ToxStrategies

Literature Review of Biomarkers of Exposure Related to Traditional and Emerging Nicotine Products
Public Summary
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A comprehensive literature review of publicly available, peer-reviewed data for biomarkers of exposure associated with nicotine delivery products concluded that additional research is needed to develop (or further refine) biomarkers that have the ability to discern both between product-use status, are readily distinguishable from environmental or other confounding exposure, and can be evaluated with relatively non-invasive methods.

Background and Objectives:

ToxStrategies was contracted by the Foundation for a Smoke Free World (the Foundation) to conduct a literature search and review of biomarkers of exposure and effect related to traditional and emerging nicotine delivery products. This review was commissioned as part of the Foundation's strategy to support research that assesses the impacts of cessation and harm reduction products. Biomarkers are necessary to gauge the use patterns and effects of traditional and emerging nicotine product use (i.e., exposure) as well as potential harm (i.e., effect). This public summary focuses on the search and review for biomarkers related to exposure associated with use of nicotine delivery products other than, or in addition to, conventional cigarettes; findings related to biomarkers of effect will be reported separately. The specific objectives related to biomarkers of exposure were to characterize the available literature relative to:

1. Ability to discern product usage status (e.g., non-smoker vs. smoker, smokeless tobacco user vs. cigarette smoker, etc.)
2. Potential confounding from other sources of exposure (e.g., environmental exposures, dietary exposures)
3. Ease/invasiveness of sample collection

Synthesis and Key Findings:

When the literature search results (i.e., the evidence base) were considered collectively, following the **Approach** and **Literature Search Results** as described below, the following key findings were observed relating to the state of the science regarding available biomarkers ability to gauge the exposure and use patterns:

- *While some studies identified biomarkers that can discern between types of products used (e.g., cigarette smokers vs. users of smokeless tobacco; electronic cigarette users vs.*

smokers of traditional cigarettes), no specific biomarker(s) of exposure was (were) identified among the literature that consistently demonstrated the capability of discerning across product categories. The inconsistency, complexity, and heterogeneity of the evidence base preclude the ability to readily make conclusions regarding the ability of available biomarkers to discern nicotine delivery product user status and/or between usage of various products. Some biomarkers were more frequently reported by the study authors as having the ability to discern between nicotine product usage levels and/or between various products than others (e.g., benzene, acrolein, 1,3-butadiene, VOCs, cotinine, total NNAL, NNN), there were no particular biomarkers that appeared to be consistently effective at doing so.[1]

- *Results varied by the products tested, the biomarkers evaluated, and the matrices in which the biomarker was assessed*. Discrete conclusions regarding individual biomarkers are difficult given the complexity and heterogeneity of study designs (e.g., controlled trials and observational studies, variations in time between product cessation or switch relative to biomarker evaluation, etc.) combined with the volume of data (or lack of data in regard to specific study attributes, in many cases). In many instances, authors discussed the likelihood of using multiple biomarkers to characterize exposure. Additional research is needed to further evaluate the utility of available biomarkers and to develop more sensitive biomarkers.

- *Potential confounding from other sources of exposure is insufficiently addressed by the current evidence base*: As the majority of studies did not address this topic (those that did most often did not do so quantitatively), the literature review suggests that more studies are clearly needed to investigate potential confounding from other sources as it relates to biomarkers of tobacco exposure or tobacco product use status.

- *The ease of sampling matrices varied within the evidence base*: Urine was the most common specimen collected for biomarker measurement; the only biomarkers for which urine was not the most common matrix were metals, for which blood was most commonly collected. A smaller number of studies measured biomarkers in saliva, and expired breath was also used to measure carbon monoxide. Testing in saliva is gaining attention, though also represents an area for additional research.

Conclusion:

Additional research is needed to develop (or further refine) biomarkers that have the ability to discern both between tobacco use status and tobacco product types, are readily distinguishable from environmental or other confounding exposure, and can be evaluated with relatively non-invasive methods. Such research can build upon the current evidence base which provides important, but not conclusive, characterizations regarding a biomarker – or biomarkers – that has these features.

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[1] Based on review of descriptive statistics resulting from the literature review and data as reported by the authors. The scope of work did not include critical appraisal of individual studies, nor did the scope include specific assessment or recommendations regarding biomarkers with the greatest utility.

