

ToxStrategies

Literature Review of Biomarkers of Exposure for Traditional and Emerging Nicotine Products: *Systematic Map*

September 7, 2018

*Innovative Solutions
Sound Science*

Contents of Systematic Map

1. Slide Deck (PPT)

- Background and approach
- Approach (protocol) for identification of relevant studies
- Results of the title and abstract screen (all biomarker types)
- Results for biomarkers of exposure

2. Evidence Tables (Excel File)

Evidence Tables BoE 09042018.xlsx

Organized into the following tabs:

Includes alternative Products

Cigarettes only

Product unspecified

Refs w Abstracts - Included

Excluded Articles

Refs w Abstracts - Excluded

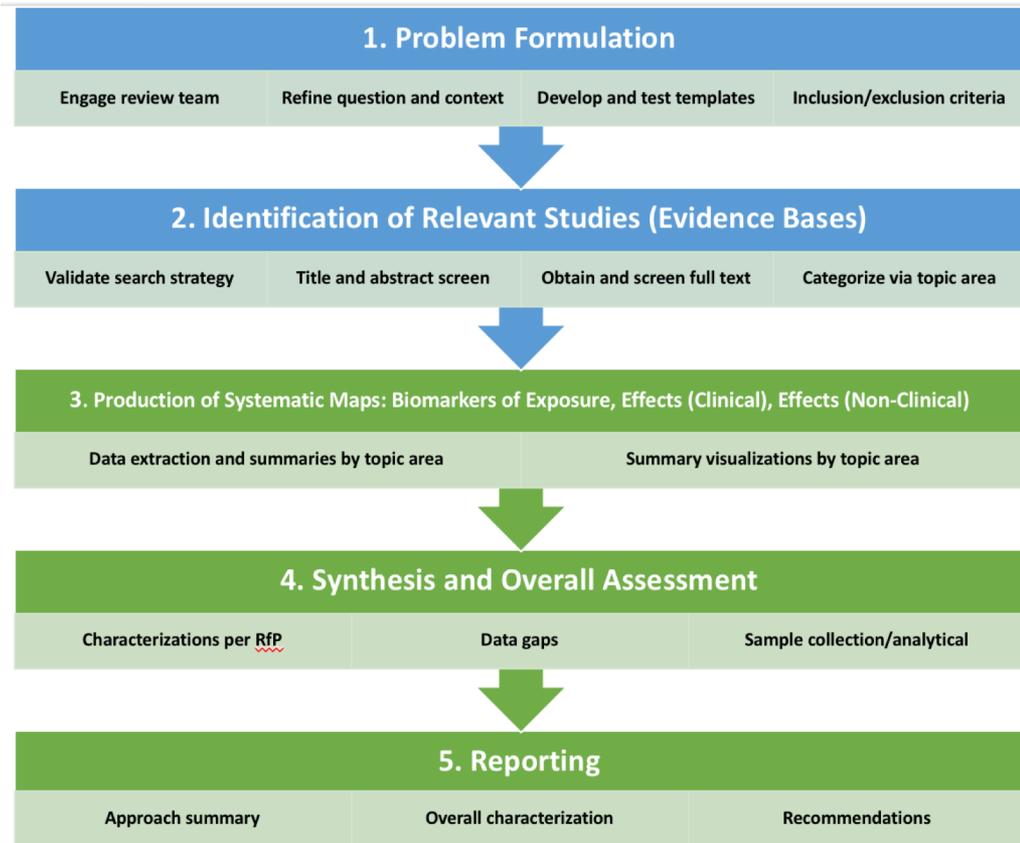
Biomarker Characterization Key

REF - FDA HPHC list

The systematic map provides a landscape of the literature via user-friendly tools; the PPT slide deck provides a summary of the approach and findings whereas the Excel Files provide sortable tabular data.

A public summary and a final written report are also available.

