

NOTE FOR THE TOBACCO EXECUTIVE COMMITTEE

BIOLOGICAL TESTING AND RESEARCH
(LIFE SCIENCES)

BACKGROUND

1. Following the earlier concern of the Research Conference that, in recent years, expenditure by the Life Sciences Section had grown to some 13% of the R&D budget, the T.D.B. on 29.11.79, called for a review of BAT's total involvement in the biological assessment of products and materials. This paper summarises the present position, both for BAT and our major competitors, and makes recommendations for future action.

BIOLOGICAL TESTING AND RESEARCH

2. The requirements for toxicological testing with animals and biological systems in the pharmaceutical, chemical and food industries is well established. While test results cannot be extrapolated to predict specific human responses - because of fundamental differences in anatomy - it is generally accepted that they can be used to give important pointers to the likely relative human response to different products and component materials.

3. There are three main reasons for a company undertaking biological testing and research:-

- (i) To provide supporting evidence as to the safety or 'superiority' of a given product or material.
- (ii) To screen products and component materials for possible toxic response, either absolutely or relative to others already in commercial use.
- (iii) To maintain a nucleus of experts capable of interpreting what others are saying in the areas of product toxicology (in our case, primarily on smoking issues)..

It would be difficult for a tobacco company to capitalise directly on Item (i). Item (ii) is a valid objective, both as an internal (in-house) check and as a basis for submission to government authorities.. (But see Paras. 4-8 below).

BAT INVOLVEMENT IN BIOLOGICAL TESTING AND RESEARCH
AND THE HUNTER COMMITTEE

4. BAT started working with animals in the mid-1960's - with the JANUS mouse-skin painting project at Battelle Institute,

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Frankfurt. Over the years, results were obtained from a series of interlocking experiments to yield a package of information on basic factors in cigarette design, e.g. Lamina v. stem v. extracted tobacco v. tobacco sheet reconstituted by a variety of processes v. Cytrel, strand-width, blend type, puff volume and, most recently, effects of cigarette ventilation and augmentation of the nicotine level.

5. During the 1970's, it became clear that, for tobacco smoke assessment, inhalation techniques, which could be much more relevant than mouse-skin painting, might well be feasible, and a great deal of effort was made to establish a comprehensive animal testing facility, based on rats. Mouse-skin painting was continued; but by that time had been transferred to the Huntingdon Research Centre, as a way of reducing costs.

6. Although in their First Report, the Hunter Committee accepted mouse-skin painting results, in their Second Report in 1979, they proposed the assessment of carcinogenicity by inhalation exposure only, to the exclusion of any mouse-skin procedures. The Committee, moreover, specified that hamsters should be used for inhalation exposure.

7. Although there may be valid reasons for preferring hamsters to other animals, such as the rat used at GR&DC, there are logical objections to the decision:-

(i) There is only one strain of hamster that has been established as giving a reliable number of laryngeal tumours, namely the one developed and patented in the U.S. by Dr. Homburger of Bioresearch Consultants of Cambridge, Massachusetts. The practical constraint to the ready adoption of these hamsters is that Dr. Homburger is unwilling to provide animals for use by third parties, unless at the same time, a substantial proportion of any assessment is contracted to his Institute. The conducting of such work in the U.S.A. is impracticable, when legal reasons are considered.

(ii) At the present time, there exists a far greater body of experience and results from work with rats. This applies particularly to the work at GR&DC to establish controlled exposure/dose conditions, which has become recognised worldwide - ironically, in particular, by the Hunter Committee itself.

8. What must be acknowledged, however, is that biological assessment by mouse-skin painting is very unlikely to carry weight in the future in the U.K. - or, with the increasing influence of the Hunter Committee, in other countries of the world.

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COMPETITOR ACTIVITY

9. An estimate, by Dr. D. G. Felton, of competitor activity in biological testing and research, is given in Appendix I. Accurate information is necessarily difficult to obtain, because of the commercial sensitivity of the work. It would appear to be clear, however, that our major competitors are maintaining sizeable programmes of work - albeit, probably mainly by external contracts, rather than in-house.

BIOLOGICAL TESTING AND RESEARCH WITHIN BAT GROUP

10. There is a strong belief by the R&D management that BAT must continue to be involved in both biological testing and biological research - a view that is supported by the Research Heads of the CAC countries. Equally, however, it is believed that the current level of activity is greater than can be justified by the use to which the results and expertise can be utilised commercially.

