Human Smoking Behavior Study

(Cigarette Yield and Body Burden of Smoke Toxins)

OMB No. 0920-0736

Request for Reinstatement with Change

SUPPORTING STATEMENT: PART A

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Abstract

The Centers for Disease Control and Prevention (CDC) received Office of Management and Budget (OMB) approval to conduct a study to elucidate patterns of human smoking behavior, to quantify biomarkers of exposure to smoke toxins under conditions of actual use, and to determine how smoking behavior modifies the relationship between cigarette yield category and biomarkers of exposure and measures of cardiovascular reactivity. Information has been collected from adult smokers of full-flavor, light and ultralight cigarettes (OMB No. 0920-0736, exp. 3/31/2010), however, the target number of respondents was not achieved during the initial approval period. CDC requests OMB approval to reinstate the information collection for two years in order to meet recruitment goals and complete the data analysis as outlined in the original approval. Changes described in this Reinstatement request include a reduction in the number of respondents and a corresponding reduction in the total estimated burden hours. There are no changes to the data collection instruments or the estimated burden per response.

A. Justification

A.1 Circumstances Making the Collection of Information Necessary

Smokers, at least partially, choose tobacco products on the basis of their perceived health risks, and cigarettes implied to be lower in tar (previously labeled as "light" or "ultra light") are perceived by some smokers as safer than full-flavored cigarettes. However, the public health data have not consistently shown differences in health outcomes among smokers of cigarettes of different machine-smoked yield categories. [1] A study that characterizes the relationship between machine-smoked yields and biomarkers that indicate exposure to toxic chemicals or predict adverse health consequences of smoking is needed to advance scientific understanding of the mechanisms whereby tobacco causes disease.

In 2007, CDC received OMB approval to conduct a study of variations in body burden of biomarkers proportional to machine-smoke yields of tar, nicotine and carbon monoxide (OMB No. 0920-0736, exp. 3/31/2010). The study was designed to elucidate patterns of human smoking behavior, to quantify biomarkers of exposure to smoke toxins under conditions of actual use, and to determine how smoking behavior modifies the relationship between cigarette yield category and biomarkers of exposure and measures of cardiovascular reactivity. Information was collected from adult smokers of full flavor, light and ultralight cigarettes, however, the target number of respondents was not achieved during the initial approval period.

The Centers for Disease Control and Prevention (CDC) seeks Office of Management and Budget (OMB) approval to reinstate information collection, with minor changes. Reinstatement will allow CDC to complete data collection and data analysis according to the study's original design specifications. The study is a joint venture involving CDC's Office on Smoking and Health (OSH) in the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), and the Division of Laboratory Sciences (DLS) in the National Center for Environmental Health (NCEH). The DLS/NCEH laboratory has established expertise of direct

relevance to the current information collection request. CDC has engaged a contractor to support data collection.

Additional information is needed to examine the relationship between cigarette smoke yield (based on machine-smoked tar and nicotine levels) and actual body burden of selected carcinogens, other toxins, and measures of cardiovascular reactivity (e.g. heart rate, blood pressure). The overall study design calls for approximately 360 established smokers, who use cigarettes with a range of machine-smoked yields, to provide urine and saliva samples for measurement of biomarkers of exposure under natural smoking conditions, and to provide their cigarette butts for determination of filter solanesol levels (another measure of exposure under natural smoking conditions). In addition, each respondent will smoke one cigarette of their usual brand during each of the two laboratory visits while smoking topography behaviors are measured and recorded, cardiovascular physiologic responses are recorded, and expired-air carbon monoxide levels are determined before and after smoking. Solanesol levels in spent cigarette butts from the laboratory smoking sessions will be compared with solanesol levels in the butts of cigarettes smoked under non-laboratory conditions. The design of the study is such that information will be available relative to both chronic habitual smoking under natural smoking conditions (e.g., biomarkers of exposure, collected cigarette butts), as well as information that must be generated within a laboratory environment (e.g., smoking topography behavior, changes in cardiovascular reactivity).

Due to delays in initiating the study and the need to balance respondents over a range of machine-measured yield categories (i.e., smokers of full-flavor, light and ultralight cigarettes), information collection was approximately two-thirds complete when the initial OMB approval expired on March 31, 2010. At that time, the data collection contractor had completed information collection for approximately 238 of the target number of 360 respondents. This Reinstatement request is submitted to permit the collection of information from the remaining122 respondents over a two-year period. Three considerations support this request:

(1) The data analysis plan. The power and specificity requirements of the study necessitate the collection of information from a total of 360 respondents, divided equally among users of full-flavor, light, and ultralight cigarettes. Conducting the planned analyses with a smaller number of respondents will compromise the power and specificity parameters established in the original study design, thus limiting the study's ability to detect differences in dependent variables.

(2) Relocation of the contractor's Human Exposure Assessment Laboratory. Because the study protocol requires respondents to come into a laboratory on two consecutive days, recruitment has focused on venues in reasonably close proximity to the lab. The lab is moving to another facility in the same metropolitan area in the summer of 2010. The new location is expected to provide new recruitment opportunities.

(3) In November 2009, CDC received OMB approval to modify the recruitment methods and to increase the payment to respondents. This change is also expected to facilitate completion of the study.

