

Minutes SRG Meeting  
Chelwood Jan 20-22 1987

Those Present: Dr R E Thornton - BATCo Chairman  
Dr S Boyse - BATCo  
Dr C P J de Siqueira - Souza Cruz  
Dr F Seehofer - BATCF  
Herr E Koehn - BATCF  
Dr F Knabjohann - BATIG  
Dr S Massey - Imperial, Canada  
Dr G Smith - BATUKE  
Mr M L Reynolds - B&W, USA - Jan 21 only

Also Present: Mr A L Heard - BATCo - Jan 20 only  
(part-time) Dr R R Baker - BATUKE - Jan 20-21 only  
Dr E Massey - BATUKE - Jan 20-21 only

External

Participation: Dr G Gori - Franklin Institute, Washington,  
USA - Jan 21-22 only  
Mr A Campbell-Johnson - UK - Jan 20 only  
Dr F J C Roe - UK - Jan 20 only  
Dr P B Farmer - Medical Research Council Laboratory  
Carshalton, UK - 20 Jan only  
Mr M Burke - UK - Jan 20 only

Tuesday 20 January 1987: PRESENTATIONS FROM EXTERNAL PARTICIPANTS

1. DNA and Protein Adducts: Dr P B Farmer

Dr Farmer described current work at the MRC laboratories, Carshalton, Surrey, England.

DNA and protein adducts excreted in urine were estimated quantitatively by GC/MS analysis, although Dr Farmer pointed out that mg quantities of such adducts as methylated guanines were excreted by subjects in normal health. Because of this background 3-methyl adenine had been used instead (background levels being  $10^{-3}$  smaller).

However most work had been carried out with protein adducts, compounds such as S-methylcysteine or S-ethylcysteine being measured. The sensitivity of this method was 1 in  $10^9$  amino acid residues, equivalent to 1 in  $10^{10}$  DNA residues, haemoglobin in 5ml blood samples being adequate and having a long half life (~ 4 months).

More recently hydroxyethylvaline adducts had been used (and ethylene oxide identified as the alkylating agent). By use of the Edman degradation technique thiohydantoin derivatives could be obtained, amenable to GC/MS techniques.

Using this method increased levels of adduct were identified in smokers compared to non-smokers and in subjects occupationally exposed to ethylene oxide.

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2. Other Noxa: Mr M Burke

Occupational exposure limits had been established for many compounds on the basis of exposure for a lifetime of working 8 hours/5 days a week. This could be applied to compounds listed in the UK ISC Third Report, possible interactive effects being ignored.

Using the long-term limits set by the UK Health and Safety Executive, and assuming each puff is diluted to 500cc in the lung, and all smoke is cleared, the following compounds exceed the exposure limits:

Acrolein  
Carbon Monoxide  
Formaldehyde  
Hydrogen Cyanide  
Cadmium compounds

On threshold: Acetaldehyde.

In consideration of these compounds individually, Mr Burke made the following comments.

Cadmium Compounds

A protein (MW 20-30,000) was excreted when chronic Cd poisoning occurred. This could be monitored in smokers to determine if significant cadmium exposure occurred.

In discussion Dr Roe referred to the animal studies on cadmium compounds being carried out at the Fraunhofer Institute, and which had resulted in lung tumours.

Formaldehyde, Acrolein, Acetaldehyde

Mr Burke said that the ciliotoxic data was of dubious value as it was measured in solution. Vapour-phase levels were needed.

The reasons why acetaldehyde was included in the third report of the ISC was obscure but at high levels it apparently produces increases in blood pressure.

Carbon Monoxide

Mr Burke was of the opinion that carbon monoxide might be a particular problem in smokers with a heart condition as it would stress cardiac output.

3. Dr Roe

Dr Roe's slides are enclosed as Appendix 1.

Dr Roe emphasized the problems caused by the lack of satisfactory animal models for lung cancer, heart disease and emphysema although a number of other approaches were available (slide 4). Currently tests for ciliotoxicity and carcinogenicity/mutagenicity were available to supplement chemical data.

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Wednesday 22 January 1987: S.R.G. DISCUSSIONS

4. Other Noxae

Various outside publications were considered as a possible basis for establishing priorities for "other noxae". These included the 1986 IARC Monograph (Appendix II), the 1986 MAK list and the third report of the ISC. A variety of views existed: while the IARC monograph considered individual smoke components as, of course, do most regulatory authorities the ISC took the view that there was insufficient evidence to incriminate individual smoke components although even they had requested upper limits for tar, nicotine and carbon monoxide. While most of the discussion centred on individual chemical constituents of cigarette smoke it was noted that free radicals and 'radioactivity' could also fall within the guidelines.

