

**DRAFT**

**COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COM)**

**DRAFT DISCUSSION PAPER: REGULATORY ASPECTS SURROUNDING THE TOXICOLOGICAL EVALUATION OF TOBACCO PRODUCTS**

**Rationale for seeking advice from the Committee**

1. The toxicological evaluation of tobacco products is a complex area of mixture toxicology and there are few relevant data available on tobacco products. A specific request has thus been put forward to the COM, COC and the COT, by the UK Department of Health, to examine scientific evidence on toxicological testing since the joint statement on the toxicology of tobacco products was issued in 2004.

2. Assays or methods used to test the toxicological potency of tobacco products have been used successfully for years for chemical products such as food additives, medicines etc <sup>[1]</sup> (Annex 1). The suitability of these tests for the evaluation of tobacco products has however been called into question by public health experts at international, European and national level. Further, the WHO study group on Tobacco Product Regulation (TobReg) in WHO Technical report series 945, noted that the potential of a product to induce different types of toxicological damage to humans needed further investigation <sup>[1]</sup> (Annex 1). A systematic review of the available data and scientific advice from the COM, on the application of these methods for the evaluation of tobacco products will help to fill a regulatory void and potentially aid policy decisions.

3. The 2004 COT/COC/COM statement <sup>[2]</sup> (Annex 2), which states that there are no realistic methods for assessing toxic exposure due to tobacco smoke is consistent with the views expressed by public health experts. Although the recommendation has always been for further experimental work to develop suitable toxicological approaches for assessing the toxicity of tobacco additives and emissions, there have been major research activities in this area since the joint statement was issued and it would be of value to examine generated data and research findings with a view to the 2004 statement being updated.

**International regulation of tobacco products**

4. The WHO Framework Convention on Tobacco Control (WHO FCTC), which is the first global treaty negotiated under the auspices of the WHO came into force in February 2005 <sup>[1, 3]</sup> (Annexes 1 and 3). Under this treaty, Tobacco Product Regulation was identified by the Tobacco Free Initiative (TFI) as one of the four pillars of a comprehensive tobacco control

program <sup>[1]</sup> (Annex 1). Progress reports presented at the second and third meetings of the Conference of the Parties (COP) to the FCTC by the working group on articles 9 and 10 of the FCTC, which are the articles that deal specifically with measuring, testing and disclosure of information on tobacco products, highlighted the importance of monitoring research the area of toxicology <sup>[4, 5]</sup> (Annexes 4 and 5). Further, the input of scientific experts is considered as central to the development of toxicological approaches <sup>[1]</sup> (Annex 1), as there are no international agreed approaches to hazard assessments of tobacco products.

5. Many countries require the tobacco industry to submit information on ingredients and emissions based on existing toxicological tests (Ames Assay, Neutral Red Cytotoxic Assay and Micronucleus Assay being the most commonly used). However, there have been debates among tobacco control experts that these tests may not be the most suitable for the toxicological evaluation of tobacco products. There is also a contention that the tests do not give enough information to draw meaningful conclusions on the toxic potential of additives and tobacco product emissions. In addition to this, some authorities request all available toxicological data (The EU), while others such as Health Canada specify the particular toxicological test to be used.

6. It was noted in the WHO monograph on advancing knowledge on regulating tobacco product <sup>[6]</sup> (Annex 6) that these methods are inadequate in evaluating tobacco products, as they were not intended to measure the biological or the epidemiological activity of these products. Recommendations from this report include calls for the development of new methods to evaluate the toxicity and health impact of tobacco products based on a range of biological activities, a call for investigation into the use of biomarkers to assess the health impact of tobacco products on humans and research to respond to claims on new products <sup>[6]</sup> (Annex 6).

7. The WHO Technical Series Report 945 noted that the understanding by which smoking causes disease is not adequate to identify with confidence the rate limiting steps in the mechanistic pathways and therefore the changes that will reliably predict risk. It is also uncertain which changes are markers of tobacco use <sup>[1]</sup> (Annex 1). Although biomarkers exist, which can measure the presence and extent of various systemic processes, which may play a mechanistic role in disease occurrence, the diseases caused by cigarette smoking involve multiple processes and it remains unproven whether an alteration of a single process will reduce disease frequency. These limitations mean that acceptance of a given biological change as a biomarker of injury and risk requires validation that a change in the biomarker independently predicts a change in the frequency of disease occurrence <sup>[1]</sup> (Annex 1).

8. To date, there has not been a critical evaluation to check the suitability of the toxicological approaches to testing tobacco products, based on a systematic review of the available evidence, the contribution of ingredients to the toxicological potency of tobacco emissions or the use of biomarkers to predict risk. In an attempt to fill these gaps, it was proposed to examine scientific evidence in the above-mentioned areas, in order to generate definitive statements on the relevance and use of certain tests for the evaluation of tobacco products. This will be invaluable in guiding regulators in making informed decisions about the toxic contents and emissions of tobacco products.

## **European Regulation of Tobacco Products**

9. The tobacco products directive (2001/37/EC) stipulates that one of the major areas that require special attention is “methodologies for realistically assessing and regulating exposure and harm attributable to tobacco products” <sup>[7]</sup> (Annex 7). This aspect of tobacco control has not received adequate attention due to limited knowledge and insufficient evidence to inform policy in this area. There is an initiative in the EU to set up an expert panel of toxicologists to examine existing toxicological tests, toxicological reports submitted by the industry and to establish some criteria for the nature of toxicological information needed to obtain relevant health data. A statement from the COT/COC/COM would be of value to this group which will be meeting in the latter part of this 2009.