Overall Approach for Literature Review



Project Team

Established expertise in conducting:

- (a) systematic literature reviews*
- (b) assessment of chemicals derived from tobacco products (in support of FDA's Center for Tobacco Products)*
- (c) biomarker research and development*
- (d) biomonitoring and pharmacokinetics as related to biomarker characterization*
- (e) evaluating and interpreting clinical and non-clinical study data*

Included toxicology, epidemiology, and systematic review experts:

- *Daniele Wikoff (toxicology, systematic review)*
- *Jon Urban (DABT, toxicology)*
- *Grace Chappell (toxicology, systematic review)*
- *Janice Britt (toxicology, epidemiology)*
- *Mina Suh (epidemiology)*
- *Brian Welsh (biomarkers, systematic review)*

Utilized DistillerSR (a tool for facilitating systematic literature searches)

Protocol for Identification of Relevant Studies from PubMed

Review Question (PECO)

The overall objective of this research is to develop a systematic map of potential biomarkers of exposure associated with nicotine delivery products

The systematic map characterizes the landscape of peer-review literature and provides summary tools (visuals, tables, etc.) that facilitate synthesis of findings as well as use of the evidence base in future research efforts

Protocol: Participants/Population

Populations: Tobacco and nicotine delivery product users and laboratory animals directly exposed in relevant study designs.

- Include: General population and worker cohorts with known use or exposure to nicotine delivery products.
- Include: Sensitive populations (i.e., pregnant women, children, non-healthy and/or patient populations) and post-mortem populations.
- Exclude: Non-user populations exposed to secondary smoke/environmental tobacco smoke (ETS). *Note: Studies on ETS populations will be excluded from further review and synthesis (i.e., full text review, data extraction, systematic map integration), but tagged at the title and abstract screening level to define this segment of the literature for the purposes of institutional memory.*
- Exclude: Populations defined solely by genotypic (e.g., genetic polymorphisms) or racial differences (e.g., where sole comparison was racial groups of nicotine delivery product users).

Protocol: Intervention/Exposure

Exposure: Use of tobacco and most other nicotine delivery products.

- Include: Any such products, including combusted cigarettes, electronic cigarettes, heat-not-burn products (a.k.a. non-combusted tobacco products; e.g., IQOS, Ploom, glo), nicotine replacement therapies (e.g., nicotine gum, nicotine patch, etc.), and oral tobacco products (e.g. chewing tobacco, moist snuff, snus, etc.).
- Include: Studies in experimental animals for relevant routes of exposure; relevant routes of exposure include oral, inhalation (nose-only and whole body exposure designs) and dermal.
- Exclude: For humans, studies with documented co-exposures to chemicals other than those from non-tobacco/nicotine products (e.g., chemical occupational exposures; exposure to smoke/vapors such as wood smoke, marijuana, etc.). *Note: Studies with clear co-exposures in title and abstract will be excluded from further review and synthesis (i.e., full text review, data extraction, systematic map integration), but tagged at the title and abstract screening level to define this segment of the literature for the purposes of institutional memory.*
- Exclude: For animals, studies with irrelevant routes of administration/exposure (e.g., intravenous, intraperitoneal).