In summary, CDC requests OMB approval to reinstate the information collection utilizing the approved enhanced recruitment methods. Reinstatement will allow CDC to complete the study as planned and to fulfill the responsibilities delegated to the agency by the Federal Cigarette Labeling and Advertising Act (FCLAA; 15 U.S.C. §1341; see **Attachment A-1**). Under the Act, CDC/OSH has delegated authority to conduct and support research on the effects of cigarette smoking on human health. Authority for CDC to collect this data is granted by Section 301 of the Public Health Service Act (42 U.S.C. 241) (**Attachment A-2**).

Recent changes in tobacco product labeling, and their impact on study procedures, are noted here. Beginning June 22, 2010, it became illegal for manufacturers to manufacture for sale or distribution tobacco products labeled or advertised with the descriptors "light," "low," "mild," or similar descriptors. The Human Smoking Behavior study requires equal numbers of smokers of cigarettes previously labeled as "ultralight," "light," or full-flavor. During the period of this Reinstatement request, several steps will be taken to accurately categorize remaining participants in the Human Smoking Behavior study after the removal of descriptors from the cigarette pack. First, when screened for eligibility a participant's current brand of cigarette will be checked against a "look up" table that contains the previous brand name with descriptor and the current brand name without the descriptor. Second, when the participant arrives at the clinic they will be asked to provide one of their unsmoked cigarettes. The filter ventilation of the unsmoked cigarette will be determined with a laboratory instrument. Filter ventilation provides a reasonable approximation of tar delivery for categorization.

Privacy Impact Assessment

The proposed study involves a minimum amount of information in identifiable form (IIF). Respondents will be recruited from communities in the vicinity of the laboratory, i.e., in the suburban Baltimore area. The data collection contractor, Battelle International (Battelle), will have access to respondents' names, telephone numbers, and recruitment screening information in order to schedule clinic appointments for study participants. Medical history information will also be collected. The personal IIF is stored in an electronic database kept on a computer in a locked and alarmed office suite, and access will be limited to Battelle laboratory personnel. The database security complies with all Federal regulations. Participation in the study is voluntary.

Overview of the Data Collection System

Each eligible participant will participate in two clinic visits over a two-day period. The first visit will be in the morning of the first day and the second visit will be in the afternoon of the consecutive day. Between visits participants will collect the cigarette butt from each cigarette that they smoke. They will also keep a diary that corresponds to their mood and activity when smoking. The cigarette butts and diary are turned in at the second clinic visit. Deleting any data collection would lead to inadequate data. Following completion of the data collection, the identifying information will be destroyed. Publication of results will be in the aggregate with no identification of individual respondents.

Items of Information to be Collected

The data collection activities for this study will involve collection of urine, saliva, breath carbon monoxide, smoking behavior (one cigarette at each visit), measures of cardiovascular reactivity (heart rate, blood pressure), ventilation hole blocking behavior and breath measurements at each of two visits over a two-day period. The first visit will be in the morning of the first day, and the second visit will be in the afternoon of the consecutive day. This schedule is important because during the morning of day 1, biomarker levels should commonly be at their nadir, while during the afternoon of day 2, biomarker levels should commonly be at their peak. This will allow a realistic approximation of smoking behavior and biomarker levels in the same individual when nicotine (and other biomarker) levels are at their lowest (after awakening and relatively few cigarettes) and at their highest (later in the day following the opportunity to smoke several cigarettes).

Identification of Website(s) and Website Content Directed at Children Under 13 Years of Age

The proposed research does not involve the collection of information through websites, or any website content directed at children under 13 years of age.

A.2 Purpose and Use of Information Collection

The main objective of the study is to determine if body burdens of selected carcinogens, cardiovascular toxins and measures of cardiovascular reactivity vary in proportion to machine-smoked yields of tar, nicotine, and carbon monoxide across a wide range of commercially available cigarettes. Another objective of the study is to determine if the relationship of machine-smoked cigarette yield to body burden of carcinogens and other toxins is modified by smoking behavior (measures of how the cigarette is smoked). A third objective is to determine if solanesol levels in spent cigarette filters (a surrogate measure of total smoke exposure) vary in proportion to machine-smoked yield of the cigarettes under both controlled (laboratory) and naturalistic (home) conditions. A summary of biomarkers, the biological matrix and laboratory method used for their measurement, and their use, is provided in **Attachment C**.

The specific aims of the study are:

Aim 1. Determine the body burden of smoke toxins and cardiovascular physiologic reactivity associated with smoking cigarettes across a wide range of cigarette yields.

The biomarkers to be measured include carcinogens and other toxic chemicals such as urinary NNAL [4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol] and NNAL-glucuronide, two metabolites of the nicotine-derived NNK [4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone], S-phenyl mercapturate (a biomarker for benzene exposure), 1,3-butadiene, acrolein, aromatic amines (primarily 4-aminobiphenyl), thiocyanate (biomarker for cyanide exposure), urine nicotine and nicotine metabolites (nicotine-glucuronide, cotinine, 3-hydroxycotinine, 3-hydroxycotinine-glucuronide, cotinine-glucuronide, nornicotine, norcotinine-glucuronide, and cotinine-N-oxide), hydroxyl-polycyclic aromatic hydrocarbons, cadmium, arsenic and saliva cotinine levels, and expired-air carbon monoxide levels. Physiologic measures will include changes in heart rate and blood pressure associated with cigarette smoking. Fulfilling this aim has

significant societal implications given that it is not known to what extent cigarette yield category determines the body burden of toxins and carcinogens and cardiovascular physiologic reactivity.

