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Suitability of biomarkers of biological effects (BOBEs) for assessing the likelihood of reducing the tobacco related disease risk by new and innovative tobacco products: A literature review

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ABSTRACT

The health risk of tobacco smoking can best be avoided or reduced by not taking up or quitting the habit. The use of new and innovative tobacco (NTPs, e.g. electronic cigarettes) can either be an aid for smoking cessation or, for those who are not able or willing to quit, an alternative for smoking conventional tobacco products. Before the use of an NTP can be regarded as an effective approach in tobacco harm reduction (THR), the implicated risk has to be evaluated by suitable toxicological methods such as the analysis of the chemical composition as well as assessment of detrimental effects in animal and *in vitro* studies. In human (clinical) studies, the NTP-related exposure to toxicants and early biological effects can be assessed by the determination of suitable biomarkers. In this review, the suitability of established and newly developed biomarkers of biological effect (BOBEs) for the indicated purpose is evaluated according to five criteria, including the association to diseases, reported difference in BOBE levels between smokers and non-smokers, dose-response relationships, reversibility and kinetics after smoking cessation. Furthermore, the effect size and the resulting sample size required in clinical studies were estimated and considered in the BOBE evaluation process. It is concluded that the rating process presented is useful for selecting BOBEs suitable for risk evaluation of NTPs in clinical and other human studies.

1. Introduction

Cigarette smoking is a major cause for morbidity and mortality of chronic diseases such as cancer, cardiovascular disease (CVD) and chronic obstructive pulmonary diseases (COPD) (US Department of Health and Human Services, 2014). Smoking cessation is by far the most effective approach in tobacco harm reduction (THR). However, for those who are not able or willing to quit smoking, switching to modified risk tobacco products (MRTPs, previously also termed potentially reduced exposure products, PREPs) could be an alternative in terms of THR (Stratton et al., 2001). New and innovative tobacco products (NTPs) such as heat not burn (HNB) tobacco products, nicotine containing oral tobacco products (like VERVE® and ZYN®) or electronic cigarettes (e-cigs) show promise for potential risk reductions in preclinical studies compared to conventional cigarettes (CC) (Farsalinos and Polosa, 2014; Smith et al., 2016).

The 'gold standard' of risk evaluation for human long-term users of NTPs would be epidemiological studies requiring study periods of years or even decades, which is not a feasible approach for regulating and marketing of consumer products like NTPs. A possible alternative approach could be to utilize fit-for-purpose biomarkers of early biological effects (BOBEs) which have been established to be strongly related (either by direct involvement in the pathomechanism of the disease or indirectly as an indicator of the pathological pathway) to a disease which might manifest years or decades later.

A scheme for the involvement of various types of biomarkers in the assessment of NTPs covering the process from external exposure (use of the NTP) to outcome (disease) is shown in Fig. 1 (Henderson et al., 1987; Stratton et al., 2001). In this scheme, four types of biomarkers are included, namely:

- o Biomarkers of exposure (BOE)
- o Biomarkers of effective dose
- o Biomarkers of potential harm (in this review termed 'Biomarkers of biological effect', BOBEs)
- o Biomarkers of susceptibility (modifying the potential harm by host factors)

This review covers the area of biomarkers of potential harm (here termed BOBEs, dotted blue box in Fig. 1). The particular interest of this review is on biomarkers of early biological effects (designated by the solid blue box in Fig. 1), which are definitely reversible upon quitting of

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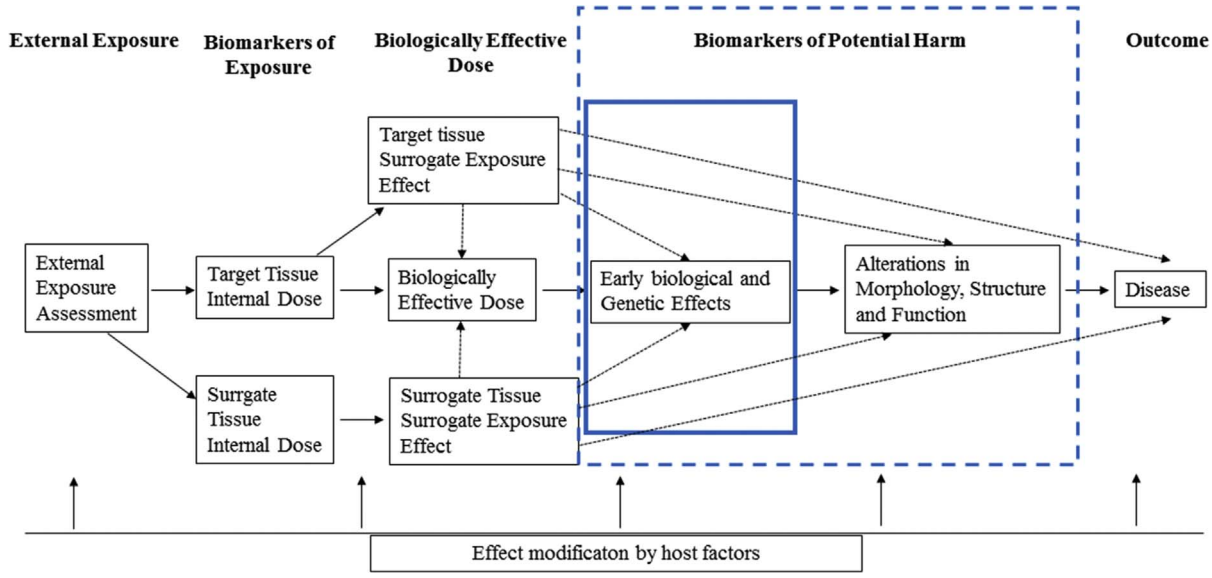

