PROPOSAL FOR AN APPLIED RESEARCH STUDY TO INVESTIGATE EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE IN NON-SMOKING JAPANESE WOMEN.

Principal scientists:

Professor Eiji Yano, Department of Public Health, Teikyo University, 2-11-1, Kaga, Itabashi-ku, Tokyo 173, Japan.

Professor Jun Kagawa, Department of Hygiene and Public Health, Tokyo Women's Medical College, 8-1 Kawada-Cho, Shijuku-Ku, Tokyo 162, Japan.

OBJECTIVES OF RESEARCH.

1. To quantify the amount of environmental tobacco smoke ("ETS") to which non-smoking Japanese women are exposed during the course of a typical week by measuring airborne nicotine and salivary cotinine.

2. To determine the difference, if any, in ETS exposure between non-smoking women living and not-living with a husband who smokes.

3. To attempt to characterize the extent of exposure to ETS outside of the home through a comparison of personal exposures to nicotine and records of observations (in a time-activity diary) of cigarettes smoked near the subject.

4. To assess the extent of misclassification of smoking in this group of Japanese women.

5. To compare exposure data and dietary information by rural and urban situation.

BACKGROUND TO THE PROPOSED STUDY.

Epidemiologic studies that have considered an association between exposure to environmental tobacco smoke ("ETS") and lung cancer have been performed in Asia, Europe and in the U.S. It is striking that meta-analysis of the Asian studies suggest a statistically significant association while a similar combined analysis of the European and U.S. studies shows no significant association. In particular, this contrast exists between the two large cohort studies performed by Hirayama in Japan and Garfinkel in the U.S. It has been suggested that the Hirayama study found significance because

Japanese women were both exposed to higher levels of ETS than U.S. women (because of smaller Japanese homes and because of a closer proximity of Japanese husbands while smoking) and because women with husbands who did not smoke were exposed to less ETS outside of the home than U.S. women (with fewer women friends smoking and a smaller percentage working, effectively suggesting a larger difference in exposure between cases and controls in Japan). This suggestion is entirely speculative. Few data are available to evaluate, in a scientific manner, whether such a difference between Japanese and American women exists now or existed in the 1960's (when the cohort studies began).

This proposed study directly addresses these issues. Some evaluation will be made as to whether the data gathered in this exercise would be of relevance to the 1960's. This will be achieved through assessing changes in smoking customs, building stock and work patterns from the 60's to the 90's.

OVERVIEW OF STUDY.

Sample selection - A total of 200 non-smoking, married women will be selected in a semi-randomized manner by a market research agency. One hundred subjects will be selected from the city of Osaka, and a further one hundred from the more rural prefecture of Okayama. Both of these regions are situated in Southern Japan, and it would be expected that they would experience a similar climate. Both of these regions were used in the Hirayama study.

Subject selection would take place by door-to-door interview in areas selected to be representative of the range of socio-economic situations in each location. Interviewers will reveal that this is an environmental study but will not mention ETS. Subjects will be selected such that around 50% are living with a husband who smokes, with the other half living with a non-smoker. Using this as the primary division, the two groups will then be matched as close as possible for age (between 25 and 55), socio-economic class (as determined by residency and principal wage owner occupation) and by working/not-working. For each of these criteria, the selection should fairly represent the general situation within the region.

Sample collection - On acceptance of a subject at first interview, a saliva sample will be taken by having the subject place a dental swab between the upper jaw and cheek for fifteen minutes. This sample will then be sealed and placed in a cool box prior to being sent the laboratory at the end of the day. Analysis of the sample for cotinine will be carried

out in a laboratory in Tokyo through the gas chromatographic method described by Feyerabend. The data from this phase of the study will be used to assess misclassification of smoking. The interviewer will then make an appointment for the start of the subjects' sample period.

On the appropriate day, the interviewer will instruct the subject on the use of the passive sampler and on the keeping of the activity diary. The interviewer also will place two additional passive samplers in the home, one in the living room and one in the kitchen. These will be left in one place for seven days. The subject will wear the personal sampler close to the breathing zone for seven continuous days. During sleep, the monitor will be placed at bedside. During activities such as showering, the monitor will be placed close by.