Approach:

Scientists and information specialists developed a systematic map[2] aimed at characterizing the landscape of publicly available, peer-reviewed data for biomarkers of exposure and effect associated with tobacco and nicotine delivery products. The project team accomplished this goal via completion of the following tasks:

1. Problem formulation and protocol development
2. Identification of studies (i.e., evidence base)
3. Review of studies and production of systematic map
4. Synthesis and overall assessment
5. Reporting

In the initial task, the project team reviewed secondary literature (e.g., other reviews on the topic) and consulted with the Foundation to develop and iteratively refine the research objective and context. Based on such, a protocol was developed (Attachment A) which provides detailed information on the searching approach as well as criteria that were implemented for inclusion and exclusion of studies. Titles and abstracts were reviewed in DistillerSR. Studies were initially categorized based on type of biomarker (i.e., exposure or effect). Full text copies of relevant studies were obtained; those still meeting inclusion criteria were further reviewed and the following type of information extracted for each study based on that reported by the individual study authors:

- Nicotine delivery product(s)
- Biomarkers evaluated (names/identification)
- Biological matrices in which each biomarker was evaluated
- Results related to the ability to discern nicotine delivery product use status, as well as between nicotine delivery products
- Other potential sources of exposure that may influence biomarker measures
- Other basic study information (e.g., study objective, methods, conclusion)

Information from the title and abstract screen and data extraction of relevant papers were compiled into systematic maps which consist of tabular summaries and data visuals (e.g., flow charts, graphs). These tools were then used to facilitate synthesis of the data as it related to specific research questions of interest. The approach, results, and findings will be reported via the systematic maps, a detailed technical report, and a public summary (this document).

Because of the overlap in research for biomarkers of exposure and effect, and in the interest of a comprehensive review, the literature search was conducted using syntax to identify studies of both biomarkers of effect and exposure, allowing for a more efficient review of the literature given that many studies evaluated both types of biomarkers and may have been duplicated if the searches were conducted separately. The review and synthesis of data relevant to each type of biomarker was conducted separately.

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[2] A "systematic map" uses a structured process to describe the state of knowledge for a question or topic (James et al.,2016. A methodology for systematic mapping in environmental sciences. Environmental Evidence 5:7).
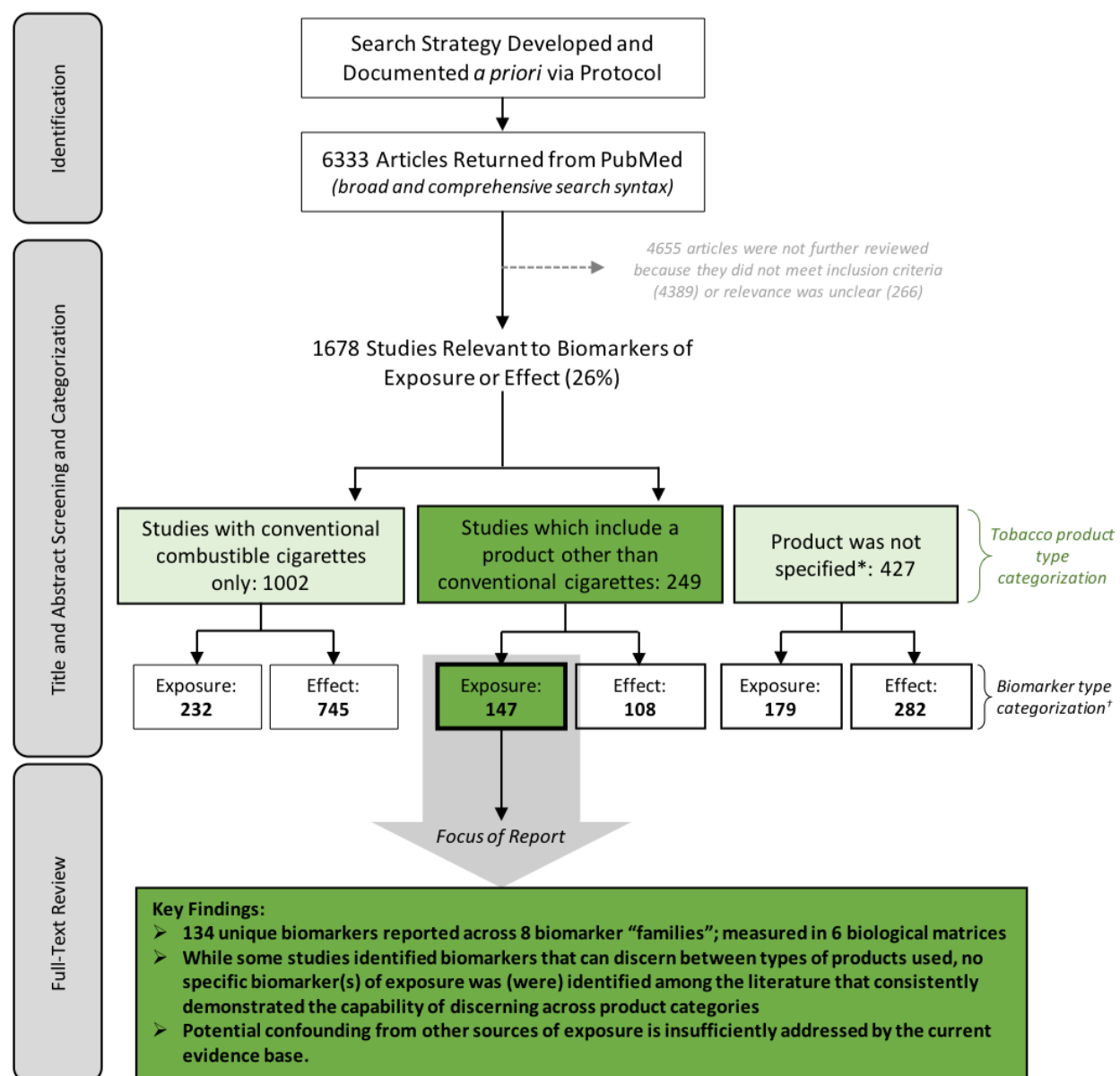
Literature Search Results

