

RESTRICTED

NITROSAMINES

CURRENT SITUATION AND FUTURE PROSPECTS

Summary of the Eighth International Meeting
on N-Nitroso Compounds,
held at Banff, Alberta, Canada,
5th-9th September, 1983

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EIGHTH INTERNATIONAL MEETING ON N-NITROSO COMPOUNDS

INTRODUCTION

The Eighth International Meeting on N-Nitroso Compounds was held at the Banff Centre, Banff, Alberta, Canada, 5th-9th September, 1983. This conference was organised by the International Agency for the Research on Cancer (IARC), who are funded by the World Health Organisation.

The meeting attracted a world-wide delegation (175) of mostly scientists, but included other people with strong interests in environmental carcinogens such as Government representatives and Union leaders. Tokyo, Japan, played host to the Seventh Meeting in 1981. The ninth meeting is scheduled to be held in Vienna, Austria, in 1986.

Mr. Miller, Canadian Member of Parliament and Minister of the Environment in Pierre Trudeau's cabinet, gave the opening address. This, more than anything, reflected the support given by the Canadian Government to the conference. Indeed, on speaking to Eastern European delegates, it became apparent that, when required, visas were issued by the Canadian authorities without undue difficulty.

The conference was divided into seven sessions, which are listed in the Technical Report on this meeting along with comments and notes on the individual papers and posters presented. 117 papers were presented which included 63 poster presentations. By far the most important session for the Tobacco Industry was the third session, on "N-Nitroso Compounds in Tobacco Carcinogenesis", although parts of other sessions were also very relevant - for example "Analysis, Occurrence and Formation of N-Nitroso Compounds" and "Metabolism and Modifying Factors".

COMMENTS ON CONFERENCE PROCEEDINGS

N-Nitroso Compounds in Tobacco Carcinogenesis

This session was chaired jointly by R. Preusmann and L. Tomatis; Dr. Hoffmann gave the opening paper. For the first time, a whole session was devoted to tobacco, reflecting the increasing interest and concern in nitrosamines in tobacco and tobacco smoke. Most of the presentations originated from the Naylor Dana Institute, Valhalla, New York, or were in collaboration with this institute. They were strongly anti-smoking but at least their scientific content was reported reasonably impartially.

It became clear during this session that a major potential problem for the Industry is the reported endogenous formation of nitrosamines - that is, the natural formation of nitrosamines in the bodies of animals.

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Hoffmann, Brunnehan and others are saying this is a major problem and they go further to suggest that tobacco alkaloids such as nicotine can be converted after ingestion (or inhalation) to tobacco-specific nitrosamines (TSN). How our industry is to protect itself from this line of attack provides a major challenge for the future.

Surprisingly, little was said at the conference concerning sidestream smoke and levels of tobacco-related nitrosamines in ambient air. In talking generally with delegates, I received the impression that nitrosamines in the context of passive smoking was not a major issue and that mainstream levels were of greater concern.

At the end of the session, Dr. Preusmann announced that, due to the lack of time, no general discussion would be held. This was most puzzling as other sessions had always finished late since speakers invariably ran overtime yet this was the only session where discussion was curtailed! I had the suspicion at the time that the "Valhalla School" were behind this in collaboration with the conference organizers, IARC. On speaking to two other delegates after this session, Dr. B.C. Challis (Imperial College, London) and Dr. A.H. Warfield (Philip Morris, USA), I found they had similar views. In fact, Dr. Challis went further to suggest that the whole session had been carefully planned and that, once the statement on nitrosamines and tobacco had been made, Hoffmann and colleagues wanted it to rest there.

The general attitude of most delegates was that nitrosamines were now considered to be causally related to tobacco carcinogenesis, especially with regard to snuff dipping and chewing tobacco. In my opinion this was by no means proven scientifically at this meeting.

Other Sessions

The first session, on the "Analysis, Occurrence and Formation of N-Nitroso Compounds", was very enjoyable and served as a good introduction to the area of nitrosamines. Some interesting chemical papers were presented, notably that of Challis and Chow.