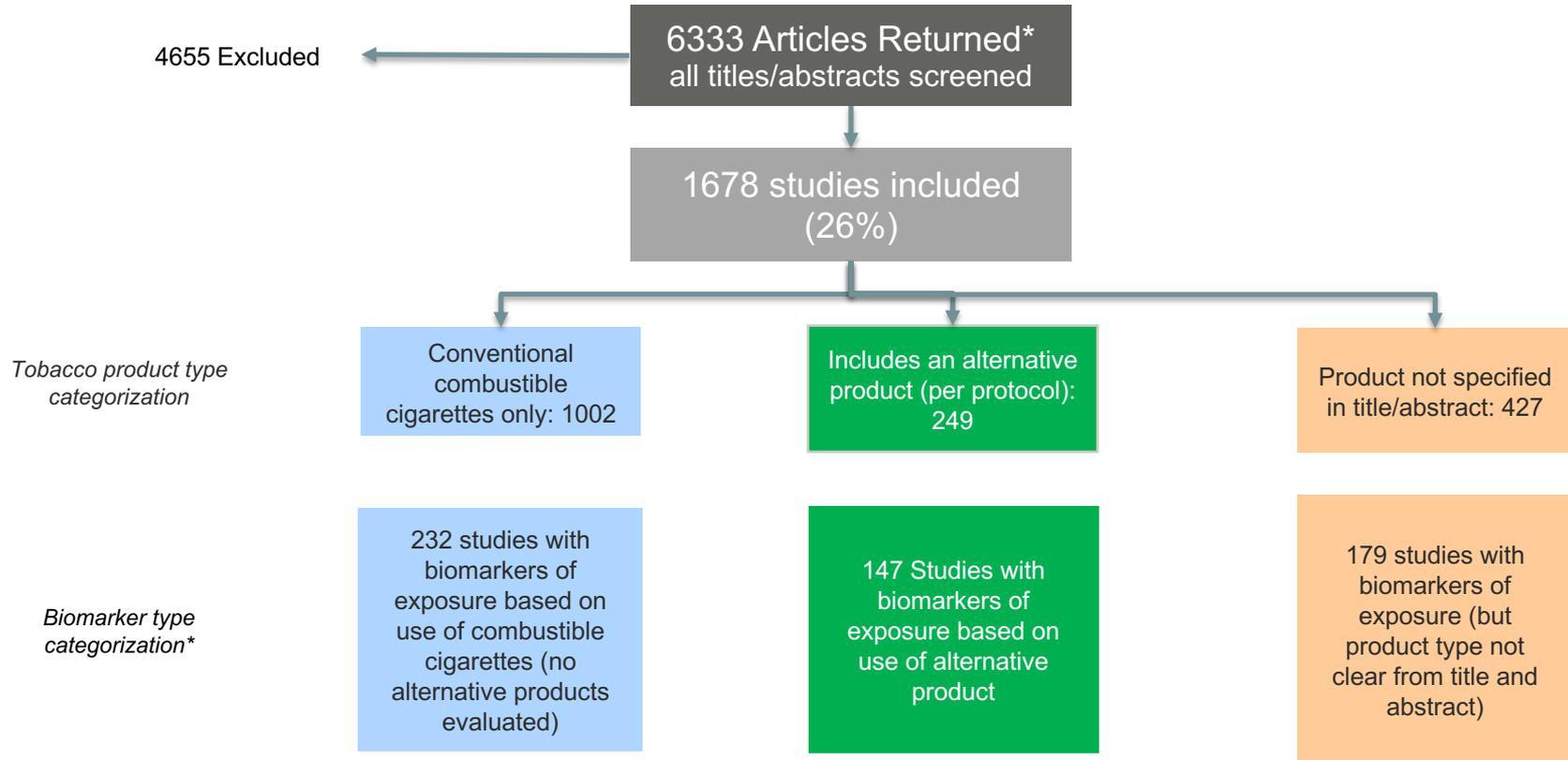
Protocol: Types of Studies to be Included

Include: For humans, include epidemiology studies, clinical studies; animals, relevant route of exposure per product type (e.g., inhalation for cigarette or e-cig); any duration.

- Exclude: For humans, studies that do not assess biomarkers at the individual level (e.g., ecological studies) and/or do not provide biomarker measures within a group or population (e.g., case series, case studies). *Note: Ecological-type epidemiology studies and case reports captured in the literature search will be excluded from further review and synthesis (i.e., full text review, data extraction, systematic map integration), but tagged at the title and abstract screening level to define this segment of the literature for the purposes of institutional memory.*
- Exclude: In vitro studies (human and non-human). *Note: Any in vitro studies captured in the literature search will be excluded from further review and synthesis (i.e., full text review, data extraction, systematic map integration), but tagged at the title and abstract screening level to define this segment of the literature for the purposes of institutional memory.*
- Exclude: Non-English language papers. *Note: Any papers not available in English that are captured in the literature search will be excluded from further review and synthesis (i.e., full text review, data extraction, systematic map integration), but tagged at the title and abstract screening level to define this segment of the literature for the purposes of institutional memory.*
- Exclude: Review papers. *Note: Any papers that are themselves reviews of the literature and/or do not provide original biomarker data that are captured in the literature search will be excluded from further review and synthesis (i.e., full text review, data extraction, systematic map integration), but tagged at the title and abstract screening level to define this segment of the literature for the purposes of institutional memory. Letters, comments, and other editorial-type articles without original data will be excluded.*
- Exclude: Studies in which full text copies cannot be obtained following reasonable measures (online). Exception will be made if the abstract contains necessary information. *Note: This pertains to papers that are initially flagged as relevant and included further review during the title and abstract screening step, but for which full text copies are found to be unavailable.*

