

**Date of IRB: July 2009
81st Medical Group
Keesler AFB, Mississippi**

Greater than Minimal Risk or Minimal Risk Human Research Protocol

This is a Progress Report ____ / Final Report __XX__

1. Protocol Number: FKE20060002H

2. Protocol Title: “Bisphenol A and Other Metabolites in Human Saliva and Urine Associated with the Placement of Composite Restorations”

3. Principal Investigator (PI): William J. Dunn, Col, USAF, DC, 81 DS/SGD, Phone: (228) 376-5190

4. Purpose: The purpose of this study is to determine the prevalence and changes in magnitude of detectable level of Bisphenol-A (BPA), Bisphenol-A metabolites and other chemicals containing the BPA moiety in saliva and urine after placement of composite fillings in adults. A secondary aim will be to estimate background population prevalence and concentrations for these compounds in saliva and urine.

5. Status of the Study. Mark the status of the study (a-g).

- a. ____ No subjects accrued in this study – termination requested.
- b. ____ No subjects accrued in this study – re-approval requested.
- c. ____ Active with ongoing treatment of subjects. Subject accrual not completed.
- d. ____ Active with ongoing treatment of subjects. Subject accrual completed.
- e. ____ Active with follow-up of subjects only – Subject accrual completed after the last IRB Continuing Review.
- f. ____ Active with follow-up of subjects only – Subject accrual completed before the last IRB Continuing Review.
- g. XX Completed. Request closure at this time.

6. Summary of Progress: This report covers the following period of time: August 2006 to June 2009

- a. Since Last Progress Report or Initiation of Study: Eight additional subjects have been enrolled for a total of seventy-eight.
- b. I have completed 100% of the study.
- c. I anticipate PCSing or separating on or about: June 2010.
- d. If this is a **FINAL REPORT**:

1. Were the protocol objectives met and how will the outcome benefit the DoD/USAF?

My part of the study is complete as one of the contributing sites in this study. The data was sent to the National Institutes of Health (NIH) to be analyzed for statistical results. The results will give us an idea of the biochemical safety of dental composite fillings by quantifying the amount of BPA.

Report Documentation Page

Form Approved
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1. REPORT DATE JUL 2009	2. REPORT TYPE Final Report	3. DATES COVERED 00-08-2006 to 00-06-2009			
4. TITLE AND SUBTITLE Bisphenol A and Other Metabolites in Human Saliva and Urine Associated with the Placement of Composite Restorations		5a. CONTRACT NUMBER Y1-DE-7002-01			
		5b. GRANT NUMBER			
		5c. PROGRAM ELEMENT NUMBER			
6. AUTHOR(S) William Dunn		5d. PROJECT NUMBER FKE20060002H			
		5e. TASK NUMBER			
		5f. WORK UNIT NUMBER			
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) 81st Medical Group, 301 Fisher St, Keesler AFB, MS, 39534		8. PERFORMING ORGANIZATION REPORT NUMBER FKE20060002H			
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) National Institute of Health (NIH), National Institute for Dental/Craniofacial Research, 45 Center Drive, Bethesda, MD, 20892-2190		10. SPONSOR/MONITOR'S ACRONYM(S) NIH-NIDCR			
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)			
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Dental composite resins are formulated from a mixture of monomers and are most commonly based on bisphenol A glycidyl methacrylate (bis-GMA). A study by Olea et al (1996) reported that detectable quantities of specific compounds, bisphenol A (BPA), bis-GMA and bis-DMA were present in saliva after placement of a dental sealant. They also reported that these compounds possess estrogenic properties. This raised concern regarding the safety of dental sealants and composite restorations. Although several studies have been conducted in humans using dental sealants, there are virtually no data available from human studies using dental composite restorations, This suggests the need for research investigating potential leaching and systemic absorption of dental composite constituents. This is particularly relevant in light of the data from the American Dental Association survey of dentists which documented a large increase in the number of composite restorations being placed in the past decade (ADA, 2001). In 1999 an estimated 80 million composite fillings were placed by U.S. dentists. Compounds containing the BPA moiety may have estrogenic activity. Therefore, the primary goal of this study is to determine the concentration of chemicals containing BPA in saliva and urine following placement of dental composites.					
15. SUBJECT TERMS Bisphenol-A; Composite Restoration; Dental Research					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT 1	18. NUMBER OF PAGES 4	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