Contact was made with Dr. Challis, who is a Senior Lecturer at Imperial College, London. He is considered to be one of the world's experts in the chemistry of nitrosamine formation, especially with regard to reaction mechanisms, and is well known in the area of nitrosamines. Consideration should be given to seeking his assistance in the reaction mechanism area.

P. Swann gave a paper on the effect of ethanol intake in the session on "Metabolism and Modifying Factors", which was very interesting. His findings indicate that, in rats, the metabolism of nitrosamines is reduced by relatively small oral doses of alcohol, which may be good news for drinkers!

An interesting paper was given by C.L. Walters in the session on "Recent Analytical / Methodological Advances in the Identification of N-Nitroso Compounds". This was concerned with the measurement of

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total nitrosamine levels. Presently in GR&DC individual nitrosamines are measured and not total nitrosamines. However, there may be a need to do this in the foreseeable future, especially if no clear weighting can be placed on individual nitrosamines with regard to biological effects.

In the last session, B. Spigelhalter gave a paper on "Occupational Exposure to Nitrosamines". This did not include any reference to cigarette smoke (mainstream or sidestream) and was mostly concerned with the measurement (monitoring) of nitrosamines in industrial manufacturing areas. Spigelhalter strongly advocated the establishment of representative data bases on individual exposure levels in combination with prospective epidemiological studies. Under these conditions it might be possible to identify risk areas and to introduce preventive measures. Interestingly, no mention of passive smoking was made in this session.

MAJOR CONCLUSIONS ON THE CONFERENCE

Endogenous Formation of Nitrosamines

The endogenous formation of nitrosamines is clearly of great interest. It has been known for a number of years that nitrosamines are formed naturally in the bodies of animals. The precursors for these nitrosamines are amines from dietary intake. It was clear at the conference that a new line of attack on the Tobacco Industry may be via endogenous formation. Hoffmann and workers suggested that tobacco alkaloids such as nicotine can be converted after ingestion (or inhalation) to tobacco specific nitrosamines. There is no sound experimental evidence to back this up at the present time; however, the implication may be enough to cause the industry difficulties.

Sidestream Smoke and Passive Smoking

Little was said at the conference concerning sidestream smoke and levels of tobacco-related nitrosamines in ambient air. The impression given at this meeting was that nitrosamines in the context of passive smoking was not a major issue and that mainstream levels were of greater concern.

Mechanisms of Formation of Nitrosamines

Most of the presentations given at the conference were concerned with the detection, measurement and biological effects of nitrosamines. There is presently a gap in knowledge of the chemical processes involved in their formation. This was abundantly clear in the "Tobacco Session" where speaker after speaker spoke about the amounts in smoke, on tobacco, etc. Very little work has been done on studying the mechanisms of formation of nitrosamines in tobacco leaf and during the combustion of tobacco. Until this essential research work is completed, long term goals to substantially reduce the levels cannot

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be attained. Short term measures can be introduced in the meantime - for example changes in agricultural practices, factory processing, better filters and manipulation of cigarette design - but they do not provide a long term solution to the problem.

Biological Effects of Nitrosamines

Although a causal relationship between nitrosamines and human carcinogenesis has yet to be established, it has clearly been demonstrated in animals (especially rodents) by many workers. In the "Tobacco Session" attempts were made to convince the conference that there was a causal relationship between the use of tobacco products and human carcinogenesis, especially in snuff dipping and chewing tobacco. The culprit, of course, was nitrosamines - present in nanogram (10^{-9} g) to microgram (10^{-6} g) amounts on tobacco and in tobacco smoke. As far as I am aware, there is no sound evidence to implicate nitrosamines in the potential carcinogenesis of cigarette smoke.

A number of modifications to the nitrosamine work programme have been made as a consequence of this conference and are included in the work programme for 1984.

A full account of the conference proceedings, together with relevant notes, is detailed in the Technical Report which is available if required.

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