

STRICTLY CONFIDENTIALTIMING OF EVENTS CONNECTED WITH PUBLICATION
OF HARROGATE MOUSE-SKIN REPORT

1. Harrogate draft report has been agreed (with the exception of one point) by T.S.C., and there seem to be no major obstacles to its acceptance by T.R.C./E.C. on 7th July 1966
2. T.S.C. now recommend that the draft then be shown to e.g. Dr. Doll, Dr. Marrian and Professor Dickens for their comments on its presentation, length and general suitability for submission to the referees of the British Journal of Cancer. The incidence of holidays and other commitments, and the probability that these three scientists will want to get other opinions, make it unlikely that we shall have clearance from them before 31st August 1966 - perhaps later.
3. It is suggested that Mr. Campbell-Johnson be asked meanwhile to consider all aspects of publicity and to submit views for consideration by T.R.C./E.C. at meeting on 1st September 1966.
4. T.S.C. to give final scientific approval as soon as possible after report received back from outside scientists, e.g. at T.S.C. meeting in mid-September 1966 or at special meeting.
5. T.R.C./E.C. to give final approval, if possible at special meeting in second half September 1966, or at latest on 6th October 1966.
6. G.F.T. to submit Harrogate report to B.J.C. on behalf of T.R.C. immediately after T.R.C./E.C. assent - 7th October 1966 at latest.
7. Immediately after submission to B.J.C., Minister, through Permanent Secretary, to be informed of impending publication on lines suggested in Appendix I - assume interview can take place by 28th October 1966 at latest.
8. Immediately after interview with Minister, implications of report to be discussed with medical and other scientists on lines suggested in Appendix II - these discussions might be lengthy and could occupy November and December 1966.
9. After discussions with medical and other scientists it might well be desirable to talk again to the Minister and/or his advisers, and to formulate plans to implement any courses of action provisionally agreed with doctors and others. Such talks might occupy the whole of January 1967 but must be completed before the publication date.
10. The Harrogate report might be expected to be published in February/March 1967
11. T.R.C. Review of Activities to be made ready for publication by 7th October 1966, so that it may form an agreed background for discussions with the Minister and with medical and other scientists. Modification of the Review might take place up to the end of 1966, but thereafter it should be printed and held in readiness for publication as soon as possible after the Harrogate Report appears in the B.J.C.

30th June 1966

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APPENDIX I

APPROACH BY U.K. HOME TRADE MANUFACTURERS
TO MINISTER OF HEALTH. SUGGESTED PROGRAMME
AND METHOD

1. Immediately after submission of Harrogate report to the B.J.C. seek an interview with the Minister via Sir A. France, Permanent Secretary.
2. U.K. Home Trade Manufacturers, represented by E.J.P., A.W.H.S.M. and R.W.S.P. and with G.F.T. as Technical Adviser, to see Minister of Health and say:-
3. We have asked for this interview so that we can tell you about the work that has been carried out by the T.R.C. and which will be described fully in a scientific paper which we hope will be published by the British Journal of Cancer early in the New Year, and also in our Review of Activities which we publish from time to time so that interested scientists can keep up to date with our progress. This review covers the whole field of our research and includes both work done under our own control and also work sponsored by us but carried out by independent scientists.
4. (a) In 1962 the T.R.C. started work at Harrogate with the following general objectives:-
 1. To develop and use biological tests which are indicators of carcinogenic and irritant effects, and
 2. To identify the smoke or smoke condensate components that might be responsible for any such effects,
 and it was decided to give priority to the problem of cigarette smoking and lung cancer.

(b) The Harrogate programme includes:-

 1. Tests designed to show the response of mouse-skin to the application of cigarette smoke condensate and smoke condensate fractions from typical U.K. flue-cured plain cigarettes.
 2. Tests of the effects on animal lungs of inhaled smoke.
 3. Tests of the effects on animal lungs of cigarette smoke condensate applied by injection and by intratracheal intubation.
 4. A test for assessing ciliastatic effects of cigarette smoke by the use of rabbit trachea.
5. We are particularly anxious not to over-emphasise in any way such progress as we have made to date. We realise a vast amount of further research is called for especially in the development of suitable tests for the last three experiments. On the other hand we do think we have made considerable progress with the first series of tests.
6. In this connection it was realised when the T.R.C. was first formed in 1962 that Wynder and others had carried out experiments on these lines and had produced skin tumours on mice. However, the scale of the earlier experiments was not sufficiently large and a number of questions remained unanswered.

