Centers for Disease Control and Prevention's response to OMB questions regarding the CDC human smoking behavior study.

Your resubmittal addresses many of our concerns. We agree that a study that compares biomarker levels among those who smoke different types of cigarettes is an important research contribution. Within this context, we agree that collecting information about how many cigarettes a person smokes a day is important. We also see the utility of analyzing the butts of cigarettes for these same smokers to understand delivery. However, we are still unclear about the utility of the component of the study that requires the participants to smoke in the laboratory.

Specifically, for Aim 1, we are unclear what hypotheses are being tested regarding cardiovascular reactivity. Are you only measuring heart rate, blood pressure and saturated oxygen?

> An objective of the study is that measures of cardiovascular reactivity vary in proportion to cigarette yield category. The hypothesis is directional, and we hypothesize that we will observe a positive correlation between yield category and cardiovascular reactivity. Data collected will include real-time measurements of heart rate, blood pressure, arterial oxygen saturation and expired-air carbon monoxide (CO), before, during and after a cigarette smoking session.

Will you have enough data for each person to be able to draw characterize the usual variability in these measurements, let alone what is stable for a subgroup defined by type of cigarette?

> The statistical power was calculated on the basis of the yield categories and should be sufficient to elucidate meaningful difference among users based on their smoking patterns and brand category selection. We acknowledge that within each group there will be differences among the participants. However, we expect such deviations to be random and by examining the cumulative results against averaged smoke intake and averaged bio-marker levels based on the yield categories should minimize differences based on the individuals' variations.

How will you take into account the cardiovascular responses that have to do with being monitored in a laboratory setting?

> The experimental design controls for between group differences in effects of the environment in that all of the subjects will be observed before, during, and after smoking. Any differences can be attributed to differences in how the products are smoked (topography/smoking behavior measures) and/or the product itself. We make no claim that laboratory smoking engenders the same response as non-laboratory smoking.

Since the sample is in no way designed to be representative of any particular population, what will the results mean from an epidemiological perspective?

> We acknowledge that the cardiovascular measures are exploratory. However, since epidemiology research shows that active smoking is one of the most important modifiable risk factors for both coronary heart disease and stroke, we

see this study as addressing an important data gap regarding the relationship between cigarette yield category and cardiovascular parameters and response. These are established, readily available, non-invasive measures of cardiac reactivity. Any information we gain will inform future epidemiologic research in this important and understudied area of public health concern.

For Aim 2, does your collection of smoking behavior data run up against the same utility concerns as your first study design?

In the originally proposed study the independent variable was the cigarette smoker. In the refocused study the independent variable is cigarette yield. The utility of the data is applied to cigarette brand varieties and not to the behavior of individual smokers.

Furthermore, what indication do you have that smoking for a short time in a laboratory setting is appropriate to correlate with body burdens that likely are influenced by longer term (prior) exposures?

This is a very reasonable question in that exposure to cigarette toxins are the result of two distinct but interrelated factors: the product and how it is consumed. The laboratory data provide a snapshot of the consumption characteristics and these data are validated by the solanesol equivalence between the laboratory and naturalistic smoking which further informs the interpretation of the biomarkers. Thus, all three are independent but related indices of smoke toxin exposure.

How will you address person to person variability in these behaviors and study effects (laboratory vs. natural setting)? Given all of these concerns, please discuss the utility of collecting these data.

The collection of laboratory data on smoking behavior is important for interpretation of any study result. Exposure is a function of product design characteristics, yield and the behavior of the user and all parts of the equation are needed to assess exposure. If we simply measured biomarkers from urine samples collected in the field (i.e., in a survey setting), any differences between yield categories could raise unanswerable questions about smoking behavior rather than to the exposure associated with the yield category.

To give a concrete example, if urinary biomarkers such as levels of the polyaromatic hydrocarbon compounds (PAHs) resulting from a high yield cigarette and those from an ultra-light cigarette are different, it could be due to differences in the product or in how the product is consumed. To facilitate interpretation of the data it is necessary to have both measure of the product and how it is consumed.

One of the questions we hope to address is how smoking in a laboratory environment compares to naturalistic settings. All prior studies have examined smoking behavior in the context of a laboratory setting. The solanesol data can provide insight regarding how biomarker levels from the lab environment

correspond to those produced by smoking under natural conditions. Determining the influence of smoking under laboratory conditions will be extremely important to future research efforts in both study design and data interpretations.

We are also testing a new method for collecting laboratory smoking behavior. In the past researchers have used a pressure transducer apparatus placed between the smoker and the cigarette to measure smoking topography. Effectively, the smoker smokes through a special cigarette holder to measure puff frequency, puff duration, and puff volume. This interface may alter the natural smoking behavior of the smoker. The use of a new technology, the LifeShirt, overcomes these limitations. The LifeShirt continuously monitors numerous physiological parameter including heart rate, respiration, chess movement, and tidal volume. The user is free to smoke their cigarettes in an unencumbered manner as they would in a naturalistic setting.

