COMMITTEES ON TOXICITY, CARCINOGENICITY, MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT, COC, COM)

JOINT STATEMENT ON THE RE-ASSESSMENT OF THE TOXICOLOGICAL TESTING OF TOBACCO PRODUCTS

Introduction

1. Article 11 of the Directive 2001/37/EC of the European Parliament and of the Council[1] sets out a requirement for the European Commission to submit, no later than 31 December 2004 and every two years thereafter, a report on the Directive's application. Such a report will aim to review, and advise on the development of, particular features of the Directive. Two areas of specific concern are;

"methodologies for more realistically assessing and regulating toxic exposure and harm"

and,

"toxicological data to be required from manufacturers on ingredients and the manner in which they should be tested in order to allow public health authorities to assess their use"

2. The Committees (COT/COC/COM) were asked to provide advice on these areas of toxicological assessment with reference to the assessment of Potentially Reduced Exposure Products (PREPS) and in particular tobacco-based PREPS which are smoked. A brief overview of the information reviewed and approach taken by the Committee's is given below. Copies of the discussion papers used by the committees can be obtained from the Committee internet sites.

http://www.advisorybodies.doh.gov.uk/cot/index.htm
http://www.advisorybodies.doh.gov.uk/com/
http://www.advisorybodies.doh.gov.uk/coc/

3. The Committees agreed that it was important to state that the ideal way forward to reduce risks and hazards of tobacco smoke was to encourage smokers to stop or people not to start in the first place any attempt to reduce toxicity should not be allowed to detract from that. Members acknowledged that the primary remit of the Committees' discussions was to provide advice based on the information provided.

Approach taken and evidence reviewed

4. The Committees considered a covering paper drafted by the secretariat (available on the Committee internet sites) and appended references. These included information from the Symposium proceedings of the 56th meeting of the Tobacco Science Research Conference [2] and a number of peer-reviewed publications in scientific journals.[3-9] In discussing these data members were reminded of the recent considerations (at COT/COC/COM meetings during 2004) on toxicogenomics where a number of studies investigating tobacco smoke had been considered.. (See above internet sites for minutes and papers) The Committees were aware that additional studies both in the public domain and possibly held by industry could have been reviewed but noted that they had been asked to provide the best advice possible in the available time based on the information provided to members. The discussion paper and appended references were considered at the COM meeting on 7 October, the COT meeting on 26 October and the COC meeting on 18 November 2004.

Generic consideration of toxicological approaches to evaluation of PREPS.

5. The Committees commented that tobacco smoke was a highly complex chemical mixture and that the causative agents for smoke induced diseases (such as cardiovascular disease, cancer, effects on reproduction and on offspring) was unknown. The mechanisms by which tobacco induced adverse effects were not established. The best information related to tobacco smoke - induced lung cancer, but even in this instance a detailed mechanism was not available. The Committees therefore agreed that on the basis of current knowledge it would be very difficult to identify a toxicological testing strategy or a biomonitoring approach for use in volunteer studies with smokers where the end-points determined or biomarkers measured were predictive of the overall burden of tobacco-induced adverse disease.

6. The Committees commented that since it was not possible to define reliable end-points or biomarkers for use in *in-vitro* investigations (with exception of mutagenicity testing see parageaph 10 below), *in-vivo* studies in experimental animals or in volunteer studies using smokers, it would not be possible to compare PREPS using such approaches.

7. The Committees also noted that some weight could be placed on investigations of markers for the tobacco-specific nitrosamine NNK (4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone) and its metabolite NNAL (4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol) as markers for exposure to a potentially relevant tobacco smoke-derived carcinogen. However, a valid investigation of carcinogenic potency of PREPS would have to examine a wide range of the 50 or so known human carcinogens present in tobacco-smoke. In addition, strategies designed to compare PREPS with regard to

one chronic disease associated with tobacco-smoke, such as lung cancer, may have no predictive value for other diseases such as tobacco-smoke induced cardiovascular disease.

8. Overall the Committees agreed that there were considerable difficulties in designing a toxicological testing strategy for the reassessment of tobacco products and that it was not possible to design a valid strategy given current understanding of the diseases associated with smoking tobacco.

Consideration of approaches currently used.

9. The Committees commented on the approaches used in the information provided. When tobacco manufacturers wish to assess the influence of any design changes on the overall toxicity of a product, a tiered testing regime has been advocated which currently consists of one or more of the following;

A bacterial test for gene mutation (e.g. the Ames test)

A test for clastogenicity and for indications of aneugenicity

In vitro metaphase analysis
In-vitro micronucleus test

Mammalian cell mutation assay (preferred choice is the mouse lymphoma assay

Cytotoxicity is assessed using the Neutral Red uptake assay.