A summary of the literature search is provided in **Figure 1.** More than 6,000 articles were identified as a result of a comprehensive search in PubMed. Screening of titles and abstracts, and subsequent screening of full-text for eligibility resulted in identification of 147 studies characterizing exposure biomarkers associated with use of products other than, or in addition to, conventional cigarettes. From these studies the following observations were made:

1. More than 800 individual biomarker measures were evaluated (i.e. >800 "biomarker measurements") across a diverse array of studies and study types (e.g., controlled trials, observational studies). Each study reported from 1 to >40 biomarkers of exposure.

2. More than 45 unique tobacco products were evaluated.

3. Biomarkers were measured in 6 biological matrices: blood/serum, expired breath, feces, hair, saliva, and urine. Urine was the most commonly collected biospecimen, followed by blood/serum, expired air, and saliva.

4. More than 100 unique biomarkers were reported; these represented 8 "biomarker groups."[3] The most frequently reported biomarkers were tobacco alkaloids, followed by volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), and tobacco-specific nitrosamines (TSNAs). The other groups included amines, elements (metals), carbon monoxide, tobacco alkaloids, as well as "others" for those that did not fit into any of the other groups (e.g., thicyanate, urine mutagenicity, and dioxins and furans, among others).

5. Less than half (~48%) of all of the biomarker measurements were reported by the study authors to have the ability to discern user status in some capacity within the given study design. All others were either unclear, specifically stated to not be able to discern, or not applicable (e.g., measurement of biomarker not compared between different usage groups).

6. Slightly over half (~57%) of all of the biomarker measurements were reported by the study authors to have the ability to discern the use of different nicotine delivery products in some capacity within the given study design. All others were either unclear, specifically stated to not be able to discern, or not applicable (e.g., measurement of biomarker not compared between different product usage groups).

7. The majority of studies did not evaluate the role of potential confounding from other sources of exposure (e.g., environmental exposures, dietary exposures). If addressed by the study authors, it was most often in the context of potential uncertainties of the given study (e.g., addressed as a limitation in the discussion).

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[3] Biomarker groupings were determined by systematic map authors; groupings were informed by secondary sources (e.g., published reviews)

 Figure 1. Summary of literature search and key findings related to biomarkers of exposure.

 * The type of tobacco product was not clear in the abstract; most commonly, the authors referred to "smokers" and did not specify further.

† Some studies included more than one type of biomarker