Further refinement of a Margin of Exposure (MOE) model to prioritize cigarette smoke toxicants for reduction research

British American Tobacco, Group Research and Development, Southampton, SO15 8TL, UK

Correspondence: damien_breheny@bat.com Poster number 13 at TSRC Annual Meeting, September 15-18 2013 Williamsburgh, VA, USA

INTRODUCTION
In January 2012, the US Food and Drug Administration (FDA) outlined seven research priority areas relating to tobacco products (1). Research area three focused on “reducing toxicity and carcinogenicity of tobacco products and smoke”. This has been coupled with an increased interest in further characterising tobacco smoke toxicants both from the perspective of future regulatory frameworks aimed at monitoring or lowering toxicant levels and from the perspective of tobacco product development focused on selective toxicant reduction as part of broader harm reduction initiatives (2,3,4).

BACKGROUND
We have previously described the use of the Margin of Exposure (MOE) model as part of a quantitative risk assessment paradigm for tobacco smoke toxicants, in conjunction with the preparation of mode of action (MOA) reviews for individual tobacco smoke toxicants (5). A MOE is a ratio between a benchmark dose (a reference point derived from either experimental or epidemiological dose-response data) and the specific human exposure. The view from EFSA is that a MOE greater than 10,000 may be considered a low priority for risk management actions (6).

We propose further segregation of tobacco smoke toxicants into bandings based on their MOEs as follows: 1–10 (top priority), 10–100 (very high priority), 100–1,000 (high priority), 1,000–10,000 (medium priority), 10,000–1,000,000 (low priority), >1,000,000 (very low priority).

We applied this approach to the WHO Study Group on Tobacco Product Regulation (TobReg) list of 18 toxicants for mandatory lowering and monitoring, with the aim of further categorising them in terms of their relative risk in the context of cigarette smoke exposure. In addition, we used the same methodology to evaluate an additional five chemicals that have been identified by the FDA on their abbreviated list of 18 harmful and potentially harmful constituents (HPHC) in cigarette smoke (7).

METHODS
For each of the 23 toxicants evaluated, data from relevant in vivo studies were used to produce a series of MOE values representative of the literature (Fig. 1).

RESULTS
The calculated MOE ranges for each toxicant are given in Tables 1 and 2. The resulting classifications of these toxicants into prioritisation bandings are presented in Table 3.

The calculated MOE ranges were used to categorise the toxicants in order of their priority for reduction in cigarette smoke (Table 3). Where possible, we have used in vivo lifetime inhalation data, and when this was absent we weighted the available alternative in vivo data in favour of chronic studies with repeated exposure where possible.

Using this approach, acrolein was identified as being the top priority due to its extremely low range of MOE values, which were calculated using data obtained from two rat inhalation studies. Cadmium, formaldehyde and acrylonitrile were categorised as ‘very high priority’, as the majority of the MOE values for these toxicants fell within the range of 10–105.

The remaining 6 toxicants for which MOE ranges could be calculated were distributed between the categories of ‘high priority’ and ‘medium priority’. It was not possible to apply this banding approach to NNK or NNN as the calculated MOE values for both of these toxicants lie above and below 10,000. In the case of 2-aminoanilphathalene there was only one MOE available.

REFERENCES
6. EFSA meeting summary report EFSA/WHO international conference with support of ILSI Europe on risk assessment of compounds that are both acute and chronic toxicants, 2010.

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