EMA</p>	<p>Case report; Level III Grade I CC 7/13 Bis-EMA caused the contact dermatitis.</p>

Table 4. Evidence for occupational bisphenol A allergic reactions in dental personnel.

Author, date	Population	Treatment	Outcome	Critical appraisal comments/strength of study/Conclusions
Kanerva and Zwanenburg, 2000	3; Finland; 3 case reports of contact dermatitis (1) 34 y.o. female dental nurse; (2) 48 y.o. female electronic assembler; (4) 33 y.o. male floor layer	Referred for dermatological patch testing.	(1) Known prior exposure to BIS-GMA; patch tested positive for DGEBA and BIS-EMA; (2) Positive patch test for DGEBA; (3) Known prior exposure to DGEBA; patch tested positive to BIS-EMA and BIS-GMA	Case report; Level III Grade I CC 7/13 Evidence for cross reactivity among DGEBA, BIS-EMA and BIS-GMA.
Kanerva, Jolanki and Estlander, 1986	21; Finland; Case reported was 20 y.o. female dental assistant; 20 control cases- no details given.	All 21 individuals were subjected to patch tests.	Only the case individual had positive reaction to epoxy resin, 1% and BIS-GMA, 2%; no reaction to other components of the resin that triggered the initial incident of dermatitis.	Case report Level III Grade I CC 7/13 BIS-GMA was likely the cause of the initial incident of allergic contact dermatitis.
Jolanki, Kanerva, Estlander, 1995	2; Finland; (1) female dental assistant with allergic contact/ hand dermatitis. (2) male process worker in a paint factory with vesicular dermatitis on his hands.	Referred for dermatological patch testing	(1) Positive patch test to 1% BPA, formaldehyde. Negative patch test to epoxy dimethacrylates and standard epoxy resin. (2) Positive patch test to 0.016% BIS-GA, HDDA, TRPGDA. Negative patch test to epoxy dimethacrylates, epoxy resin, BPA.	Case Report Level III Grade I CC 8/13 (1) The dermatitis was likely caused by BPA; when the patient avoided exposure to it, symptoms stopped. (2) The dermatitis was likely caused by BIS-GA, HDDA, TRPGDA, which he was sensitized to at work. (no cross-reactivity between Bis-GA and BPA)

<p>Kanerva, L, Estlander, T. Jolanki, R. 1989.</p>	<p>7; Finland; 6 dental nurses and 1 dentist (all female) with contact dermatitis. Year of diagnosis ranged from 1979-87.</p>	<p>Patch tests with standard, dental, acrylate, rubber, antimicrobial series. Prick tests done for common environmental allergens.</p>	<p>100% positive to the resin they used→ 4/5 were +ve to BisGMA 2/5 to MMA 3/5 to aliphatic acrylates (TREGDA, TREGDMA).</p>	<p>Case Report Level III Grade I CC 7/13 Not all pts were tested with same series of patch tests. BUT Very extensive patch test series, prick test excluded environmental triggers. BPA may trigger contact dermatitis</p>
<p>Aalto-Korte <i>et al.</i>, 2003</p>	<p>3; Helsinki; Finland; (1) 52-year old dentist with 3-year history of hand dermatitis (2) 23-year old oral hygienist apprentice with a history of allergic rhinitis and childhood hand and foot dermatitis (3) 51 year-old cabin servant on a passenger ship with contact dermatitis to inexpensive jewelry and metal buttons</p>	<p>Referred for dermatological patch and prick tests</p>	<p>(1,3) Negative prick test to: control environmental series, (1)dental care allergens, (3) natural rubber latex. (1)Positive patch test to: BPA, p-tertiary butyl catechol and Merthiolate. (2) Positive prick tests to some environmental allergens Positive patch test to: BPA, p-phenylenediamine base, p-tertiary butyl catechol, Evercare Soft vinyl glove, disposable vinyl glove (3)Positive patch test to: nickel sulfate, balsam of Peru thiuram mix, TETD, BPA, Swehand Combex and Swehand Combex-Light vinyl gloves.</p>	<p>Case Report Level III Grade I CC 7/13 -(2,3)→ occupational contact dermatitis from BPA detected in <i>Evercare</i> disposable vinyl gloves -(2,3) reacted to p-tertiary butyl catechol, (not found in <i>Evercare</i> gloves) and to <i>Evercare</i> gloves. →No proof that the use of vinyl gloves leads to sensitization to p-tertiary butyl catechol. -(3)had occupational dermatitis from the BPA found in household vinyl gloves</p>

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