2. Protocol Outcomes Summary: *Provide in abstract format a summary of the protocol objectives, materials, methods, and results. Include tables/figures, and conclusions and applications.*

Dental composite resins are formulated from a mixture of monomers and are most commonly based on bisphenol A glycidyl methacrylate (bis-GMA). A study by Olea et al (1996) reported that detectable quantities of specific compounds, bisphenol A (BPA), bis-GMA and bis-DMA were present in saliva after placement of a dental sealant. They also reported that these compounds possess estrogenic properties. This raised concern regarding the safety of dental sealants and composite restorations. Although several studies have been conducted in humans using dental sealants, there are virtually no data available from human studies using dental composite restorations. This suggests the need for research investigating potential leaching and systemic absorption of dental composite constituents. This is particularly relevant in light of the data from the American Dental Association survey of dentists which documented a large increase in the number of composite restorations being placed in the past decade (ADA, 2001). In 1999 an estimated 80 million composite fillings were placed by U.S. dentists.

Compounds containing the BPA moiety may have estrogenic activity. Therefore, the primary goal of this study is to determine the concentration of chemicals containing BPA in saliva and urine following placement of dental composites. Presence of BPA, BPA metabolites, and other BPA-containing compounds above background levels in urine may indicate systemic absorption of these chemicals from saliva following dental restoration. The purpose of this study is to determine the prevalence and changes in magnitude of detectable levels of Bisphenol-A (BPA), Bisphenol-A metabolites and other chemicals containing the BPA moiety in saliva and urine after placement of composite fillings in adults. A secondary aim will be to estimate background population prevalence and concentrations for these compounds in saliva and urine. Saliva and urine samples will be collected before and after placement of composite restorations in a study population of 80 adult patients who need dental restorative treatment. These samples will be assayed for the specified components of interest. Consenting participants will be asked to receive composite restorations for class I posterior occlusal lesions, on buccal pits or lingual grooves of molars, and on any anterior surfaces needing restorative care. No randomization of patients will be performed as the background concentrations for these components will be determined from their pre-treatment samples. If the patient consents to be a participant the patient will be administered a baseline questionnaire by an interviewer to obtain basic demographic information and specific diet and eating patterns. The participant will be informed of the procedures for providing a saliva and urine sample. At this visit the patient will be asked to provide a saliva and urine sample. The patient will also be told that saliva and urine sample will be collected at the time of the placement of the composite restorations. Two saliva samples will be collected post placement, one during the first hour and a second 2 – 4 hours post-placement. One to two urine samples will be collected between 1 to 6 hours after placement. The patient will also be administered a follow-up questionnaire when the final samples are collected.

All patients will be assigned a study number and all data will be collected, labeled, and analyzed with this number. All data will be stored without patient identifiers at the NIDCR after merging clinical, questionnaire and laboratory data. Backup copies will be made by staff in the Biostatistics Core and stored off site as well as on site. US Air Force personnel will not have access to laboratory data and laboratory personnel will not have access to patient identification data to ensure privacy and confidentiality of the participants. No additional assays will be performed on urine or saliva samples besides those specifically stated in the protocol.

Prior to the initiation of the study samples of the specific composites used in the study will be tested for their composition. Specific types of class I cavities will be modeled using dentaform casts. Exact amounts of composite material needed to restore these cavities will be assessed. All qualifying tooth surfaces for the study will be filled with the composite materials selected by Air Force dentists. All composite materials will be from the same lot and all placed by using standardized procedures. All other dental care will be provided per the normal protocol practiced in the U. S. Air Force.

Data will be analyzed using paired t-tests (means of two pre-placement samples) versus the first (within 1-hr post-placement) sample for urine and saliva, separately (log scale). We will also attempt to model the concentration curves as a function of time since placement of composites to determine the excretion and elimination rate of BPA from the human system.