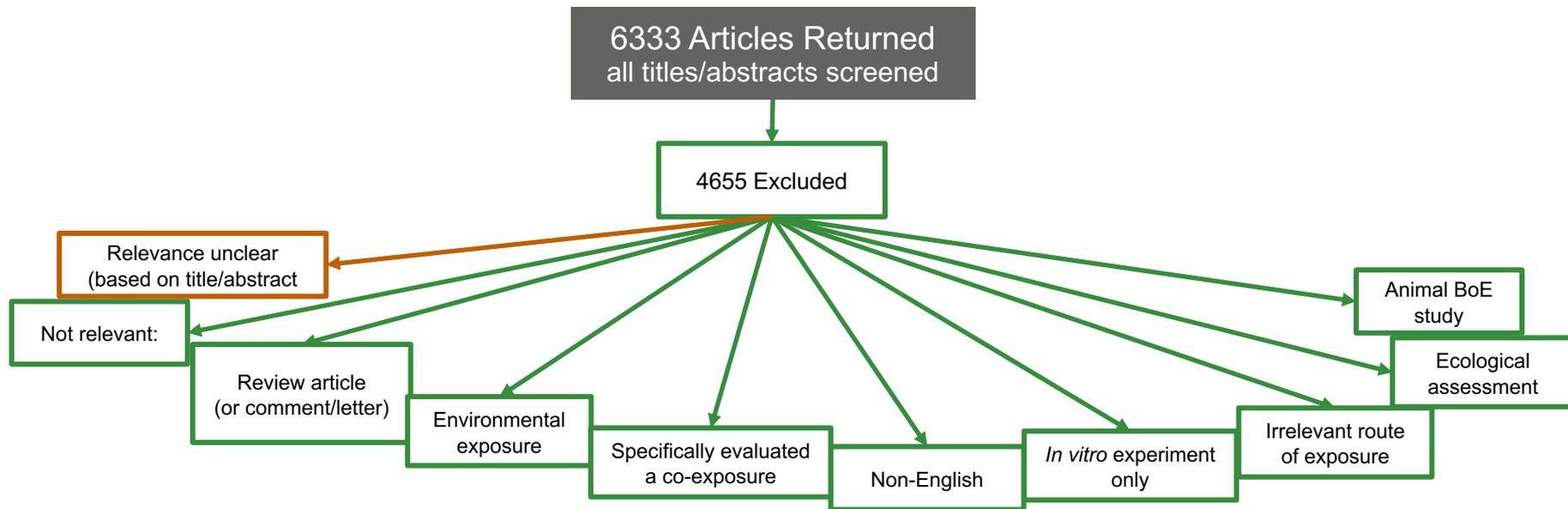
Results: Title and Abstract Screen

Flowchart for Biomarkers of Exposure Public summary updated 8/8/18



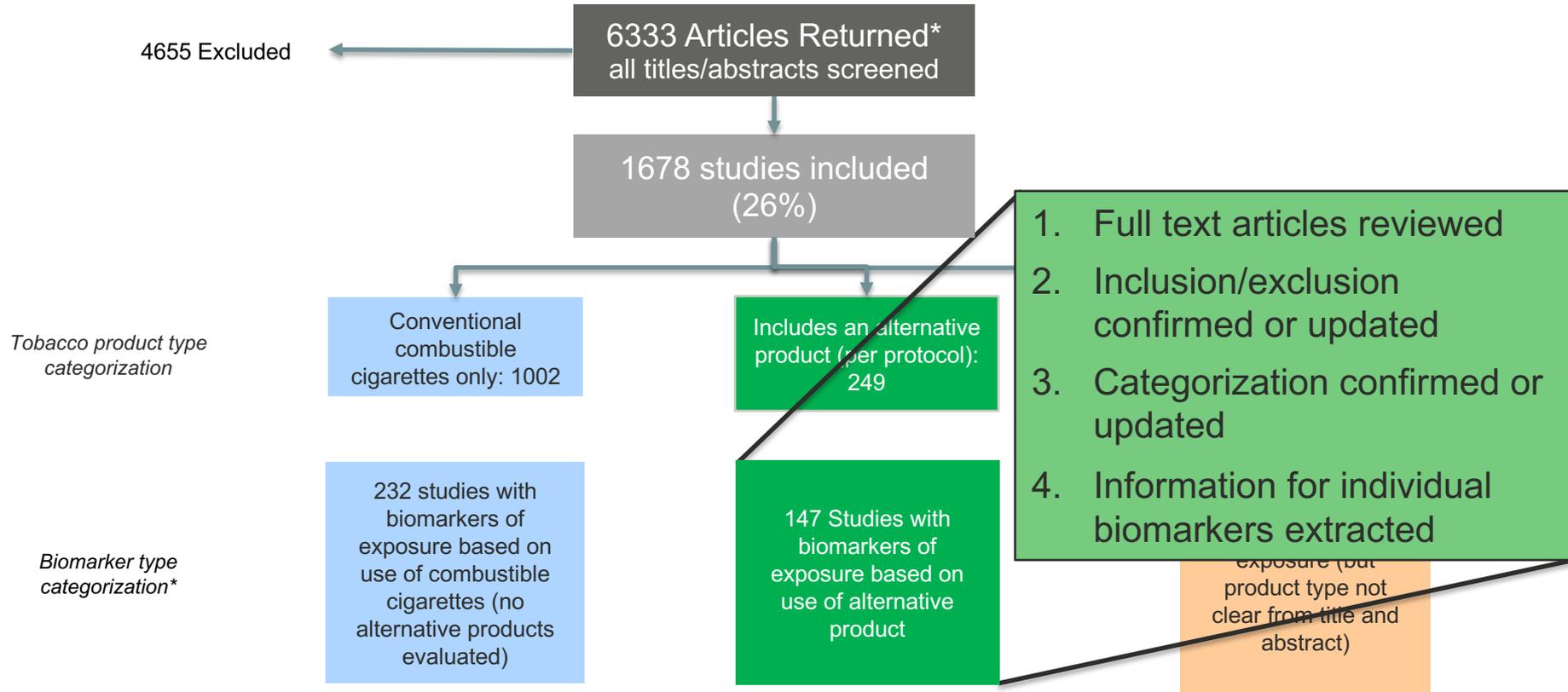
*Because of the overlap in research for biomarkers of exposure and effect, and in the interest of a comprehensive review, the literature search was conducted using syntax to identify studies of both biomarkers of effect and exposure, allowing for a more efficient review of the literature given that many 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. This slide deck focuses on biomarkers of exposure only.

Excluded Studies – Categories and Themes



Systematic Map for Biomarkers of Exposure (Results from Extraction)

Focus: studies with biomarkers of exposure associated with use of an alternative nicotine product



*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. This slide deck focuses on biomarkers of exposure only.

Data Extraction Approach

Full text versions of all articles that included any nicotine delivery product other than conventional combustible cigarettes were obtained, reviewed, and data extracted if study still met inclusion criteria following full text review:

Study details were extracted:

- tobacco product(s)
- objective
- study type
- study design
- authors' conclusions
- notes

Study information collected in DistillerSR.

One “study level” form per study

Individual biomarker details were extracted:

- biomarker name
- biological matrix in which biomarker was measured
- ability of biomarker to discern between product use status (i.e., sensitivity)
- ability of biomarker to discern between product types
- potential sources of exposure noted (i.e., sensitivity)
- reported result/conclusion regarding specific biomarker

Biomarker information collected in DistillerSR.

Multiple “biomarker level” forms per study (1 to >40 per study); each “biomarker level” = data set (= 1 to >40 data sets per study)

Data Extraction Notes

Extracted information limited to that reported by the author (= no interpretation from analyst)

- **One exception:** in the extraction questions related to discernment (sensitivity) of biomarkers, if the author did not explicitly address this topic, the form included a response field for the analyst to indicate if the study appeared to contain information which would inform the ability to discern, as well as the direction of such a determination. These are recorded separately from the author-reported information

Extracted information generally copied directly from the study

- Applies to text fields (e.g., study design, objective, results descriptions) vs. categorical fields (e.g., yes/no)
- Due to aggressive timeline, efforts focused on efficiently (and accurately) collecting necessary information; pending use of systematic map in the future, this should be noted in any data utilized from the map

Biomarker names and product types extracted as reported by authors

- Analysts have grouped biomarkers to “families” for purposes of systematic map, but identification field was extracted as author reported (with general accommodation for synonyms)

