

TECHNICAL EXCHANGE MEETING

GR&DC, JUNE 1982

Session 5: Biological Research

Wednesday, 9th June

9.00 p.m. - 11.30 a.m.

Co-ordinator: Dr. R.E. Thornton

Leaky Lungs (Mrs. J. Ramsdale)

Smoke Inhalation Studies (J. Bevan)

Mutagenicity (Dr. E.D. Massey)

Passive Smoking (Dr. R.E. Thornton)

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Introduction

The main objective of biological research is to design cigarettes with minimum biological activity. Although it is possible to relate some tests to diseases which have been associated with smoking, this is not always possible. In this case minimum biological activity, as defined by the specified test, is considered sufficient in its own right.

In some cases Governments, or other statutory bodies, have introduced legislation relating to the testing of chemicals. This was exemplified by the case of ZORBONITE, a filter additive designed to reduce the level of nitric oxide in smoke. This material had given favourable results in most tests but had been shown to possess strong sensitising activity. This implied an allergic response in humans and, on this basis, its projected use was abandoned.

A number of contract research studies are being carried out. Satisfactory progress is being maintained on current projects, work has started on a new one ("Leaky" Lungs, discussed later) and several are being considered, notably work on examining the role of nicotine in affecting metabolism. Work on nitric oxide retention is also being considered.

In discussion, there was broad agreement on this programme. It was noted that one contract study (the enzyme induction work) complemented AHH work being carried out in Canada. Further information was requested on studies relating to Atherosclerosis (Professor Caro).

Leaky Lungs

Work on leaky lungs originated at Northwick Park Hospital, N. London, when the phenomenon of "shock-lung" was being investigated. This is an often-fatal condition in which lungs fill with fluid. It had been found that smokers had more permeable lungs than non-smokers, as measured by transport of a radioactive chelate through the lung wall. The change was reversible and thus a quick, simple, non-invasive test of lung function presented itself. Correlation with the magnitude of the change and carbon monoxide levels in blood had been demonstrated. This did not necessarily demonstrate a causal relationship; carbon monoxide was chosen because of its simple assay. Further work was now under way to investigate the relationship between carbon monoxide delivery and "leakiness".

In discussion, there was strong support for this work, the related work of J. Hogg in Canada being noted. Attempts to reproduce the effect in animals were now under way, both at Northwick Park Hospital and in Southampton, although it was pointed out that background noise levels might be very high. However, the test might have utility in examining sidestream smoke.

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Smoke Inhalation Studies

A period of intensive development has resulted in the introduction of radically new protocols for the testing of low (including ultra-low) delivery products by rat inhalation. These became necessary in order to achieve a significant pathology effect from relatively low amounts of smoke components from such cigarettes. Using these techniques, studies will be completed on expanded tobacco and on cigarettes containing 100% reconstituted tobacco.

Techniques for measuring biological activity in response to sidestream smoke have also been developed. The further development of techniques for measuring activity of sidestream smoke is planned, including a full programme of studies on reduced sidestream products. Additionally, further consideration of markers for smoke deposition is in hand. Markers being considered included Catechol and Cadmium, as well as more conventional markers such as nicotine and the [SCN]⁻ radical.

Discussion indicated considerable interest in the results which will come from the use of these newly developed techniques. The question of measurement of sidestream smoke activity was considered to be an industry rather than an individual company concern. This matter is under review.

Mutagenicity

The rationale for conducting mutagenicity studies was firstly put forward under the evidence for the effect of mutagens on the incidence of genetic diseases, using mutagenesis as indicative of carcinogenesis and as a reply to the increasing sphere of legislation. The concepts of structural (chromosome) and molecular (gene) mutations were examined and linked to the requirement of using a battery of mutagenicity tests to detect agents acting at these two levels.

The establishment of the Ames test at GR&DC to detect gene mutations was described and the following experiments using this assay discussed:

1. BAT collaborative study (Southampton, Hamburg, Montreal) for evaluating the mutagenic potency of a series of cigarette smoke condensates. A remarkably good agreement between the laboratories was found.
2. Sidestream smoke from cigarettes smoked under normal conditions was of equal potency to mainstream smoke but had a reduced potency when smoked under enclosed conditions. These conditions will be further investigated and experiments carried out to investigate products with reduced sidestream deliveries.
3. Investigation of a Japanese hemin filter claimed to eliminate mutagens from cigarette smoke. In a smoking situation the filter did not eliminate mutagens, only reduce them by 11%.
4. The specific activity of a plain cigarette was found to be lower than that of a ventilated filter cigarette. Further investigation of smoking variables that modulate mutagenicity will be investigated.

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Japanese experiments on the link between tobacco protein content and reduced mutagenicity were also described and put forward as an area for future work. The mutagenicity test battery will also be completed by a test to investigate the ability of chemicals to damage chromosomes.

In discussion, considerable interest was expressed in the areas of work described for the future. It was generally agreed that biological work, including mutagenicity on sidestream, should proceed at GR&DC since the expertise is available and it is preferable to influence the approach and techniques later required by outside agencies. The issue of whether this work should be "pooled" on an industry basis was raised and unresolved.

The planned tobacco deproteinisation work was also endorsed as part of an approach to produce the maximum opportunity of producing products that will have the minimum interaction with biological systems. These studies should also be carried out in parallel with experiments on the influence of human smoking conditions on mutagenicity and smoke chemistry in an attempt to understand the various interactions in smoke mutagenicity modulation.

Passive Smoking

Papers subsequent to and including Hireyama (January 1981) were discussed. This is an area of substantial debate and controversy and the deliberate misquotation of scientific results (e.g. those of Feyerabend, Higenbottam and Russell) were discussed.

Clearly, however, this is an area of considerable importance.

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