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6. Continued
We ensured that the number of mice used and the quality of the animal husbandry would be such that reliable quantitative data would be obtained. We also used improved methods of condensate production and application.
7. Looking back now over the three years we are sure that we made the right decision. Our work has confirmed Wynder's general findings that smoke condensate painted on the backs of mice will produce tumours, but our research has gone beyond this in several important aspects.
8. Considerable progress has been made towards the identification of the cigarette smoke constituents that cause skin cancer in mice, and we think that we have been successful in locating the particular fraction of cigarette smoke in which these constituents occur.
9. Though we have not yet been able to remove this fraction selectively, our research indicates that we can produce acceptable cigarettes with a substantial reduction of total condensate in which this particular fraction occurs.
10. By a combination of blending and a higher efficiency filter, we have been able to reduce the condensate in these filter cigarettes by as much as 50% compared with conventional plain cigarettes, and by about 30% when compared with the main filter cigarette brands.
11. Our object in approaching you is to acquaint you with this situation and, if you agree, we would like to discuss our results in whatever detail is necessary with the medical authorities who, we think, are the right people to judge to what extent the results of our work may be relevant to the problem of smoking and health.
12. Dependent on the views expressed by these gentlemen there could be a number of problems that your Department and the industry would have to discuss in detail, but we suggest this is something we leave until after we have had the opportunity of talking to these various specialists.

*much
amount of
smoke
etc*

13. We have in mind the following scientists who could, each in his different field, advise on the right course to be followed from the point we have at present reached:-
1. Sir Charles Dodds as Consultant to T.R.C.
 2. Representatives of the R.C.P., including Dr. C.H. Fletcher, Secretary of the R.C.P. Committee on Smoking and Health.
 3. Professor Sir Alexander Hadow, Director of the Chester Beatty Institute.
 4. Lord Cohen

and we should be glad to know whether in your opinion these are the best people to approach and whether you would wish to add additional names and we hope members of your own Department to these discussions.

30th June 1966

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STRICTLY CONFIDENTIALAPPENDIX IICIGARETTE SMOKE RESEARCH

- . Brief for Meetings of Representatives of U.K. Home-Trade Manufacturers and Their Scientific Advisers with Medical and Other Scientists.

It is suggested that Representatives of the three largest U.K. Home-Trade Manufacturers, together with their scientific advisers, should meet medical and other scientists, either singly or in groups, probably during November and December 1966. This paper outlines a brief from which the manufacturers' representatives might speak.

1. In 1962 the T.R.C. started work at Harrogate with the following general objectives:-
 - (i) To develop and use biological tests that are indicators of carcinogenic and irritant effects, and then
 - (ii) To identify the smoke or smoke condensate components that might be responsible for any such effects.
2. For the purpose of this work the T.R.C. accepted as a working hypothesis the validity of the contention that tobacco smoke can contribute directly to lung cancer.
3. The tests that the T.R.C. Laboratories set out to develop were directed towards assessment of the following:-
 - (a) the response of mouse-skin to the application of cigarette smoke condensates and smoke condensate fractions from typical U.K. flue-cured plain cigarettes.
 - (b) the effects on animal lungs of inhaled smoke.
 - (c) the effects on animal lungs of cigarette smoke condensate applied by injection and by intratracheal intubation, and
 - (d) the ciliastatic effects of cigarette smoke as assessed by the use of rabbit trachea.
4. Development of suitable tests for the first three of these experiments has proved difficult, but work will continue until satisfactory methods are devised. We expect, in the next few years, to publish a succession of reports in these various fields, and we have approached you now to tell you of the results of our mouse-skin experiments, the Report on which is to be published in the British Journal of Cancer in the first few months of 1967. (Copies available for confidential circulation to a number of members of the medical profession, and other outside scientists).
5. We wish to discuss these results with-you, in advance of publication, in the light of the views that were expressed by the medical profession and by us at the time of the 1962 R.C.P. Report. We also wish to discuss the resultant research by tobacco manufacturers into the modification of cigarettes.

