

RB/PSD/4(t)

9th October, 1974

R.S. Wade, Esq.,
Imperial Tobacco Products Limited,
P.O. Box 4500,
Montreal,
Quebec, H3C 3L7,
CANADA.

Dear Sir,

Thank you for your two recent letters. I am sorry that I have not replied sooner and hope that this has not caused any delays.

My main concern is that the work programme suggested, although necessarily brief, is too broadly based and that not all of the projects suggested could be tackled adequately, even superficially, in one year.

At this stage, direct links with the Southampton programme would not be possible until ITPL personnel had some background in techniques, etc., but this prospect should also be borne in mind as a future objective.

I have made some comments below and do appreciate that, not having been involved in the detailed discussion, I may not have the complete picture.

Concerning the exposure system to be used, I agree that it would be preferable if a common machine could be used in Montreal and Southampton. This is particularly important if studies are to be transferred to Southampton for further elaboration, and also because we are now in a position to estimate IPM 'dose' received by various regions of the respiratory system of a range of species under well-defined exposure conditions. Because of the lack of availability of machines from commercial suppliers, we have developed a versatile B-A.T. system, which has already been used successfully for work with guinea pigs, rats, hamsters and mice. We have a Dentonwill machine in the laboratory, which is not sufficiently versatile or precise for our work. Until after other machines, such as the Oak Ridge system, have been examined in detail, we will stick with the B-A.T. machine. Drawings for the construction of the B-A.T. unit can be made available. Owing to pressure of work here, we could not undertake to construct another machine before summer of next year. Preliminary work would have to go ahead on Jim Hogg's machine.

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As mentioned before, the work detailed in the project proposals is broadly based, and I do not think it would be possible to attempt, within the 1st year, all the projects suggested, unless they were done in a very cursory manner, bearing in mind the number of people who will be actually doing preparation of samples and analyses. For example, whichever single project is considered, it would be necessary to carry out a number of experiments, probably spread over several months, to establish exposure conditions necessary to induce the change of interest, optimum sampling time, reproducibility of response, etc., etc. It is certainly not possible to "agree" a priori, for example, that exposure to 5 rather than 10-20 cigarettes will be "sufficient". This implies some knowledge of the response of the particular biochemical system being investigated, which at present is just not available. Some work could usefully be done on any project to decide if there is a particularly responsive species of animal for that study. Similarly, the number of animals to be used for comparative studies cannot be pre-set until some indication of variability of response to a stimulus has been assessed. Six animals per dose level, for instance, is almost certain to be inadequate for quantitative work.

I would still prefer the approach to this type of work to be based upon potential relevance of the study to the human situation. The connection may at times be tenuous, but the relevance of the study should be considered before work begins. It would certainly have to be when projects reached the stage of being written for publication. The classical toxicology search for any indicator of response may not be the right approach in this case.

For these reasons, I would tend to fight shy of the wide-spread, multi-project approach suggested. From the outlines given, I think at this stage there may be a lack of appreciation of the practical problems associated with doing smoke toxicity work. This, hopefully, is where the Southampton group could be of help.

The lung biochemistry work carried out so far in Southampton has been concerned with lysosomal enzymes, lung collagen and elastin content. I would like to see some work in this general area, since this seems to be an area where biochemistry, physiology and histopathology studies could be readily linked. You already know of previous work started here on mucopolysaccharide synthesis. Project 3 of your list would, I think, be a valuable complementary study to our own projected programme. I agree that this project would be difficult, but I do not think the others suggested will necessarily be easier.

In June, the work on membrane characteristics carried out at ITPL seemed to be ripe for development to in vivo studies, perhaps in relation to changes in lysosome characteristics in response to smoke exposure. This seems to have been lost along the way since then. Does this mean that the project has been discussed and discarded for the present?

I hope that the comments are useful. Within reason, I think that, at this stage, any training in lung biochemistry

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methods, experiment design, smoke inhalation methodology, within-species variation, sensitivity of enzymes, etc., will be useful. This work could be getting under way within the suggested framework until we could more formally standardise exposure techniques and inter-link projects sometime next year.

I apologise again for the delay. Things are fairly hectic at the moment.

Yours sincerely,



RICHARD BINNS

cc: R.M. Gibb, Esq.

N.o.o. or RMG copy

cc: Dr. D.G. Felton

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