Dr Roe had also commented on the problems associated with the restricted range of animal tests evaluating relative risk and additional problems existed in respect of likely synergistic/antagonistic effects.

After further consideration it was suggested that other noxae should be considered at two levels:

1. Compounds where recent scientific data had not yet been evaluated by regulatory authorities.
2. Compounds where regulatory authorities had made, or were likely to make recommendations which would result in pressure to alter the product.

Under these two categories the following were considered:

- 1(a) Compounds forming adducts with DNA or Proteins - While Dr Farmer had developed an interesting analytical approach to measuring exposure the interpretation of his results were, at present, equivocal. It was agreed that this area should be monitored, but at present, no further action was required. However a literature review, and possible opinion on the likely sources of the ethylene oxide moiety attached to proteins, was required.
- 1(b) Bis-dichloromethylether - After discussions it was agreed that a literature survey should be carried out on possible analytical methods for measuring this compound, its possible occurrence in the environment generally and its biological properties, to be ready for the next meeting.
- 1(c) Free Radicals - TAC (UK) were having a presentation on this subject in February from an UK expert, Dr B Halliwell. It was agreed that this subject would be reconsidered at the next meeting after a report on Dr Halliwell's presentation.
- 1(d) Heavy Metals - Further work on cadmium was known to be in progress, but had not yet been published. Accordingly, it was agreed to watch for developments in this area.

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2. Compounds receiving attention by regulatory bodies in Canada and Germany are listed in Appendix III and those identified by the IARC and the UK ISC can also be considered here.

Polycyclic hydrocarbons, nitrosamines - No new evidence had occurred on polycyclic hydrocarbons in recent years and Dr Roe's results (no increase in skin painting activity with 10x excess of benzo(a)pyrene) were noted. Likewise Dr Roe reported that the recent meeting arranged by the ISC on nicotine and its metabolites (especially tobacco-specific nitrosamines) was likely to conclude that these compounds were not sufficiently important to preclude the development of low tar normal nicotine products.

Nevertheless, because these compounds were known animal carcinogens they were likely to be the subject of constant attention by regulatory authorities.

If Mr Burke's method of prioritization was accepted the following compounds exceed TLV levels and result in the following prioritization order: Carbon Monoxide

Acrolein

Formaldehyde

Hydrogen Cyanide

Acetaldehyde

possibly cadmium depending on chemical form

It is to be noted that acrolein, formaldehyde and acetaldehyde are all ciliotoxic.

Finally it was noted that country-to-country valuations in the attitudes of regulatory bodies towards other noxae are inevitable.

Further discussion on the other noxae was agreed (see p.7)

With regard to Mr Burke's comments on carbon monoxide in relation to smokers with a heart condition, it was felt that medical advice was available on appropriate changes in life style for those suffering from this, or any other illness.

#### 5. Research on Nicotine - Dr S Boyse

For further details see hand-outs by Dr Boyse (Appendix IV).

Major recommendations were that further work should be carried out in areas of nicotine receptors, and the effects of nicotine and psychological tests on performance and memory.

#### 6. Other Projects

Visits were pending to Professor Clamp in Bristol with regard to his ulcerative colitis project and to Dr Carter in London regarding his project on atrial natriuretic peptide factor. Work in both these areas was about to start.

It was noted that Professor Caro, whose project on atherosclerosis the SRG had felt unable to support, has written a letter requesting that his project be reconsidered. It was not felt that the position of the SRG should be revised on this account.

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7. Conference on Nicotine

A Symposium on nicotine will take place in Brisbane, September 1987 as a satellite of the IUPHAR conference of Pharmacology. Dr Thornton and Dr Boyse will be attending this on behalf of BATCo and will be reporting back to the SRG on the outcome of the conference.

8. Possible New Projects

- a) With regard to the question of the effects of nicotine on performance, Dr Stavrou of the Royal Free Hospital had been approached with regard to his computerized tests on psychological function. He had expressed interest in carrying out a small study on the effect of smoking in these tests as a preliminary to a possible long-term project. It was hoped that a further proposal would be available in May.

A group in the Psychology Department in Leeds University headed by Dr Ian Hindmarch might also be approached on this question.

- b) In the area of nicotine receptors Dr Susan Wonnacott, currently funded by the TAC, tentatively suggested that BAT might consider continuing her funding when it terminates in 1988.
- c) Jeffrey Gray - Professor of Psychology at the Institute of Psychiatry in London - had approached Dr Boyse about possible funding for a joint project with Professor Raymond Levy and Dr Barbara Sahakian on the effects of nicotine in patients with Alzheimer's disease. The sum requested was approximately £66,000 over 3 years. There was general agreement on this and it was noted that Dr Thornton and Dr Boyse would visit the group and report further in May.