Aim 2. Determine if the body burden of smoke toxins (biomarkers of exposure) associated with smoking cigarettes with a range of machine-smoked tar and nicotine levels is modified by smoking behavior.

Smokers require sufficient levels of nicotine to prevent withdrawal symptoms. According to the nicotine titration hypothesis, smokers will adjust their smoking behavior throughout the day and when smoking cigarettes in different yield categories to maintain an accustomed level of nicotine.[2] For example, some studies report that smokers change their smoking behavior by increasing the total volume of smoke puffed per cigarette and/or by slightly prolonging puff duration when switching to lower yield cigarettes.[3,4] In contrast to those studies, this study will not have smokers switch between cigarette brands or between cigarette yield categories but rather will provide a detailed understanding of the relationship between an established pattern of smoking behavior for a cigarette yield category and smoking-related biomarkers for the major yield categories of cigarettes consumed in the U.S.

Aim 3. Determine if the machine-smoked yield of "tar" is significantly positively correlated with solanesol levels in spent cigarette filters (a measure of mouth level exposure to tobacco smoke), which in turn will be significantly positively associated with levels of carcinogens and other toxins in smokers.

Solanesol in the spent cigarette filter has been proposed as a marker for estimating smoke uptake regardless of how a cigarette is smoked.[10] If a significant positive correlation can be established between filter solanesol levels and machine-smoked yields and between solanesol levels and biomarkers of exposure, solanesol in spent filters can be used in population-based studies of smokers and to screen products marketed with claims of reduced exposure.

What the proposed study adds. The proposed study will extend the results of earlier studies by providing information about the actual body burden of carcinogens and non-cancer biomarkers of exposure among established smokers of cigarettes of a wide range of machine-derived smoke yields. This study will also assess smoking behavior among the participants. A long held theory of smoking behavior posits that people smoke for the delivery of nicotine within a narrow range, maintaining levels of nicotine above those associated with tobacco withdrawal symptoms and below those that are associated with toxicity.[9] It may be that the smoker titrates intake of nicotine in smoke within a fairly small range, so that body burdens of toxins and carcinogens are similar across cigarette types. On the other hand, it may be that there is a significant reduction of some biomarkers following chronic use of low machine-yield cigarettes, without reductions (or even with increases) in other biomarkers. This study will clarify these important issues.

Assessing cardiovascular endpoints. Previous studies have focused almost exclusively on exposure to lung carcinogens in smoke. While cancer is an important and often fatal outcome of

exposure to cigarette smoke, cardiovascular disease is a more frequent outcome than all smoking-related cancers combined.[10] The laboratory component of the study will allow real-time measurements of cardiovascular endpoints, such as changes in heart rate, blood pressure, and expired-air carbon monoxide (CO), before, during and after a cigarette smoking session. Cardiovascular reactivity, CO saturation of hemoglobin and increased resting blood pressure are considered contributors to the cardiovascular risks associated with chronic smoking. These measures are clearly important in elucidating how tobacco causes disease yet there are very few studies that have examined whether these measures differ as a function of cigarette yield category. [11,12]. This study will address this critical research gap.

Assessing smoking behavior. The two laboratory visits will be used to assess puffing (volume, velocity, duration, time between puffs) and inhalation behavior to determine if the relationship between cigarette yield category and levels of biomarkers of exposure is modified by distinct, quantifiable measures of how the cigarette is smoked (smoking behavior). These measures can only be obtained with a high level of accuracy in a controlled laboratory environment. In addition, the laboratory visits will be used to collect unique information about the study participant, such as smoking history (e.g., cigarettes smoked per day), to assess any differences in average daily cigarette consumption and smoke exposure. For instance, if smoker A consumes 30 cigarettes/day and smoker B consumes 20 cigarettes/day it would be logical to assume that smoker A has a higher exposure. However, if smoker B typically consumes more of the cigarette (leaves a shorter butt), takes more frequent (or larger puffs), the overall exposure for B could exceed that of smoker A.

The role of laboratory and naturalistic smoking on filter solanesol levels. In the proposed study, solanesol levels in spent cigarette filters collected during an extended period of naturalistic smoking will be compared to levels in the filters of cigarettes smoked in the laboratory. This evaluation will determine if filter solanesol levels vary in proportion to the yield category of the cigarette similarly under both controlled (laboratory) and naturalistic (home) conditions. Laboratory smoking is the standard for evaluating smoking patterns, so such a comparison among a large number of smokers will be an important addition to the science.

The results of this study will have theoretical and practical implications. Ultimately, the information gained from this study can help the public health community to determine if some smokers experience a reduction in exposure to carcinogens and other toxins, or a reduction in cardiovascular reactivity, by smoking cigarettes with reduced machine-smoked yields. The study may also assist in determining if a reduction in some toxins is accompanied by an increase in others. For example, if smokers increase their puff duration to achieve a certain nicotine level, they may have lower levels of tobacco-specific nitrosamines but take in more carbon monoxide. This is a conjecture for which evidence for or against can be generated in the proposed study.

Carbon monoxide levels and heart rates will be provided to participants if they are interested in knowing them. An average range for comparison will also be provided.

Privacy Impact Assessment

The IIF will be stored in an electronic database kept on a computer in a locked and alarmed office suite in the contractor's facilities. The database security complies with all Federal regulations. Access will be available only to the contractor's designated laboratory personnel. The computer program that allows access to the database is password protected and requires a secure ID token for access. All contractor personnel are trained in privacy principles and all undergo yearly human subjects' protection training. While the database with IIF will be kept separately from the database of questionnaire responses and other study data, identifying numbers will be used to connect the two databases; therefore, the contractor has the ability to link data to respondent. The sensitive information includes medical history of heart or lung disease, smoking history, and free, voluntary pregnancy testing if requested by the respondent. Participation in the study is voluntary.