With respect to sample selection, we are not clear exactly how you are using 'race' in your sampling frame.

Race is not important to the objectives of the study. Race will not be used as recruiting criteria and is not specifically exclusionary or inclusionary.

Since you are not trying to establish a representative sample, why does it make any difference whether a Hispanic person smokes more than 30 cigarettes per day?

Survey data shows that there are racial/ethnic differences in smoking prevalence and in the average number of cigarettes smoked per day by current smokers (e.g., **http://oas.samhsa.gov/2k6/raceCigs/raceCigs.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5320a2.htm).** Smokers that consume fewer cigarettes per day may not be established smokers and those that smoke large numbers of cigarettes per day may not be typical of average smokers in their racial/ethnic group. A range was established to encompass the expected number of cigarettes consumed per day by non-Hispanic white, non-Hispanic black, and Mexican American smokers. Recruiting participants that smoke within these ranges will assist us in recruiting established smokers that are not dissimilar in terms of cigarettes smoked per day than others in their racial/ethnic group.

Furthermore, even if it were a representative sample, what does the average minimum vs. average maximum tell you?

It tells us that the participant's daily smoking falls within a typical or common range of cigarettes per day for their racial/ethnic group. In addition, a range is desirable to give some variance for the analyses.

We would think that you'd want the participants to all smoke about the same amount (e.g., a pack a day, etc).

While a pack day may be typical for some smokers, it may be high for smokers of other racial/ethnic groups such as African American smokers who tend to smoke

about 9 cigarettes per day. Recruiting pack a day African American smokers may result in a sample of "heavy" rather than typical smokers. Also, as noted above, a range gives some variance for the analyses.

What would be the value to the study of collecting measurements from participants who only smoked one cigarette per day?

We do not anticipate that there will be a substantial number of applicants who only smoke one cigarette per day. Among the three racial/ethnic groups, non-Hispanic blacks typically smoke the fewest number of cigarettes per day and that is approximately 9 cigarettes per day (**http://oas.samhsa.gov/2k6/raceCigs/raceCigs.htm**).

At minimum, we note that such participants would not produce enough cigarette butts for the third aim of the study.

See response above. We do not anticipate that there will be a substantial number of applicants who only smoke one cigarette per day. In the event that a participate smokes only a few cigarettes per day, their data provides a wider range of exposure thereby allowing us to test the fidelity of estimated body burden from the butt solanesol levels.

The consent form presents some protocol related issues for the first time (we didn't see them discussed in the Supporting Statement).

We question the idea of giving participants a pack of cigarettes.

We have provided cigarettes to study participants in other studies. Participants are provided with a pack of cigarettes to minimize the chance that they will smoke a brand different than their normal brand. Because this study is designed to examine body burden as a function of cigarette design or delivery type, we want to ensure individuals are smoking their normal brands of cigarettes. A person who returned butts of different brands of cigarettes would unnecessarily complicate the data analysis and could skew the findings. Providing cigarettes should minimize any opportunities for brands switching and reduce any unnecessary complications in the data analysis and interpretations.

We question the idea of requiring a pregnancy test (as opposed to screening out people who think that they might be pregnant, and the offering a pregnancy test to those who might so desire).

The pregnancy test will be removed from the protocol.

We question the idea of giving subjects their biomarker levels, including exhaled CO, given that we cannot give the participants any meaningful context for these results. NHANES and other studies only give the results to participants when the clinical significance of the measurement can be explained (e.g, is it above or below a level that requires follow up).

Participants will be given their breath carbon monoxide levels at their clinic appointment. In our experience, many participants are interested in knowing what their CO levels are, in particular because the number is visible on the monitor

after they blow into it. Oftentimes, they ask about the number. We explain that a non-smoker typically blows 0 (or less than 3) parts per million (ppm) while a smoker typically blows around 15 ppm or greater (depending on time last smoked) and that the value goes up after smoking. Other study results will be available when published by CDC. Other individual biomarker levels will not be provided to participants.

In addition, we have a number of concerns about the consent form itself. The consent form seems much too long to keep a person's attention. Was this format ever submitted to the IRB?

Battelle and CDC's IRBs have reviewed and provided continued approval of our study protocol and consent form. The new CDC IRB expiration date for the study is 12/8/2007.

Within the consent form, we suggest rephrasing 'Financial Considerations' to 'incentives' and rephrase the first sentence; we view incentives as a positive motivational influence, not compensation.

The consent form was reviewed and approved during all IRB reviews of the study. The consent form cannot be revised without resubmitting the entire package.

We note that the IRB approval for this package expired at the end of 2005. Given that we are now in 2007, any approval would be contingent upon an updated IRB approval. Assuming that your IRB approval has indeed expired, we would suggest the consent form be reworked before resumbittal.

As noted above, CDC IRB approval for the study has been extended until 12/8/2007.