At the start of the seven day period, the interviewer will collect a further saliva sample. At the end of the study period the interviewer will return to the subject, collect a final saliva sample, collect all three nicotine monitors and conduct a short interview on the subject's and her family's basic diet. All samples will then be returned cold to the laboratory where they will be kept frozen prior to analysis. Women with husbands who are smokers also will be asked about the number of cigarettes smoked per day by the husband, how many of these were smoked at home, how close the subject would typically be during smoking and how many hours per day was the husband at home.

Subjects will be given a small fee for their contribution to the study.

ANALYTICAL CONSIDERATIONS.

Three analytic tools will be used in this study -- passive monitors for airborne nicotine, saliva swabs for cotinine and time activity diaries.

1. The passive monitor for nicotine will be of the design recently evaluated by R.J Reynolds Tobacco Company. These monitors consist of a sodium bisulfate treated filter held in a synthetic cassette behind a porous windscreen of known diffusion characteristics. They have known uptake rates for nicotine, and hence if the precise exposure time is recorded, it is possible to quantify the average exposure to airborne nicotine over the seven day period. It will be essential to ensure that the Japanese laboratory running the analysis can do so in an appropriate manner. Consequently, it is suggested that a set of twenty monitors spiked with low levels of nicotine and twenty monitors exposed to similar concentrations of ETS should be split and analysed both in Japan and in the

RJR research laboratories. This cross-check will have to be completed successfully before proceeding with the main study stage.

Appropriate storage of these devices is essential, and Japanese interviewers will be fully instructed in their use. The interviewers also will carry a blank cassette each day. These blanks will be included in the sample analysis in order to check both leakage and clean analytical handling in the laboratory.

Analysis will be by capillary gas chromatography with nitrogen specific detection.

2. Saliva collection entails the use of dental swabs that should be placed between the upper jaw and cheek for a minimum of fifteen minutes. Samples will be sealed in individually identified tubes and stored cold in the field, and frozen in the laboratory prior to analysis by gas chromatography with nitrogen specific detection after the method developed by Jarvis and Feyerabend. Again, validation of the laboratory will be prerequisite to proceeding with the main study. In this 10 subjects known to be exposed to ETS will be asked to place two dental swabs in their mouth for thirty minutes. One set of swabs will be sent frozen to Feyerabend of New Cross Hospital, London while the other ten will be analyzed in Japan. Once this is completed successfully, the main study will begin. Also, blanks soaked for 2 minutes in an artificial saliva solution will be carried around all day by the interviewers and submitted for analysis.

3. The time activity diary and the questionnaire will be developed in conjunction with a market research agency in Japan. The basis for this will be documents used in studies by RJR in the U.S. and by BAT in the U.K. Considerable attention will be given to the format of data entry and subsequent analysis during the development of these documents.

TIME-SCALES.

The main study should be timed to run within the fall season in Japan, in order to represent known climatic conditions. Hence, all preparatory work with the development of diaries and analytical cross-checks should be completed by August 1991. The sampling then should be completed within the month of September, with data analysis completed by December. A full report will be submitted by January 1992.

BUDGET.

This is currently a tentative estimate of the cost of completing to complete this project. All sums are in U.S. dollars.

Development of diary and questionnaire with market research agency	**20,000**
Subject recruitment and sample collection	**50,000**
Analysis of cross-check samples for nicotine at $50 per sample	**2,000**
Analysis of cross-check samples for cotinine at $50 per sample	**1,000**
Analysis of nicotine samples for main study (including 50 blanks)	**32,500**
Analysis of cotinine samples for main study (including 50 blanks)	**32,500**
Consumable supplies and transportation of samples	**20,000**
Data analysis and report preparation	**30,000**
Other overhead (i.e., supervision by Dr. C. Proctor of all phases of the study, including the preparation of a publishable report)	**45,000**
Total estimated budget	**243,000**