A.3 Use of Improved Technology and Burden Reduction

The study makes use of automated and electronic information collection techniques. A brief computer-assisted telephone interviewing (CATI) instrument (**Attachment D – Computer-Assisted Telephone Screening Instrument)** has been designed to support respondent screening and recruitment. The instrument will collect basic demographic data (age, gender, race/ethnicity), and elicit respondent's initial willingness to participate in the study. Use of the CATI will reduce the burden to the respondent because it normally reduces the amount of time necessary to respond to a questionnaire. Computer-assisted telephone interviewing also captures data more accurately than paper and pencil methods. This reduction of time and improved accuracy will result in a lower cost overall for the project.

An additional brief questionnaire to confirm eligibility will be administered at the first laboratory clinic visit. This will be a computerized questionnaire administered by laboratory clinic staff (**Attachment E-1 – Visit 1 Eligibility Screener**). Participants will be asked to read and sign two copies of a consent form; one will be for their records and one will be kept in a locked file at the laboratory clinic (**Attachment E-2 – Informed Consent Form**).

A.4 Efforts to Identify Duplication and Use of Similar Information

A review of the literature was conducted with researchers from CDC and the contractor, Battelle Centers for Public Health Research and Evaluation (Battelle), to determine the current state of knowledge.

The issues to be resolved. The average sales-weighted machine-smoked yields of tar from American-manufactured cigarettes have fallen from 21.6 mg in 1968 to 12.0 mg in 1998, and nicotine levels have fallen from 1.35 mg to 0.88 mg during that time[5]. In order to understand the relationship between cigarette yield and actual exposure to smoke toxins, it is necessary to determine the body-burden of carcinogens and other smoke toxins in smokers of a wide range of machine-yield cigarettes.

What we already know. Small sample laboratory studies of emissions generated by machine-smoking of cigarettes indicate that people smoke both low- and medium-nicotine cigarettes more intensely than would be implied from smoke emissions generated by machine smoking.[2,6] For

example, in a study of 72 smokers of low-yield (0.8 mg of nicotine or less per cigarette by standard Federal Trade Commission (FTC) machine-smoked measures) or medium-yield (0.9–1.2 mg of nicotine per cigarette by FTC measures) cigarettes, observed smoking patterns were programmed into a piston-type smoking machine. Smoke was generated from each smoker's usual brand of cigarettes for assays of nicotine, carbon monoxide, tar, and the two lung carcinogens (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and benzo[a]pyrene (B[a]P)). For comparison, the FTC protocol was also used to assess levels of targeted components in the 11 brands most frequently smoked by study subjects. Compared with the FTC protocol values (35 mL puff volume), smokers of low- and medium-yield brands took in statistically significantly larger puffs (48.6 and 44.1 mL, respectively) at statistically significantly shorter intervals (21.3 and 18.5 seconds, respectively-FTC value is 60 seconds). They also drew larger total smoke volumes than specified in the FTC parameters. If smokers took in the amounts of toxins generated by machine-smoking using parameters that mimicked the human smoking, they would receive, with low- and medium-yield cigarettes respectively, 2.5 and 2.2 times more nicotine and 2.6 and 1.9 times more tar than FTC-derived amounts, as well as about two-fold higher levels of NNK and B[a]P.[2]

Even when human smoking patterns are mimicked by programming human puff profiles into a smoking machine, there is some distinction in toxin yield between low- and medium-yield cigarettes. The following table shows this distinction even in a relatively small sample study that utilized only low-yield and medium-yield (FTC) cigarettes.[2]

Component of Smoke	Low-Yield n=30 Geometric Mean (95% CI)	Medium-Yield n=42 Geometric Mean (95% CI)
B[a]P, ng/cigarette	17.9 (15.3-20.9)	21.4 (19.2-23.7)
NNK, ng/cigarette	186.5 (158.3-219.7)	250.9 (222.7-282.7)
Nicotine, mg/cigarette	1.74 (1.54-1.98)	2.39 (2.20-2.60)
"Tar", mg/cigarette	22.3 (18.8-26.5)	29 (25.8-32.5)

What we need to know:

1. Is there a difference in actual body burden of smoke toxins among smokers of cigarettes of different yield categories, i.e, with a broad range of machine-smoked yields?

2. Is there a difference in cardiovascular biomarkers and reactivity among smokers of cigarettes of different yield categories?

Small studies have attempted to address the first question, but the second remains unanswered. In one study, the influence of the smoking parameters (puff profile, puff duration, puff volume, puff frequency) on the delivery of tobacco-specific nitrosamines (TSNAs) in mainstream smoke was investigated by manipulating smoking-machine settings (changing individual settings by holding the others constant, a process that would be difficult to duplicate with human smokers).

