SUPPORTING STATEMENT: PART A

Cigarette Yield and Body Burden of Smoke Toxins
(Human Smoking Behavior Study)

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Submitted by:

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A. Justification

A.1 Circumstances Making the Collection of Information Necessary

Pursuant to 15 U.S.C. §1341 of the Federal Cigarette Labeling and Advertising Act (FCLAA), the Centers for Disease Control and Prevention (CDC) has delegated authority to conduct and support research on the effects of cigarette smoking on human health. This authority also allows CDC to collect and analyze information, studies, and other data relating to the effect of cigarette smoking on human health. CDC's Office on Smoking and Health (OSH) has been delegated the responsibility of implementing this provision. The Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) in a joint venture with the Division of Laboratory Sciences (DLS), National Center for Environmental Health (NCEH), CDC, requests approval by the Office of Management and Budget to conduct a study of variations in body burden of biomarkers proportional to machine-smoke yields of tar, nicotine and carbon monoxide. 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 – Authorizing Legislation**). The OSH/NCCDPHP and DLS/NCEH are specifically interested in this research due to its public health impact and laboratory measures that will be obtained. The DLS/NCEH laboratory has previously conducted a study with similar data collection activities, including collection of urine, saliva, breath, cigarette puff parameters and cigarette butts.

Smokers, at least partially, choose tobacco products on the basis of their perceived health risks and cigarettes advertised as “light” and “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 will advance scientific understanding of the mechanisms whereby tobacco causes disease.

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 (ultralight, light, and full-flavored 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) varies in proportion to machine-smoked yield of the cigarettes under both controlled (laboratory) and naturalistic (home) conditions.

This is an *ad lib* smoking and laboratory smoking study to determine the relationship between cigarette smoke yield (machine-smoked tar and nicotine levels) and actual body burden of

selected carcinogens, other toxins, and biomarkers associated with cardiovascular risk (nicotine and its metabolites, urine cadmium, expired-air carbon monoxide, heart rate, blood pressure, oxygen saturation). Approximately 360 established smokers of cigarettes with a range of machine-smoked yields will provide urine and saliva samples for measurement of biomarkers of exposure under natural smoking conditions, and cigarette butts for determination of solanesol levels (another measure of exposure under natural smoking conditions). In addition, each will smoke **one cigarette of** their usual brand during **each of the** two laboratory visits while smoking topography behaviors are measured and recorded, with measurement of cardiovascular physiologic responses and expired-air carbon monoxide levels before and after smoking. Spent cigarette butts from the laboratory sessions will be collected so that solanesol levels can be compared with those of the *ad lib* smoked cigarettes. 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). **Participants will be provided with a pack of their own brand of cigarettes at their first appointment to minimize the possibility that they will smoke a brand other than their current, usual brand during the study period. It has been our experience that participants will smoke whatever brand is immediately available if they run out of their regular brand; we want to reduce unnecessary complications in the data analysis and interpretation.**

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 (ultralight, light, and full-flavored cigarettes).

The biomarkers to be measured are listed in Attachment B and 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, blood pressure and oxygen saturation (SVO_2) 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 in order 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 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.

The results of the proposed 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.

A.3 Use of Improved Technology and Burden Reduction

This is a one-time experimental study with 360 participants. In order to collect only the minimum information necessary for the purposes of the proposed study and to reduce the burden on the respondent, the study has been carefully designed and will make use of automated and electronic collection techniques. A brief computer-assisted telephone interviewing (CATI) instrument (**Attachment B – Computer-Assisted Telephone Screening Instrument)** has been designed to conduct 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 C – 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 D – 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 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 it were true that the smokers actually took in the amounts of toxins generated by machine-smoking using parameters that mimicked the human smoking, they would have received, 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, however, 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 increasing 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 resulting smoke emissions. Studies in which machines were programmed to smoke like actual smokers have shown higher yields of smoke toxins than are generated under FTC smoking regimens, 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 biomarker measured was cotinine and its glucuronides (an indicator of nicotine intake).

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 among chronic smokers of cigarettes with a wide range of machine-smoked 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 others. This study will clarify these important issues.