Information extracted was targeted to provide a landscape of the literature

- *Such information should be regarded as draft/preliminary with respect to synthesis and integration; further assessment of biomarkers should involve critical appraisal of each study recognizing the complexity and heterogeneity of the evidence base.*

Summary Extraction Statistics

Total Articles:	147
Total "data sets":	880
Number of Biomarker Families:	8
Number of Unique Biomarkers - Individual:	134
Number of Unique Tobacco Products:	>40*
Number of Unique Biological Matrix Types:	6
Number of Unique Potential Confounding Exposures:	13

* In some cases, similar products may be referred to differently in different studies (e.g. "smokeless tobacco" vs. specific products; a variety of low-yield cigarettes)

Summary of Nicotine Delivery Products Identified

Non-combustible

Electronic Cigarettes
Heat Not Burn Products
Novel tobacco vapor product (not e-cig)
Hydro cigarette

Smokeless

Chewing Tobacco
Snus
Dipping tobacco
Moist snuff
Nasal snuff
Iqmik
Dissolvable tobacco (“orbs,” sticks, strips, tablets)
Maras powder
Gutka
Nicotine replacement therapies (patch, gum, lozenge, inhaler)

Combustible

Conventional cigarettes
Reduced/low nicotine cigarettes
Reduced ignition cigarettes
Low tar cigarettes
Low yield Cigarettes
OMNI Cigarettes (reduced carcinogen tobacco, carbon filter)
Bidi
Pipe
Cigar (large, small)
Cigarillo
Hookah
Cheeroot
Chillum
Activated carbon granule filter cigarette
Sheesha
Waterpipe

Summary of Biomarkers of Exposure Reported for Alternative Product Studies

Articles that included an alternative product: 249

Biomarkers of exposure: 147 articles

880 individual measurements reported

A total of 134 individual biomarkers were reported, which can be sorted into the following eight biomarker “groups”

Amines		
Acyclic	Aromatic	Hb adduct

Carbon monoxide

Elements	
Heavy metals	Essential metals

Other					
Dioxins and furans	Non-specific glucuronides	Phosphates	Propylene glycol	Thiocyanate	All others

PAHs		
Hb adduct	Parent	Metabolite

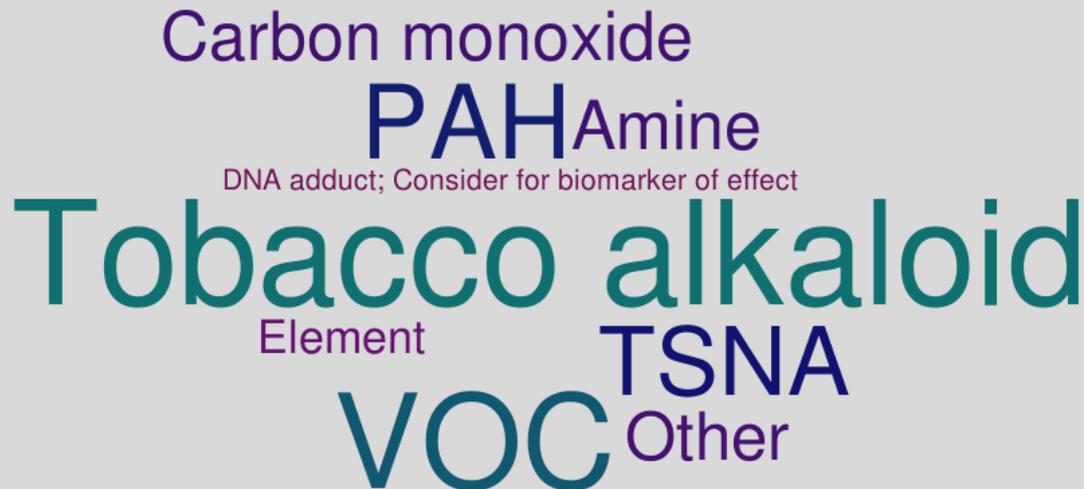
Tobacco alkaloid	
Parent	Metabolite

Tobacco-specific nitrosamines (TSNA)		
Hb adduct	Parent	Metabolite

VOCs			
Hb adduct	Parent	Metabolite	Mercapturic acid metabolite

An additional group not represented here is DNA adducts; in some cases, the authors report DNA adducts as a means of measuring exposure; however, these should also always be considered for a biomarker of effect.