Six different cigarette brands were investigated, including filter cigarettes with very low to medium smoke yields and nonfilter cigarettes with high and very high smoke yields. The puff profile (shape of the puff) and puff duration did not influence the TSNA yields. Increasing puff volume and puff frequency, however, resulted in increased TSNA levels. The dependency of the TSNA delivery on the total volume was almost linear, at least up to a total volume of approximately 500 mL/cigarette, and was the same for the same total volume regardless of whether the change in volume was due to an increased puff volume or a puff frequency.[7]

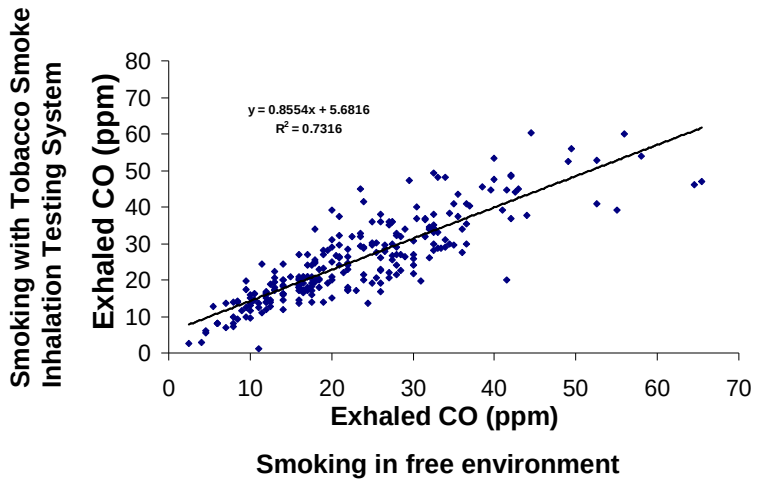
These previous studies have mimicked human smoking with smoking machines, and measured the machine-generate smoke emissions. Studies in which machines were programmed to smoke in a manner similar to actual smokers have shown higher yields of smoke toxins than are generated by smoking machines operating with the less intense FTC smoking regimen, but a comparable increase in body burden of toxins has not yet been demonstrated.

Bernert and co-workers determined differences in cancer biomarkers (urinary TSNAs and 4-aminobiphenyl hemoglobin adducts) in smokers of either "regular" or "light" cigarettes.[8] They were unable to detect differences in these biomarkers as a function of cigarette type. However, because of the study design, the statistical power to detect a difference was low. The cigarettes tested had a relatively narrow range of FTC "tar" and nicotine levels, and appeared to have been dichotomized as "regular" or "light" based on product labeling rather than as a continuous measure. Measures of smoking behavior and several other important covariates were not included. Biomarkers associated with cardiovascular disease and other smoking related mortalities were not tested.

In another study, urine samples from smokers were collected and analyzed for 1-hydroxypyrene (1-HOP), and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL plus its glucuronides) – both of which are lung carcinogens.[6] Forty-seven of the participants who provided the urine samples smoked regular cigarettes, 80 smoked light cigarettes, and 48 smoked ultralight cigarettes. No statistically significant differences in lung carcinogens were observed among the smokers of regular, light, or ultralight cigarettes. Unfortunately, the confidence bounds around the means within each group were very wide, and the study may not have been sufficiently powered to find a difference if there had been one. Other than the two lung carcinogens (1-HOP and NNAL), the only other exposure biomarker measured was cotinine and its glucuronides (an indicator of nicotine intake).

<u>The relationship between laboratory and naturalistic smoking.</u> Two independent studies have assessed the relationship between naturalistic smoking and smoking a cigarette through a mouthpiece under laboratory conditions. Reliability data were obtained when the smoking behavior of subjects (n = 7) was measured while drawing puffs through the mouthpiece on four separate experimental days or when subjects (n = 10) smoked on two separate days, once conventionally, and once through a mouthpiece. [13] Smoking behavior measures did not differ significantly between conditions, suggesting that laboratory assessed smoking behavior provides a valid and reliable index of smoking and an indirect measure of smoke exposure. In another report (n = 260 subjects), a good correlation was found between the levels of exhaled CO when volunteers smoked cigarettes freely and when they smoked with the puff analyzer (Figure 1; Melikian and Djordjevic 2004/unpublished data) [2,6].

Figure 1. Correlation of exhaled CO when smokers smoke under naturalistic conditions *vs.* exhaled CO when cigarettes are smoked in laboratory with a puff analyzer mouthpiece



Conducting the study in one area, will not bias the results. A World Health Organization analysis of 46 reports from around the world, with the preponderance of studies from North American locations, failed to find meaningful differences in smoking behavior by location.[14] In that review, even the amount of the cigarette left unsmoked showed no regional variation. In addition, the 1988 Surgeon General's Report showed remarkable similarities in measurements of smoking behavior across 32 U.S. laboratories.[15] Because of these authoritative findings, it can be concluded that performing the study in area (Baltimore, Maryland), with adequate statistical power to accommodate the inter-individual differences in topography, will produce unbiased results.

A careful review of the literature shows that the information to be collected in this study is not available through other sources.

Table A.4-1. Persons contacted to avoid duplication

Persons contacted	**Date most recently contacted**
Pamela I. Clark, PhD Battelle Centers for Public Health Research and Evaluation	June 2006
Deon Harvey, PhD Battelle Centers for Public Health Research and Evaluation	June 2006
Wallace Pickworth, PhD Formerly at the National Institute on Drug Abuse/Now at Battelle	June 2006
David Ashley, PhD CDC Division of Laboratory Sciences (at time of initial contact)	June 2006
Clifford Watson, PhD	June 2006

CDC Division of Laboratory Sciences	
Patricia Richter, PhD CDC Office on Smoking and Health	August 2010

A.5 Impact on Small Businesses or Other Small Entities

No small businesses will be involved in this study.