7. Demographic Information (a-e)

a. Target accrual number. What is the target accrual number approved by the IRB? 80

b. Non-accrual. If no subjects have been accrued since the last IRB review, the reason(s) for non-accrual should be provided. N/A

c. Total number of subjects accrued since activation of the study. What is the total number of a) adult male subjects (≥ 19 years) = 43 ; b) adult female subjects (≥ 19 years) = 35 ; c) pediatric male subjects (< 19 years) = 0 ; d) pediatric female subjects (< 19 years) = 0 .

d. Total number of subjects accrued by the ethnic origin. How many of the subjects accrued to date since activation of the study are in the following six ethnic categories? a) Caucasian = 53; b) Black, not of Hispanic origin = 18; c) Hispanic = 2; d) Asian/Pacific Islander = 5; e) American Indian/Alaska Native = 0; and f) Other or Unknown = 0 .

e. Explanation of subject accrual demographics. The demographics of the subject population must not reflect a disproportionate representation of one gender or minority/majority group which was either not approved by the IRB or is not reflective of the study site patient population. Explain how the subject accrual demographics comply with the requirement. The reason (s) for any appearance of inequitable recruitment of the subjects should be addressed.

Male/female ratio is appropriate. Ethnic ratio is appropriate.

8. Summary of Subject Experiences since the Last Report

a. Status of Subjects: The health status of all patients has not changed. This dental treatment is simple restorative dentistry and this will not change a patients' health status. There is no intended benefit to the patient from the study other than data gathering that will give the dental profession vital information on the leaching effects of some chemicals from dental fillings.

b. Summary of Adverse Events:

1) Unanticipated adverse event (s) reported to the IRB. From initial approval of the study to the present has any subject enrolled in your study suffered an unanticipated adverse event, which was reported to the IRB? No

2) Frequency of serious adverse events. From initial approval of the study to the present has the frequency of serious, but expected, adverse events been greater than predicted in your study? No

3) Adverse Events Which Occurred at External Sites. From initial approval of the study to the present have there been any external adverse event reports submitted to the IRB where the adverse event was related or possible related to the drug/intervention and were both serious and unexpected? No

9. Subject Withdrawal

a. Involuntary subject withdrawal. Were any subjects withdrawn from your study because of medical problems or complications? No

b. Voluntary subject withdrawal. Did any subject voluntarily withdraw from your study for non-medical reasons? Yes. Three patients withdrew from the study. These three patients received their filling but never returned for the final urine and saliva collection.

10. Current Risk-Benefit Assessment: There are no foreseen risks in this study. The current ICD adequately addresses the known risks and benefits.

11. Current information accuracy assessment. Is the informed consent document / assent form(s) still acceptable, i.e. the information contained in the document is accurate and complete and there is no new information that may have been obtained since the last IRB review which should be disclosed to the subject? No. ICD will be amended to reflect deletion of several associate investigators.

12. Bibliography. Conduct a new literature search and list publications which may be related to your protocol and report significant findings. No new literature was found on this topic.

13. Protocol Personnel Changes: Have there been any Principal (P.I.) or Associate Investigator (A.I.) changes since the last annual review? _____ Yes ___XX___ No

- a. Additions:
- b. Deletions:

14. Status of Approved Funding:

a. No funding from the Surgeon General Office (SGO) was requested in the original protocol.

b. I have received External Resources to support this study in the form of: A grant sponsored by the National Institute of Health (NIH)/National Institute for Dental/Craniofacial Research (NIDCR) totaling \$20,000.00.

15. Publications/Presentations: None

15.1. List Awards or Exceptional Achievements Associated With Publications/Presentations: None

Certification of Principal Investigator

My signature certifies that the above titled research has been conducted in full compliance with the HHS/FDA Regulations and IRB requirements/policies governing human subject research. I understand that a Progress Report is required in order to maintain continuation approval and any changes in the study/methodology must be approved by the IRB prior to implementation. If the study has never been initiated and I am requesting termination (Item 5.c. above), my signature certifies this request. If the study is completed (Items 5.d. & 6.c. above) and I am requesting closure, my signature certifies that the information provided on this form represents an accurate final report.



Signature of Principal Investigator
WILLIAM J. DUNN, Col, USAF, DC
81 DS/SGD

18 June 09
Date