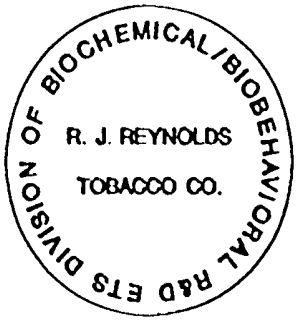
January 20, 1991



To: Dr. A. W. Hayes

From: C. R. Green

Re: Trip Report - Munich ETS Meeting

On Monday, January 14, 1991, a joint meeting was held among VdC Scientific Department, Reserca and RJRT scientists. The purposes of this round-table discussion were to update each other on our recently completed ETS studies, to review work in progress and to consider research which needs to be conducted. Those scientists attending the meeting were as follow:

VdC -	F. Adlkofer, G. Scherer, F.-D. Heller, T. Tricker and C. Conze
Reserca -	A. Bjornberg, C. Enzell and M. Curvall
RJRT -	W. Hayes, L. Mueller, D. Doolittle and C. Green

VdC Research

Much of the recent VdC ETS research has focussed on human dosimetry experiments. Male volunteers are isolated from all external sources of ETS and are required to eat a low PAH diet. Under this regime, the volunteers are subjected to multiple 8-hr. exposures in a test room where the particle and nicotine levels are 4.0 mg/m^3 and 71 ug/m^3, respectively. COHb levels in the subjects' blood are measured and are found to be elevated due to the 24 ppm concentration of CO present in the test room. Urine concentrations of cotinine, hydroxyphenanthrene, thioethers and mutagenicity (Ames) are measured. Compared to pre-exposure levels, cotinine and thioethers are increased while mutagenicity is not.

In some studies, subjects are required to wear a breathing mask which removes all of the ETS particles. Increases of cotinine and thioethers in urine are not affected by wearing the particle filter.

Additional VdC studies on ETS benzene were discussed and are described in a recent publication, J. Cancer Res. Clin. Oncol. (1990) 116:591-598; see attached document. The conclusion by the VdC scientists is that "it is highly questionable whether exposure to benzene from ETS under real life conditions poses a cancerogenic risk to the general population,..."

Dr. Heller told of the VdC's participation in an IARC population exposure study named MONICA. Specifically, the VdC scientists are surveying 5,000 subjects in Augsburg, Germany by salivary cotinine measurements to determine the extent of smoker misclassification. The cut-off point for nonsmokers is 20 ng/ml of cotinine in saliva.

Finally, Dr. Tricker showed us a research proposal submitted to the VdC by G. Neurath and G. Grimmer which would investigate the distribution of ETS components into the gaseous and particulate phases; see attached. Drs. Enzell and Green remarked that the separation of ETS into its phases is not straightforward and unless care is taken, artifacts can be formed. No details were given on the separation methodology to be used. Drs. Enzell and Green were asked to formally review the proposed research for the VdC.

Reserca Research

Dr. M. Curvall reviewed her studies of the pharmacology of nicotine and the use of cotinine as a biomarker for ETS exposure. No new details were presented. Dr. Curvall did reveal during a private conversation that she had attempted without success to find additional metabolites of nicotine other than cotinine in saliva. She opined that for general surveys of ETS nicotine exposure, salivary cotinine is the biomarker of choice.

Dr. Curvall is cooperating with Dr. Pershagen in a study of Swedish children to evaluate their exposure to ETS and its relationship to respiratory disease. Dr. Curvall's contribution, salivary cotinine measurements, has already been completed.

RJR Research

Recent ETS research conducted at RJRT was reviewed by Drs. Green and Doolittle. Although these talks will not be discussed herein, there was great interest expressed by the other scientists in the NOEL investigations. Many feel that establishment of a threshold level for biological effects is a key solution to the ETS problem.

Conclusion

Two main points resulted from the day-long discussion: both a biomarker for ETS particulate exposure and a life-time animal study are needed. Many felt that solanesol is the best possibility as a particulate biomarker. More should be done to follow solanesol's metabolism in animals and man. Measuring solanesol in plasma should be investigated. Dr. Green volunteered to pursue this area of research. Dr. Enzell said that Reserca may be in a position to synthesize ^{14}C-labeled solanesol.

In particular, Dr. Adlkofer felt that a life-time animal exposure study would be extremely helpful in discussing ETS exposure with regulatory authorities. A lifetime study similar to RJRT's recently completed 14-day study would be excellent. Dr. Adlkofer feels that RJR is uniquely qualified to conduct such a study.

Next Steps

Participants agreed that future meetings, on a 6-month basis, to discuss our mutual progress would be beneficial. RJRT volunteered to host the next meeting in Winston-Salem.

Attachments (2)

XC: Mary Ward
Tom Griscom
Richard Marcotullio
Lutz Mueller
John Reynolds
Dave Doolittle
Bob Suber
Sam Simmons
Don deBethizy
Arnold Mosberg
Chris Coggins
ETS Division Members