A.6 Consequences of Collecting the Information Less Frequently

This is a one time study. The data collection activities for this study will involve collection of urine, saliva, breath carbon monoxide, smoking behavior (one cigarette at each visit), measures of cardiovascular reactivity (heart rate, blood pressure), ventilation hole blocking behavior and breath measurements at each of two visits over a two-day period. The first visit will be in the morning of the first day, and the second visit will be in the afternoon of the consecutive day. This schedule is important because during the morning of day 1, biomarker levels should commonly be at their nadir, while during the afternoon of day 2, biomarker levels should commonly be at their peak. This will allow a realistic approximation of smoking behavior and biomarker levels in the same individual when nicotine (and other biomarker) levels are at their lowest (after awakening and relatively few cigarettes) and at their highest (later in the day following the opportunity to smoke several cigarettes). Deleting any data collection would lead to inadequate data.

There are no legal obstacles to reduce the burden on study subjects.

A.7 Special Circumstances Relating To The Guidelines Of 5 CFR 1320.5

This study complies fully with guidelines of 5 CFR 1320.5. No exceptions to the guidelines are required.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A.8.A. A 60-Day Federal Register notice was published in the *Federal Register* on March 4, 2010, Vol. 75, No. 42, pages 9901-9902 (**B – Federal Register Notice**). No public comments were received in response to this Notice.

A.8.B. The following table (Table A.8-1) lists the names of some of the scientists who reviewed the study material:

A.8-1. Non-agency Personnel Contacted

Name	Agency	Email	Phone Number
Dr. Patricia Richter, Toxicologist	NCCDPHP/OSH	pir1@cdc.gov	(770) 488-5825
Dr. David Ashley, Director, Office of	OS/CTP/FDA	david.ashley@fda.hhs.gov	(301) 796-9326

Science, Center for Tobacco Products, Food and Drug Administration			
Dr. Clifford Watson, Research Chemist	NCEH/DLS	cow1@cdc.gov	(770) 488-7638
Dr. Pamela Clark, Research Professor	Formerly with Battelle. Currently with the University of Maryland	clarkp@umd.edu	(301) 405-8624
Jennifer Malson Laboratory Director	Battelle	malsonj@battelle.org	(410) 372-2724
Dr. Wallace Pickworth, Senior Health Researcher	NIDA/Battelle	pickworthw@battelle.org	(410) 372-2706

The original consultations with the above individuals (except Jennifer Malson, whose involvement with the study began in 2008) took place in 2004 and are ongoing. There were no major problems that arose during consultation. Early development plans and collaborations were discussed between NCCDPHP and NCEH.

A.9 Explanation of Any Payment or Gift to Respondents

The study population is smokers of legal age in Baltimore, Maryland, who will be recruited by placing study advertisements in local newspapers and posting study flyers on public bulletin boards in the areas near the geographic location of the laboratory clinic. Enhanced recruiting to reach target smoker populations will include advertisements printed in local newspapers, distributed on cars, gate latches and doors, and handed out to potential participants and distribution of flyers to individuals seen smoking near the laboratory with a number to call if they are interested in hearing more about laboratory research opportunities related to smoking. To compensate each study subject for his/her time and inconvenience, remuneration will be according to the schedule shown in Table A.9-1. Because the completion of each visit represents a considerable investment of study resources, and subjects who drop out or are non-compliant after their first visit must be replaced, we plan escalating reimbursements for each completed visit and a bonus of a gift certificate worth $25 for a local merchant for completing all parts of the study. Also, because recruitment efforts for smokers of cigarettes in particular yield categories is difficult, we will use a referral incentive; any participant that enrolls in the study and also refers another person who enrolls in the study will receive a $25 referral bonus. Our incentive of $80 for completing both visits is in accordance with our previous study, the Menthol Crossover Study, with similar procedures (OMB No. 0920-0606, exp. 10/31/2004). The Menthol Crossover Study required three visits and we found that escalating reimbursements appeared to decrease our drop-out rate between visits 2 and 3 by 23%. We also found in the Menthol Crossover Study that a referral incentive increased the number of eligible participants in hard-to-reach cells by seven (e.g. African American non-menthol smokers), better than what we accomplished via multiple advertisements and flyers.

The payment to respondents is compensation for time and inconvenience. Institutional Review Boards (IRBs) for the protection of human subjects at CDC and Battelle, contractor, have

completed their reviews of the protocol for this study (**Attachment I –IRB Approval)**. Both have found that the proposed incentives are sufficient to compensate people for the inconvenience caused by study participation, but do not represent an unreasonable inducement to participate.

Table A.9-1. Payment Schedule.