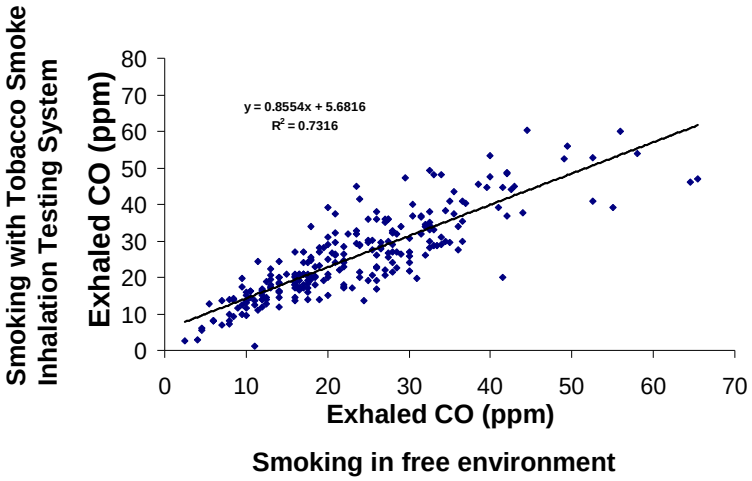
Assessing cardiovascular endpoints. Previous studies have focused almost exclusively on exposure to lung carcinogens in smoke. While cancer is an important and often fatal outcome of exposure to cigarette smoke, cardiovascular disease is a more frequent outcome than all smoking-related cancers combined.[10] The laboratory component of the study will allow real-time measurements of cardiovascular endpoints, such as changes in heart rate, blood pressure, arterial oxygen saturation 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 and effect 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 individual daily 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's 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 relationship between laboratory and naturalistic smoking. 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



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 varies in proportion to the yield category of the cigarette 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.

Conducting the study in one location, the Baltimore facility, 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 at one site, with adequate statistical power to accommodate the inter-individual differences in topography, will produce unbiased results.

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 Services	June 2006
Clifford Watson, PhD CDC Division of Laboratory Services	June 2006
Patricia Richter, PhD CDC Office on Smoking and Health	June 2006

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)**, 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 (during the day after 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 February 9 2005, Vol. 70, No. 26, pages 6878-79 (**Attachment E – Federal Register Notice**). The Federal Register Notice was submitted for further public comments. Comments and response to comments are located in **Attachment F – Federal Register Comments and Response to Comments**.

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, Senior Scientist Officer	NCEH/DLS	dla1@cdc.gov	(770) 488-7962
Dr. Clifford Watson, Research Chemist	NCEH/DLS	cow1@cdc.gov	(770) 488-7638
Dr. Pamela Clark, Senior Health Researcher	Battelle	clarkp@battelle.org	(410) 372-2750
Dr. Deon Harvey, Laboratory Director	Battelle	harveyd@battelle.org	(410) 372-2742
Dr. Wallace Pickworth, Senior Health Researcher	NIDA/Battelle	pickworthw@battelle.org	(410) 372-2706

The original consultations with the above individuals took place in 2004 and are ongoing. There were no major problems that arose during consultation. The Federal Register Notice was submitted for further public comments. 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. 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. Also, should recruitment efforts for smokers of cigarettes in particular yield categories become difficult, we will institute a referral incentive; any participant who refers an eligible participant will receive a $10 incentive. Our incentive of $80 for completing both visits is in accordance with our previous study, the Menthol Crossover Study, with similar procedures. 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 that the $10 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 G – CDC IRB Letter of 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	$30
Complete Visit 2	$50
TOTAL	**$80**

A.10 Assurance of Confidentiality Provided to Respondents

The CDC Privacy Act Officer has reviewed this OMB application and has determined that the Privacy Act is applicable. The applicable Privacy Act system of records is 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems."

All biologic samples will be identified by study and ID number only. The database with personal identifying information is electronic and will reside on a computer in a locked and alarmed office suite. The database security complies with all Federal regulations. Access will be available only to contractor (Battelle) laboratory personnel. The computer program that allows access to the database is password protected and requires a secure ID token for access. All Battelle study personnel are trained in privacy principles and all undergo yearly human subjects' protection training.