In-vivo studies in experimental animals to investigate biomarkers of disease.

Studies in smokers (volunteers) to examine effects on smoking and biomarkers following switching from one tobacco product to a PREP.

Advice from COM on mutagenicity

10. The COM considered the available information and agreed that using suitable protocols it was possible to compare mutagenicity *in-vitro* of different PREPS which could be useful to assess hazard. However, the results of such *in-vitro* tests had no predictive value for risk of *in-vivo* mutagenicity or cancer. No conclusions could be drawn on the approaches using toxicogenomic methods. The available biomonitoring approaches were too limited to draw any conclusions regarding a comparison of PREPS.

Advice from COT on Toxicology testing

11. The COT concluded that *in-vitro* cytotoxicity testing could be used as part of an overall approach for comparing PREPS but the data could not be extrapolated to the *in-vivo* situation and the outcome measured in such tests had no predictive value with regard to tobacco-smoke associated diseases.

The COT considered that studies in smokers (volunteers) to investigate tobacco-based PREPS should take account of smoking behaviour in addition to investigation of biomarkers of disease. The COT concluded that there were currently no adequate biomarkers for tobacco-smoke induced diseases and no conclusions could be reached on the available data. The COT concluded that smoke chemistry could not be used to compare PREPS.

Advice from COC on carcinogenicity

12. The COC commented on the complexity of tobacco indiced cancer and noted that the mechanism(s) and information on the chemical agents responsible for tobacco induced cancer in humans had not been fully elucidated. In addition members noted the importance of the interaction between chemical carcinogens and susceptibility factors regarding the pathogenesis of tobacco induced cancer. The COC concluded that there is no strategy which could be used to compare PREPS for carcinogenic potency and that the approaches used are not informative on the risk of tobacco induced carcinogenicity. The COC agreed that it was not possible to draw conclusions on the carcinogenic risk of tobacco-based PREPS on the available biomarker studies reviewed [6-9]. The COC commented on the need to examine a wide range of biomarkers of carcinogenicity and their interaction with susceptibility factors.

Overall conclusions of the Committees

The Committees agreed that analysis of tobacco smoke constituents was not useful in comparing tobacco-based PREPS or predicting risks associated with tobacco smoking.

14. The Committees agreed that the current *in-vitro* tests and *in*-vivo approaches used in experimental animals used to evaluate the toxicity of tobacco products and tobacco-based PREPS are not informative on risk of diseases induced by tobacco-smoke.

15. It was noted that comparative assessemtns between PREPS can be undertaken for data generated in some *in-vitro* mutagenicity tests, but the data cannot be extrapolated to *in-vivo* mutagenicity.

16. The Committees agreed that the available biomonitoring studies in volunteer smokers were too limited to draw any conclusions regarding comparisons of tobacco-based PREPs.

17. The Committees cautioned that biomonitoring studies which focused on one disease (such as cancer) in volunteer smokers had no predictive relevance to other tobacco smoke-induced diseases such as cardiovascular diseases.

18. The Committees advised that future progress on the proposed approach to reduce tobacco smoke-induced disease by modification of

tobacco products could only be made when detailed mechanistic information on tobacco-induced diseases were available.

November 2004
COT/04/09; COC/04/S4 & COM/04/02

References

1. Directive 2001/37/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco products, (2001).

2. Recent Advances in Tobacco Science, Toxicological Evaluation of Tobacco Products, Symposium Proceedings, 56th Meeting of the Tobacco Science Research Conference, (2002). September 29-October 2, 2002, Lexington, Kentucky, U.S.A.

3. Andreoli C et al Toxicology In-vitro, 17, 587-594, (2003)

4. Gebel, S., Gerstmeyer, B., Bosio, A., Haussmann, H-J., Van Miert, E. and Müller, T., Gene expression profiling in respiratory tissues from rats exposed to mainstream cigarette smoke, Carcinogenesis, 25(2), 169-178, (2004).

5. . Obot CJ et al. Characteristation of mainstream cigarette smoke-induced biomarker responses in ICR and C57Bl/6 mice. Inhalation Toxicology, 16, 701-719, (2004).

6. . Breland et al. Acute effects of Advance™: a potential reduced exposure product for smokers. Tobacco Control vol 11, 376-378, (2002).

7. Breland AB et al. Tobacco specific nitrosamines and potential reduced exposure products for smokers: a preliminary evaluation of Advance™. Tobacco Control, 12, 317-321, (2003).

8. Hughes JR et al. Smoking behaviour and toxin exposure during six weeks use of a potential reduced exposure product: Omni. Tobacco Control vol 13, 175-179, (2004).

9. Hatsukami DK et al. Evaluation of carcinogen exposure in people who used “reduced exposure” tobacco products. JNCI, 96, 844-852, (2004).