10. Within the European Union, a harmonised reporting system <sup>[8]</sup> (Annex 8), which was adopted in 2007, requires tobacco manufacturers to submit available information on the toxicity of their manufactured products, which include cardiovascular toxicity, transfer studies, in vitro toxicological studies, dermal/inhalation carcinogenicity, chronic studies, etc. These reports are collected in order to assess the toxicity of these products, assess the safety of ingredients and ultimately for regulation purposes. The joint statement on the toxicity of tobacco products since issued in 2004 <sup>[2]</sup> (Annex 2) has been the DH line but an update in the light of recently published data would be very useful in informing policy.

## **National Regulation of Tobacco Products**

11. Dossiers submitted to the Department of Health on the toxicity of ingredients (such as additives) used in the manufacture of tobacco products indicate that ingredients have little or no effect on the overall toxicity of the cigarette. However, there is an element of uncertainty associated with these studies since there are no reliable models for assessing the individual contribution of additives to the toxicity of tobacco smoke. Standard protocols thus need to be established to evaluate the toxicity of tobacco products and their emissions.

12. The Committee is therefore asked to review MUT/09/05 together with associated information in the light of the four areas under consideration (i.e. the suitability of the toxicological tests used for the evaluation of tobacco and its products, whether there are validated biomarkers of effect, disease, harm, injury or risk, whether reduced exposure translates to reduced harm and the effect of ingredients or additives on overall toxicity to tobacco products).

13. The Committee is asked to specifically answer the following questions:-

- Do existing toxicological tests give an indication of the toxicological potency of tobacco and its products?
- What are the adverse health effects of additives or ingredients added to tobacco products?

- Does the addition of an ingredient or additive lead to increased toxicity of tobacco smoke?
- Are there validated biomarkers of effect for tobacco and its products and can these biomarkers be used to predict risk, harm, injury or disease?
- Is reduced exposure an indication of reduced harm, risk or injury?

**Secretariat**  
**May 2009**

## References

1. World Health Organisation (2006). The Scientific Basis of Tobacco Product Regulation. WHO Technical Report Series – No. 945.  
[http://www.who.int/tobacco/global\\_interaction/tobreg/tsr/en/index.html](http://www.who.int/tobacco/global_interaction/tobreg/tsr/en/index.html).
2. Committees on Toxicity, Carcinogenicity, Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC, COM). (2004). Joint Statement on the Re-assessment of the Toxicological Testing of Tobacco Products.  
<http://cot.food.gov.uk/pdfs/cotstatementtobacco0409>.
3. World Health Organisation (WHO) Framework Convention on Tobacco Control (2004). [http://www.who.int/fctc/text\\_download/en/index.html](http://www.who.int/fctc/text_download/en/index.html).
4. A/FCTC/COP/2/8. (26 April 2007). Elaboration of guidelines for implementation of the Convention (decision FCTC/COP1 (15): Article 9: Product regulation. WHO Report at the second session of the Conference of the Parties to the Framework Convention on Tobacco Control.
5. FCTC/COP/3/6. (21 August 2008). Elaboration of guidelines for implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control. Progress report of the working group at the third session of the Conference of the Parties to the Framework Convention on Tobacco Control.
6. WHO monograph on advancing knowledge on regulating tobacco products.
7. Tobacco Products Directive. (2001). Directive 2001/37/EC of the European Parliament and of the Council of 5 June 2001 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco products. Official Journal of the European Communities.
8. SANCO C6 TPE/ub D (2007) 360206. Practical Guide on Reporting on tobacco product ingredients. (Brussels, 31 May 2007). European Commission Health & Consumer Protection Directorate-General.

## **Annexes – Relevant extracts from References**

Annex 1: World Health Organisation (2006). The Scientific Basis of Tobacco Product Regulation. WHO Technical Report Series – No. 945.

Annex 2: Committees on Toxicity, Carcinogenicity, Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC, COM). (2004). Joint Statement on the Re-assessment of the Toxicological Testing of Tobacco Products.

Annex 3: World Health Organisation (WHO) Framework Convention on Tobacco Control (2004).

Annex 4: A/FCTC/COP/2/8. (26 April 2007). Elaboration of guidelines for implementation of the Convention (decision FCTC/COP1 (15): Article 9: Product regulation. WHO Report at the second session of the Conference of the Parties to the Framework Convention on Tobacco Control.

Annex 5: FCTC/COP/3/6. (21 August 2008). Elaboration of guidelines for implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control. Progress report of the working group at the third session of the Conference of the Parties to the Framework Convention on Tobacco Control.

Annex 6: World Health Organisation. Monograph: Advancing Knowledge on Regulating tobacco products. 2001.

Annex 7: Tobacco Products Directive. (2001). Directive 2001/37/EC of the European Parliament and of the Council of 5 June 2001 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco products. Official Journal of the European Communities.

Annex 8: SANCO C6 TPE/ub D(2007) 360206. Practical Guide on Reporting on tobacco product ingredients. (Brussels, 31 May 2007). European Commission Health & Consumer Protection Directorate-General.