While the database with identifying information 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 (Battelle) has the ability to link data to respondent. The determination that the Privacy Act is applicable, even though the contractor will only maintain

the identifiable information for a limited amount of time, is based on the fact that sensitive information is being collected, and legal determinations by HHS attorneys in the past have upheld this view. The sensitive information includes medical history of heart or lung disease, smoking history, **and free, voluntary pregnancy testing if requested by the participant**.

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.

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 is a voluntary activity. The Public Health Service Act 301 serves as the authorizing legislation. 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.

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.

CDC's Institutional Review Board (IRB) approved the study activity protocol and procedures. (**Attachment G – CDC IRB Letter of Approval**)

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 will 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.12A This is a one-time study over two years. There will be no annual collections of data. The final completion goal will be 360 participants; 180 each year. 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.

The study procedures and questionnaire are modest enough to produce only a limited burden to respondents, yet extensive enough to cover all relevant substance areas. Additional participants will be recruited as needed to account for drop outs, "no shows" and non-compliance. We estimate screening approximately 500 participants to yield the 360 eligible respondents who complete both visits over the two-year study period. Table **A.12-1** summarizes burden on an annualized basis for 500 telephone interviews and 180 eligible respondents (one-half of the total respondents). The 180 eligible respondents estimated to complete visit 2 are the same respondents estimated to complete visit 1.

The response burden was estimated based on the researchers' previous experience with similar types of data collections. The total burden for each respondent who completes screening, visit 1 and visit 2 will be two hours and five minutes. The CATI screening will take five minutes. Visit 1 will take one hour, which includes a short screening item, 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 also take approximately one hour, which includes compensation, discussion of quit opportunities if requested, collection of cigarette butts, biologic sample collection (urine, saliva, breath carbon monoxide), smoking behavior **of smoking one cigarette**, ventilation hole blocking procedure and breath measurements. The clinic visits will occur on two consecutive days.

A.12-1. Estimates of Annualized Burden Hours

Respondents	Procedure	No. of Respondents	No. of Responses per Respondent	Average Burden per Response (in hours)	Total Response Burden Hours
Smokers	CATI Screening	500	1	5/60	42
Eligible Smokers	Visit 1 (Day 1)	180	1	1	180
Eligible Smokers	Visit 2 (Day 2)	180	1	1	180
Total		500			402

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. Wage is based on current minimum wage.

A.12-2. Annualized Cost to Respondents

Respondents	Procedure	No. of Respondents	No. of Responses per Respondent	Hourly Wage Rate	Total Respondent Costs
Smokers	CATI Screening	500	1	$5.15[1]	$216
Eligible Smokers	Visit 1 (Day 1)	180	1	$5.15[1]	$927
Eligible Smokers	Visit 2 (Day 2)	180	1	$5.15[1]	$927
Total					$2070

[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

This project will take approximately two years to complete once OMB approval is received. The estimated total cost to the government for this two-year study is $1,255,963. This total includes $463,893 in contract costs to Battelle and $792,070 in other costs to the federal government. The other federal costs include salary, fringe, travel, and supply expenses related to the involvement of Dr. Patricia Richter, Dr. David Ashley, Dr. Clifford Watson and their laboratory staff.

A.14-1 Annualized Cost to the Government

	Annual Cost
Salaries	$122,137.00
Fringe Benefits	$ 30,300.50
Other Administrative Costs	$243,597.50
Battelle Contract	$231,946.50
Total	$627,981.50

A.15 Explanation for Program Changes or Adjustments

This is a new data collection.

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, 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
Start-up	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
Monthly Progress Reports	Within 1 month of the contract award date
Final Report	Immediately following completion data analysis; 24 months after OMB approval
Publication	24 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.

List of Attachments

Attachment A	Authorizing Legislation
Attachment B	Computer-Assisted Telephone Interviewing Instrument
Attachment C	Visit 1 Eligibility Screener
Attachment D	Informed Consent Form
Attachment E	Federal Register Notice
Attachment F	Federal Register Comments and Response to Comments
Attachment G	CDC IRB Letter of Approval
Attachment H	Recruitment Advertisement/Flyer
Attachment I	Table of Biomarkers
Attachment J	Reference List