Biomarker Reporting – Frequency



Tobacco alkaloids, (and their respective metabolites) were the most frequently measured biomarkers of exposure for articles that included non-cigarette nicotine delivery products (alone or in addition to cigarettes), followed by VOCs, TSNAs, and PAHs (and their respective metabolites).

Word cloud depicts the biomarker families according to the frequency of their appearance in the extraction table. Large size and green color represents more frequent biomarkers, small size and purple color represents lower frequency.

Ability of Biomarkers to Discern Nicotine Product Usage Level, and Between Nicotine Product Types

Biomarker family:	Ability to discern:	Blood/ Serum/ Plasma	Exhaled Breath	Saliva	Urine
Amines	Usage level		NA	NA	
	Between products		NA	NA	
Carbon monoxide	Usage level			NA	<5 results
	Between products			NA	<5 results
Element*	Usage level		<5 results	<5 results	
	Between products		<5 results	<5 results	
Other	Usage level		<5 results		
	Between products		<5 results		
PAH	Usage level	NA	NA	<5 results	
	Between products	NA	NA	<5 results	
Tobacco Alkaloid†	Usage level		NA		
	Between products		NA		
TSNA	Usage level	<5 results	NA	<5 results	
	Between products	<5 results	NA	<5 results	
VOC	Usage level		NA	NA	
	Between products		NA	NA	

Key:

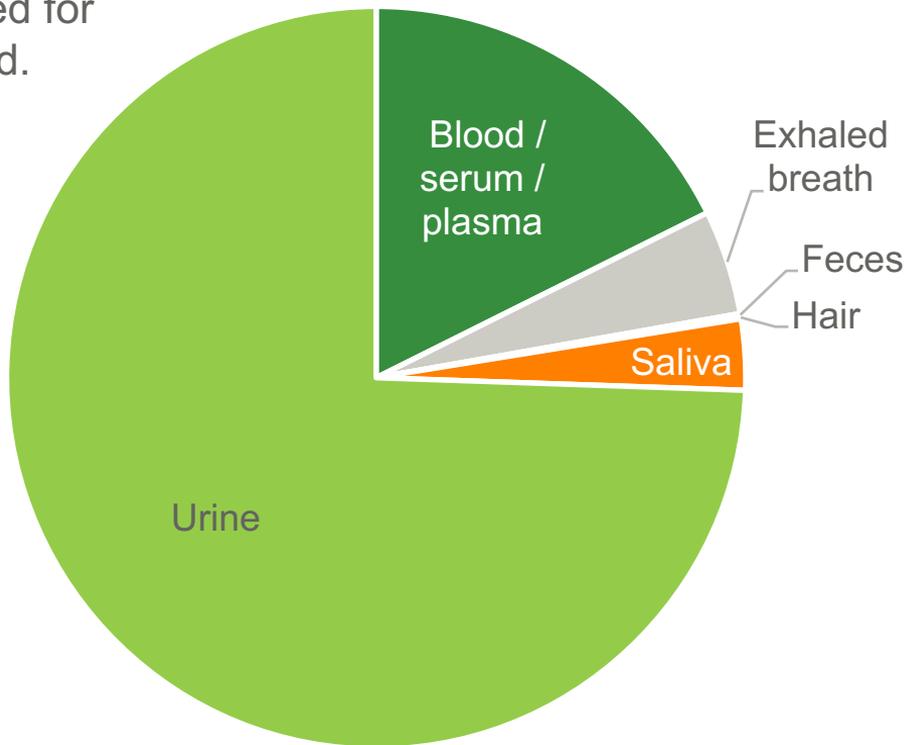
- Could discern
- Could not discern
- Unclear

- Overview of biomarker results for articles that included nicotine delivery products other than, or in addition to, conventional combustible cigarettes.
- Pie charts demonstrate the distribution of the results for the ability to discern both usage level, organized by biomarker group, and biological matrix sampled.
- Pie charts are displayed only for biological matrices / biomarker groups for which ≥ 5 results were reported.