Activity	Total
Complete Visit 1	$10
Visit 1 Eligibility Screener	
Smoking through the machine	
Carbon Monoxide Measurements	
Bringing in 4 smoked butts	
Urine and Saliva Specimens	$10
Keeping Appointment on Time	$10
TOTAL VISIT 1	**$30**
Complete Visit 2	$10
Smoking through the machine	
Carbon Monoxide Measurements	
Urine and Saliva Specimens	$10
Butt Collection	$20
Keeping Appointment on Time	$10
TOTAL VISIT 2	**$50**
Bonus for completing all parts of the study	**Gift certificate worth $25 for a local merchant**
TOTAL	**$80 plus gift certificate worth $25 for a local merchant**

A.10 Assurance of Confidentiality Provided to Respondents

This information collection has received IRB review and approval (**Attachment I).**

A. Privacy Act Determination. The CDC Privacy Act Officer has reviewed this OMB application and has determined that the Privacy Act is applicable. The contractor will have access to IIF including respondent names, contact information, data collected during laboratory visits, and selected medical history information. IIF and response data will be maintained in separate electronic files as a safeguard against inadvertent disclosure, but response data will be linkable to IIF. The applicable Privacy Act system of records is 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems." B. Safeguards. The IIF will be stored in an electronic database kept on a computer in a locked and alarmed office suite in the contractor's facilities. The database security complies with all Federal regulations. Access will be available

only to the contractor's designated laboratory personnel. The computer program that allows access to the database is password protected and requires a secure ID token for access. All contractor personnel are trained in privacy principles and all undergo yearly human subjects' protection training. The contractor will maintain IIF data used for visit scheduling in files that are separate from response data files, however, response data files can be re-linked to IIF through unique respondent identifier codes. The sensitive information includes medical history of heart or lung disease, smoking history, and free, voluntary pregnancy testing if requested by the respondent. All biologic samples will be identified by study and ID number only.

Participant smoking sessions will be video taped. Video tapes will be identified by ID number only and will be stored in a locked cabinet. Video tapes will be destroyed after data analysis is complete.

Following completion of the data collection, the identifying information will be destroyed. Publication of results will be in the aggregate with no identification of individual respondents.

C. Consent. The consent form is included as **Attachment E-2**.

D. Voluntary Nature of Participation. Participation in this research project is voluntary. Participants, who are screened as either eligible or ineligible, also will be asked if they would like the contractor (Battelle) to keep their information on file for future studies. This information will not be shared and will be stored in a separate database in a locked and alarmed office suite as noted above. Similarly, password protections and secure ID access will be in place.

A.11 Justification for Sensitive Questions

The study will ask questions of a sensitive nature. During the screening interview questions will inquire whether the study subject has ever been told by a healthcare professional that they have/had lung or heart problems or have been diagnosed with cancer. Some people feel uncomfortable discussing medical conditions such as lung disease or heart problems. Smoking histories will also be obtained. In addition, women will be asked if they are pregnant, breastfeeding, or trying to become pregnant. These questions are necessary because we are not including people with cancer or heart or lung problems or un-established smokers (daily smoking for less than two years) in the study. These groups are not included because it is unethical to enroll participants with tobacco-related diseases, novice smokers, or pregnant or breastfeeding women into a smoking study. If a woman does not know if she is pregnant, she will be offered a free, voluntary pregnancy test. Smoking histories are necessary in order to have an accurate picture of the subject's baseline smoking levels. The smoking history information will also aid in analyzing the smoking behavior data. Basic demographic data such as age and gender will also be collected to establish the prospective respondent's eligibility to participate in the study.

Prospective subjects will be informed that the study involves cigarette smoking and will require them to smoke their own brand of cigarette for inclusion into the study. The basic procedures of the study will be explained.

A.12 Estimates of Annualized Burden Hours and Costs

A.12.A. Study participants will be established smokers, defined as smoking daily for at least two years, smoking a minimum number of 6 cigarettes per day, and a maximum number of 40 cigarettes per day, and aged 18 or older.

Individuals who are interested in participating will be screened for eligibility during a brief five-minute computer-assisted telephone interview (CATI; see **Attachment D**). We estimate screening approximately 150 individuals to yield complete data collection on the target of 61 respondents per year. Persons who express continued interest in study participation after the CATI will undergo five additional minutes of eligibility screening at the first laboratory visit (**Attachment E-1**). Individuals who enroll in the study will also go through a consent process (see **Attachment E-2**). Participants will be recruited in the areas near the geographic location of the laboratory clinic in Baltimore, Maryland (see recruitment materials in **Attachment F**).

Each respondent who enrolls in the study will make two one-hour visits to the Human Behavior Assessment Laboratory. The visits will occur on two consecutive days: Visit 1 will be scheduled in the morning of the first day, and Visit 2 will be scheduled in the afternoon of the second day. Samples, measurements, and behavioral information will be collected at each visit, which will last about one hour (**Attachment G-1**). Visit 1 will include the informed consent process, biologic sample collection (urine, saliva, breath carbon monoxide), smoking behavior of smoking one cigarette, ventilation hole blocking procedure and breath measurements. Visit 2 will include compensation, discussion of quit opportunities if requested, biologic sample collection (urine, saliva, breath carbon monoxide), smoking behavior of smoking one cigarette, ventilation hole blocking procedure and breath measurements. In addition, at Visit 2, each respondent will submit the cigarette butts of all cigarettes smoked since Visit 1 and a completed Smoking Diary Form (**Attachment H**) at each laboratory visit. The estimated burden for the Smoking Diary Form is ten minutes. The response burden for each element is based on the research team's previous experience with similar data collections.

OMB approval is requested for a two-year period. Table A.12-1 summarizes the estimated annualized burden based on the number of respondents needed to complete the study. This estimate represents a subset of the total number of respondents involved in the overall study. The total estimated annualized burden for this Reinstatement request is 151 hours.

A.12-1. Estimated Annualized Burden Hours

Type of Respondent	Form Name	No. of Respondents	No. of Responses per Respondent	Average Burden per Response (in hours)	Total Burden (in hours)
Adult Smokers	CATI Screener	150	1	5/60	13
	Visit 1 Screener	70	1	5/60	6
	Smoking	61	1	10/60	10

	Diary				
	Laboratory Visit	61	2	1	122
	Total				151

Information about the overall study plan is presented in Section B.1. Data analysis for the overall study will include information collected during the original OMB approval period, as well as information collected during the period of this Reinstatement request.