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6. The biological tests described in this first report from Harrogate were designed to show the response of mouse-skin to the application of cigarette smoke condensates and smoke condensate fractions from typical U.K. flue-cured plain cigarettes.
7. In this work we recognise that mouse-skin tests with smoke condensates suffer from certain experimental limitations. First, no account can be taken of the effects of very volatile smoke constituents; and, second, the time interval that must elapse between production and application of the smoke is long compared with the time interval that elapses between the lips and the lungs of a cigarette smoker.
8. These mouse-skin experiments had also the specific objectives (so far as these experimental limitations allowed) of
 - (a) verifying that cigarette smoke condensate mouse-skin carcinogens were stable and non-volatile, and
 - (b) Investigating the possibility that smoke condensate (commonly called 'tar') carcinogens might be artifacts of storage.
9. In advance of the publication of the Harrogate mouse-skin report we can say:-
 - (a) That the results show:-
 - (i) There is a dose response relationship with all the materials tested; that is, the yield of tumours increases with the quantity of material applied.
 - (ii) The 'tar' component contributes substantially to the mouse-skin carcinogenicity of 24-hour old smoke condensate.
 - (iii) The neutral fraction accounts for practically all the activity of the 'tar'.
 - (b) That the report has revealed the following new information:-
 - (i) The mouse-skin carcinogens in cigarette smoke condensate are stable.
 - (ii) These carcinogens are not artifacts produced only on ageing.
 - (iii) The semi-volatile constituents of cigarette smoke condensate do not add greatly to the mouse-skin carcinogenicity of the non-volatile constituents commonly called 'tar'.
10. Research work continues on the possible effects of many other constituents of cigarette smoke, such as volatile irritants.
11. Research also continues, by fractionation techniques developed at Harrogate, into identification of the fraction or fractions of the 'tar' to which mouse-skin carcinogenicity may be attributable and which it might ultimately be possible to eliminate or reduce selectively in cigarette smoke.
12. We thought it proper at this stage to seek the views of medical men on the relevance, in the human context, of filter cigarettes that are acceptable to those who are going to smoke, but that yield substantially less 'tar' to the smoker.

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13. By 1964 there were indications that 'tar' was an important source of cigarette smoke condensate mouse-skin carcinogens. This suggested the development, in manufacturers' laboratories, of commercially acceptable filter cigarettes with substantially less 'tar' than conventional plain cigarettes. (It will be necessary to explain, in relation to paragraphs 13 - 20, the part played by nicotine in these modified cigarettes and to give our views about nicotine in the health context. A separate paper on this will be submitted to T.R.C. shortly).
14. The first step towards the objective of reducing 'tar' was achieved by filtration and blending techniques; and commercially acceptable filter cigarettes (yielding about 40% - 50% less 'tar' per cigarette than conventional plain cigarettes, and about 30% less than the main filter cigarette brands) have now been included in the Harrogate mouse-skin programme to test their specific mouse-skin carcinogenicity.
15. Experiments are also being carried out with additives to filters, and other means of 'tar' reduction are being continuously investigated.
16. It may be that the medical profession, having examined the first Harrogate mouse-skin report and the results to date on tests of cigarettes with lower tar, will consider that the manufacturers should market cigarettes modified in this way. Some such cigarettes are already on the market, and the volume is being increased; but they have not so far been announced as lower-tar brands, because the manufacturers do not feel that they can make an announcement unless the medical profession say that there is some merit in doing so.
17. Moreover, if a substantial demand were created at this moment it could not yet be satisfied. The reason for this is that trade leaf stocks do not contain sufficient quantities of the types required for a modified cigarette of this kind. Rhodesian tobaccos have a particular part to play in this connection; and although overall stocks of Rhodesian tobacco in the U.K. may last for perhaps 18 months there is a shortage of the grades of tobacco that are especially suitable, and there is obvious uncertainty about future supplies.
18. It will be appreciated that a fundamental change of this kind in the characteristics of cigarettes involves major alterations in manufacturing equipment and techniques, and in the whole policy of tobacco leaf buying, so that it is a physical impossibility for the industry to achieve a complete conversion in a few weeks or months.
19. We believe, however, that we could within the next year or thereabout (provided the Rhodesian problem is solved) be in a position to market acceptable filter cigarettes (for the majority of smokers if need be) with a 'tar' reduction of 40% - 50% compared with conventional U.K. plain cigarettes, and about 30% compared with the main existing U.K. filter brands. We also believe that we could then be in a position to tell the public that these brands yield less tar. We think, however, that if we announced this too early we might merely have brought about a demand we could not satisfy.
20. In the meantime, sufficient results should shortly be available of tests of smoke condensate from filter cigarettes that yield reduced tar; and by mid-1967 similar results should be available in connection with the incorporation of an additive to filters.

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Notes:

- (i) After discussions with medical and other scientists, and dependant on their outcome, a further talk with the Minister will probably be necessary. At this talk we would hope that acceptable courses of action could be agreed in the light of the advice given by the medical profession. We would also hope that we could at this stage get the Minister's agreement to a moratorium on official publicity until such time as the industry can be in a position to meet any widespread demand for lower tar cigarettes.
- (ii) We are likely to be closely questioned, by the Minister and by medical people, on our attitude to nicotine reduction and/or nicotine content labelling or other forms of publicity. This is a matter on which there are widely varying views among manufacturers. These should be discussed by T.R.C./E.C. at an early date. Meanwhile we are preparing a paper on this subject for submission to T.R.C.
- (iii) When the Harrogate mouse-skin report is published, if not before, we are likely to be pressed for some form of tar labelling or published tar statistics. A separate memorandum on this subject will be submitted for consideration.

30th June 1966

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