11. Of the three main areas of work:-

- (i) bioassay method development
- (ii) inhalation studies with rats
- (iii) mouse-skin painting - via external contract

It is thought that (i) and (ii) are important in keeping BAT in a strong position vis à vis the increasingly hostile external environment. With mouse-skin painting, however, while it is still viewed internally as of value in the screening of new products and materials, it is very unlikely that the results obtained could be of real commercial value.

12. All CAC countries agree with this view. They also agree that, if the activity were to be stopped, it would be relatively easy to re-introduce it again at a later date. This, however, would not be the case with inhalation studies or, if the scientific team were to be disbanded, with bioassay method development.

RECOMMENDATIONS

13. The mouse-skin programme should be terminated. The immediate implication would be the cessation of condensate production at GR&DC. This would result in 9 part-time and 1 full-time female assistants becoming redundant. In addition, a compensation payment to Huntingdon Research Centre would need to be negotiated. No approach has been made to H.R.C., but a figure of £27,000 is included in the 1980 budget estimates.

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14. Continue inhalation testing with rats, and maintain a positive stance vis à vis the Hunter Committee, and the medico-scientific world in general on the value of such work.

15. Reduce, but maintain, some activity in the area of bioassay method development - especially for short term assessments.

16. If these recommendations are approved, a 2-3 year programme of inhalation testing and bioassay method development would need to be agreed with the CAC countries. Such a programme, however, would most likely cover the following topics:-

(i) Product evaluation by the 6-week (short-term) inhalation test of, inter alia

- a) Vapour phase filters
- b) Ventilated cigarettes
- c) Cigarettes with increased nicotine content
- d) Expanded tobacco
- e) Side-stream smoke

(ii) Development of short-term bioassay protocols for product testing, e.g. mucus production, specific enzyme inhibition, DNA binding.

(iii) Establishment of a reliable protocol for long-term (animal life-time) inhalation test with rats.

(iv) Importance of the interaction of diet with smoking in long-term experiments. This has implications in cardiovascular research.

17. The 1980 R&D programme, that was submitted to and approved by the T.E.C. on 3.1.80, anticipated the broad acceptance of the above recommendations. If implemented without delay, the effect in 1980 would be reductions of:-

Revenue expenditure	£142,000
Capital expenditure	No major items were foreseen
Staff	10

As mouse-skin experiments take 2-3 years to complete, cancellation of experiments planned to start in 1980, means that similar reductions in revenue expenditure will also occur in 1981 and 1982.

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The Tobacco Executive Committee is requested to approve the immediate implementation of the above recommendations - which have been discussed in detail with Personnel Department, Millbank and in outline with the CAC countries.



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10.1.80

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BIOLOGICAL RESEARCH

<u>Company</u>	<u>In-house</u> £	<u>Site</u>	<u>External</u> £	<u>Remarks</u>
<u>U.K.</u> Imperial Tobacco	-	Huntingdon, UK	400,000	2 Inhalation experiments - (on cardiovascular response with nicotine aerosols) - monkeys and hamsters
"		IFREB, France	30,000	Small toxicity study on HCN reinforced smoke
Gallaher*	some	Battelle, Geneva Various hospitals	500,000 (guesstimate)	Research in Switzerland will be very expensive.
Carreras*	-	Hazleton Res. (Europe) Inveresk Laboratories Midhurst Med. Centre	500,000(?) or a bit less	Smoking and Health research 50% of budget, which exceeds £1 million
<u>U.S.A.</u> Philip Morris	Negligible(?) (60 rats on psychological programme)	InBiFo, Cologne	1,000,000	Both mouse-skin and inhala- tion research on rats. Scale of InBiFo indicates substantial investment.
R.J. Reynolds	?	Bioresearch Consultants, Cambridge, (Mass.) Bioresearch Laboratories, Montreal, Canada, (some work on nitrosamines)	?	Both have been used in the past. Currently ?
Lorillard	some?			
Council for Tobacco Research	-	Microbiological Assoc. Bethesda, Md.	?	Direct contract large-scale 5000 mice life-time inhala- tion and other studies.

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SEITA

Considerable (some product work for marketing, some for general industry)
Difficult to disentangle specific projects from
"grants-in-aid", e.g. to GEFT, a TRC-like programme.

*N.B. The Gallaher/Carreras/Celanese consortium (Budget £5m) to investigate CYTREL has been disbanded.

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