A.12B. There are no costs to the respondents other than their time. Bus passes will be freely available to participants as needed. Respondents are participants aged 18 years or older. Average hourly wage is based on current minimum wage. The estimated annualized cost to respondents is $1,096.00, as summarized in Table A.12-2.

Table A.12-2. Estimated Annualized Cost to Respondents

Type of Respondent	Form Name	No. of Respondents	No. of Responses per Respondent	Total Burden (in hours)	Average Hourly Wage	Total Cost
Adult Smokers	CATI Screener	150	1	13	$7.25[1]	$94.00
	Visit 1 Screener	70	1	6	$7.25[1]	$44.00
	Smoking Diary	61	1	10	$7.25[1]	$73.00
	Laboratory Visit	61	2	122	$7.25[1]	$885.00
	Total					$1,096.00

[1] Minimum Wage as stated in the Fair Labor Standards Act of 1938, as amended, Title 29, Sections 201-219, United States Code.

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers

There are no additional costs to respondents or record keepers.

A.14 Annualized Cost to the Government

For the proposed two-year Reinstatement period, the estimated annualized cost to the government is $723,517. Costs include costs of project coordination and oversight through CDC's Office on Smoking and Health (OSH) and CDC's National Center for Environmental Health (NCEH), costs of analyzing samples and specimens in NCEH laboratory facilities, and the cost of the data collection contract with Battelle.

The Office on Smoking and Health (OSH) scientist serves as the technical monitor for the project and is responsible for ensuring all OMB and human subject approvals, providing guidance to the contactors and CDC laboratory staff on technical aspects of the project, and facilitating timely and effective communication between CDC staff and contractor staff. The OSH scientist is allotting a higher percentage of effort during the reinstatement period as this is when the majority of the data analyses, presentations at scientific meetings, and publication of study findings will occur. Additional CDC salaries cover NCEH laboratory personnel responsible for completing analyses of samples collected from study respondents, and completing laboratory smoking machine calibration for all brands to relate solanesol measured in the discarded cigarette filter butts to mainstream smoke deliveries. CDC personnel costs also cover data and quality control review and statistical data analysis that will occur after completion of the clinical portion of the study. CDC's laboratory and administrative costs include the costs of laboratory supplies; costs of laboratory equipment, fees, and maintenance; data entry; and travel expenses for senior CDC personnel (Dr. Patricia Richter, OSH, and Dr. Clifford Watson, NCEH).

The data collection contractor, Battelle, is responsible for recruiting respondents, scheduling visits to its Human Exposure Assessment Laboratory, collecting samples and specimens, and shipping samples to NCEH for analysis. The annualized cost of the contract with Battelle is $311,344. Funds were awarded during the previous OMB approval period (FY09) and will be drawn down by Battelle during the period of this reinstatement request.

The estimated annualized costs to the government are summarized in Table A.14-1.

A.14-1 Annualized Cost to the Government

CDC/NCEH		
0.25 FTE OSH Technical Monitor	$ 27,526	
1.5 FTE NCEH Laboratory Staff	$132,000	
Laboratory and Administrative	$252,647	
Subtotal, CDC/NCEH	$412,173	
Contract with Battelle	$311,344	
TOTAL		$723,517

A.15 Explanation for Program Changes or Adjustments

There will be a reduction in the estimated annualized burden since last approval due to a reduction in the number of respondents.

A.16 Plans for Tabulation and Publication and Project Time Schedule

As a descriptive study, we will analyze means, confidence bounds and standard errors. Before confidence bounds on the means can be constructed, the distribution of the smoking behavior

measurements (puff volume, puff duration, puff count, inter-puff interval) must be characterized. Graphic displays, such as histograms or boxplots, will provide evidence as to whether the data has a symmetric distribution, such as normal or skewed. Should the distribution be skewed, logarithms of the measurements could be computed and the geometric mean constructed.

CDC will review the qualitative and quantitative data from the study and consolidate them into an integrated data system. Final results will be made available to other Federal, state, and local agencies and the scientific community. The results obtained from the study will be published in peer-reviewed journal articles and, as such, will be in the public domain. In addition to CDC's National Center for Environmental Health and National Center for Chronic Disease Prevention and Health Promotion, other clients for the results include the Tobacco Control Research Branch of the National Cancer Institute, National Institutes of Health, the Center for Tobacco Products, U.S. Food and Drug Administration, and the scientific community at large.

The project time schedule is presented in Table A.16-1.

A.16-1 Estimated Timeline for Key Activities

Activity	**Time Schedule**
Restart	2 weeks after OMB approval
Begin to Recruit volunteers	2 weeks after OMB approval
Visit 1	Within 1 week of recruiting; 3 weeks after OMB approval
Visit 2	1 day after Visit 1; 3 weeks after OMB approval
Analyze data	Within 2 weeks of data collection; 5 weeks after OMB approval and continuing throughout the 2-year study period
Final Report	Immediately following completion of data analysis; 24 months after OMB approval
Publication	24-36 months after OMB approval

A.17 Reason(s) Display of OMB Expiration Date is Inappropriate

No exemption from display of expiration date is requested.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions to certification are sought**.**