It was also felt that a possible protective effect of long-term smoking in the development of Alzheimer's disease was a separate but equally important issue that should be investigated. It was decided to ask Mr Peter Lee, a BATCo Consultant, to review the literature in this field and ask his advice about a prospective study. Dr Massey also noted that Dr Verner Knott in Canada might be involved in such a project and he agreed to pursue the matter and report to the SRG in May.

- d) Dr Thornton said that a provisional application had been received from Professor V V Kakkar for work related to the development of atherosclerosis. The full project had not yet been received but would probably relate to mechanistic studies involving a polypeptide growth factor thought to be involved in the development of a plaque.

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- e) Dr Gori noted that correlations had been made between mental illness such as schizophrenia and manic-depression and heavy smoking. It was believed that there may be therapeutic benefits of smoking to these patients. It was suggested that this area should be closely watched in the future.

Dr S Massey would also report on Verner Knott's possible work in this area in May.

- 9. Dr Seehofer gave a general overview on his visit, with Graham Smith, to Japan. For further details see their report (Appendix V).

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Thursday 22 January 1987

10. Report on visit to Japan

Dr Smith explained the background and highlights of the visit to Japan made by himself and Dr Seehofer.

In particular it was noted that Dr Hireyama now works in virtual isolation. A substantial amount of work on nicotine is being carried out under contract and in the context of a substantial programme of work on other materials. Much work had been done on self-administration of these materials by monkeys, as described in the visit report.

Delegates felt that the visit had been very successful in establishing the scope of relevant research in Japan and in breaking the ice. In particular the work of Dr Tomoji Yanagita, on behavioural effects of nicotine in comparison with other materials, was thought to be of considerable interest.

It was considered essential to capitalize on the visit by keeping in active contact.

11. Scope and Venue of next meetings

It was decided that future meetings would retain the broad format of the present meeting with presentations by outside speakers addressing themes identified by the SRG. The following programme was suggested:

May 25-27 1987, Hamburg - Social Acceptability of Smoking, further views on Other Noxae.

Nov 2-4 1987, Rio de Janeiro - Research work sponsored by Tobacco Industry.

April/May 1988, UK - Molecular Biology.

Possible Speakers

Hamburg: Prof. Pavlik, Prof. Jurna, Dr Yanagita

Rio de Janeiro: Dr Sheldon Sommers, Representative of Japan Tobacco Inc.

UK: Dr Currie, Prof. Bloom, Dr Carter

12. Final Discussion, critique

During the final discussion the meeting's progress towards assessing other noxae was reviewed. It was concluded that a further discussion was needed (to be incorporated into the May 1987 meeting of the SRG) and that BATCo (Dr Boyse and Dr Thornton) would produce a discussion paper which would attempt to integrate the views propounded at Chelwood, together with other relevant material. Delegates would then attempt to reach some conclusions on the prioritization of "other noxae".

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Action Points

1. The scientific literature relating to DNA and protein adducts should be monitored in the future, and a literature review on the likely origin of the ethylene oxide moiety attached to proteins should be prepared. GS
2. A literature survey on bis-dichloromethyl ether should be carried out: the means for measuring it; its possible occurrence in the general environment, and its biological properties. GS
3. A report to be given on Dr Halliwell's presentation on Free Radicals. GS
4. It was agreed to fund Professor Raymond Levy's application on nicotine effects and Alzheimer's Disease for the sum of £66,000 over 3 years. Drs. Thornton and Boyse would visit the group and report back in May. RET/SB
5. Peter Lee, a BATCo consultant, should be asked to review the epidemiological literature in the field of long-term smoking and the development of Alzheimer's Disease. Dr Massey would investigate possible work in this field going on in Canada. RET/SB/SRM
6. It was decided to keep in active contact with Japanese scientists following a visit made by Drs. Seehofer and Smith. GS
7. Drs. Thornton and Boyse would produce a discussion paper on "other noxae" for presentation at the next SRG meeting. Delegates would then attempt to reach a conclusion on the prioritization of other noxae. RET/SB
8. Organization of next meeting (Hamburg). RET/SB/EK

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**Appendices**

1. Copy of Dr Roe's slides
2. Dr Massey's IARC etc. list
3. Lists from Germany and Canada's regulatory bodies
4. Proposals for research on nicotine by Dr Boyse
5. Report on a visit to Japan by Drs. Seehofer and Smith.

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