Fig. 1. Scheme for assessing the potential harm of NTPs by making use of various types of biomarkers (according to the IOM Report 2001 (Stratton et al., 2001) and NRC 1987 (Henderson et al., 1987), with modifications). The dotted blue box indicates the general application area for BOBEs. The solid blue box designs the particular area of interest in this review. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

smoking and would therefore be suitable for application in NTP clinical studies.

There are several definitions used for a BOBE in the scientific literature. For example, the IOM Report of 2001 (Stratton et al., 2001) defines a biomarker of potential harm as "(a) measurement of an effect due to exposure; these include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm; also includes preclinical changes". A very similar definition of BOBE is described in the LSRO Report of 2007: "A 'biomarker of effect' is a measured effect including early subclinical biological effects; alterations in morphology, structure, or function; or clinical symptoms consistent with the development of health impairment or disease." In the US Surgeon General Report of 2010 (US Department of Health and Human Services, 2010) entitled 'How tobacco smoke causes disease', the term "Biomarkers of biologic events with the potential to lead to harm" is used for a BOBE. In their review on the validation of biomarkers of harm, Gregg et al. applied the following definition: A BOBE is "a significant, objective, measurable, alteration in a biological sample, after smoking a tobacco product, that is known to be on a pathway predictive of pathologic change, or a surrogate for that pathway, which is altered in a proportion of smokers and is reversible on cessation of smoking." (Gregg et al., 2006).

For the purpose of this review, the definition of Gregg et al. (2006) appears to be the most suitable, since it contains two important additional elements, which were not considered in the other descriptions cited above, namely, 'reversibility on cessation of smoking' and the fact that also 'surrogates for a pathological pathway' can be used as BOBE.

The objective of this review is to evaluate BOBEs for their suitability to be used in clinical studies on NTPs (in particular, THB products and e-cigs). The following factors are to be considered in the BOBE evaluation process:

1. Relationship of a BOBE to a (smoking-related) disease
2. The BOBE should indicate physiological/biochemical changes at an early stage of the pathological process leading to a disease
3. Direct or indirect involvement of the BOBE in the pathological pathway
4. Difference in BOBE levels between smokers (S) and non-smokers (NS)
5. Number and size of studies
6. Size, (statistical) significance and consistency of the evidence reported in the literature for differences between S/NS
7. Dose-response relationship between the BOBE level and the smoking dose (DRS), including statistical significance of the DRS
8. Impact of smoking cessation (CE) on the concentration of the BOBE
9. Reversibility
10. Kinetics of the change in the BOBE level (e.g. half-life): Are changes acute (observable within hours, days), subchronic (weeks) or chronic (months, years)
11. BOBE levels in ex-smokers (Ex) compared to S and NS (S/Ex, Ex/NS)
12. Invasiveness: Non-invasive BOBEs that can be determined in blood, urine, saliva, exhaled breath, exhaled breath condensate, sputum or in the intact organism; invasive BOBEs include biomarkers that are determined in biological samples requiring a relatively invasive collection method such as bronchio-alveolar lavage (BAL), biopsy or similar. Invasive approaches are only justified if no equivalent non-invasive methodology is available.
13. Measurability: The BOBE should be measurable by established and validated analytical or clinical method with a reasonable sample throughput.

Based on these criteria, a rating of a series of BOBEs will be presented. Additionally, BOBEs with a broader data base extracted from the literature are evaluated by estimating the effect sizes and the resultant sample sizes.

2. Methods

Although not intended to be a systematic review or meta-analysis, the principles and best practices for literature review were followed (JPT CHH, 2011; Khan et al., 2003; Moher et al., 2015; Morton et al., 2011). The preparatory steps for generating the review included:

2.1. Identifying the data sources

The MEDLINE database provided by the US National Library of Medicine (NLM) was used as the key source for published articles on the subject of interest. As a second source of relevant papers, references in key articles and review articles on smoking-related BOBEs were identified ("cross referencing"). A further source for candidate articles were monographs released by authoritative bodies such as the Institute of