*In addition to the biological matrices shown here, there was a single report of: *an element (cadmium) measured in hair, for which the ability to discern both usage level and between products was not clear, and †a tobacco alkaloid (nicotine equivalent) measured in feces, for which the ability to discern both usage level and between products was not clear.*

Ease/Invasiveness of Sample Collection: Biological Matrices

Urine was the primary sample type used for biomarker evaluation, followed by blood.



Other Potential Sources of Exposure (possible confounding)

Potential confounding sources of exposure	Number of biomarker measurements
Authors indicate none exist	22
Automobile or diesel exhaust	8
Cannabis use	1
Diet	54
Endogenous processes	3
Environmental (not specified)	16
ETS	31
Incomplete combustion from heating systems	2
Methodological background	2
Medication: Nicotine-containing medicines noted	5
Not addressed	882
Occupational	16
Pesticides	4
Pollution	7
Occupational: genotoxic chemicals (general)	2
Tobacco products not surveyed	4

- The vast majority of the articles did not include information regarding potential sources of exposure in addition to product use, that may influence biomarker measurements.
- Among those that did, it was typically a general discussion or identification; e.g. “environmental” or “dietary”

Additional Information in Excel Workbook: Sortable, Filterable, Data Summarization

1	RefID	Reference	Product(s) evaluated	Objective	Study Type:	Type of observational study:	Design	Conclusion	Additional notes:	Biomarker (original)	Biomarker (condensed)	Biomarker Family	Biomarker Family, Subfamily	Biological matrix	Ability to discern usage
2	1758839	KJ Ruth, JD Nea Cigar, Cigarette, f	This study ass methods							For each marker and combination of markers Thiocyanate	Thiocyanate	Other	Cyanide metabolite	Blood/serum/	Can discern
3	1758839	KJ Ruth, JD Nea Cigar, Cigarette, f	This study ass methods							For each marker and combination of markers Carbon monoxide	Carbon monoxide	Carbon monoxide	Carbon monoxide	Exhaled breath	Can discern
4	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: 2-ethyl-aniline	Hb adduct: 2-ethyl-aniline	Amine	Amine, Hb adduct	Blood/serum/	Cannot discern
5	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Blood/serum/	Not address
6	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: 4-hydroxy-l-(3-pyridyl)-1-but	Hb adduct: 4-hydroxy-l-(3-pyridyl)-1-but	TSNA	TSNA, Hb adduct	Blood/serum/	Can discern
7	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: 4-Aminobiphenyl	Hb adduct: 4-Aminobiphenyl	Amine	Amine, Hb adduct	Blood/serum/	Can discern
8	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: 3-aminobiphenyl	Hb adduct: 3-aminobiphenyl	Amine	Amine, Hb adduct	Blood/serum/	Can discern
9	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: Aniline	Hb adduct: Aniline	Amine	Amine, Hb adduct	Blood/serum/	Cannot discern
10	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: Toluidine	Hb adduct: Toluidine	Amine	Amine, Hb adduct	Blood/serum/	Cannot discern
11	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: 2,4-dimethyl-aniline	Hb adduct: 2,4-dimethyl-aniline	Amine	Amine, Hb adduct	Blood/serum/	Can discern
12	8086771	B Falter, C Kutz Cigarette, Snuff	A new analytic observational	Case series						the Hb adducts In conclusion, f note that a sHb adduct: Anisidine	Hb adduct: Anisidine	Amine	Amine, Hb adduct	Blood/serum/	Cannot discern
13	8319620	G Schäffler, C B Cigarette, Snuff	Hemoglobin a methods							Mild alkaline tri In conclusion, we have show Hb adduct: 4-hydroxy-l-(3-pyridyl)-1-but	Hb adduct: 4-hydroxy-l-(3-pyridyl)-1-but	TSNA	TSNA, Hb adduct	Blood/serum/	Not address
14	8319620	G Schäffler, C B Cigarette, Snuff	Hemoglobin a methods							Mild alkaline tri In conclusion, we have show Hb adduct: 4-Aminobiphenyl	Hb adduct: 4-Aminobiphenyl	Amine	Amine, Hb adduct	Blood/serum/	Can discern
15	8319660	SS Hecht, SG Ce Cigarette, Snuff	This paper des Other : Unclear; very limited info							Figure 3 present Although the biological signif Hb adduct: 4-hydroxy-l-(3-pyridyl)-1-but	Hb adduct: 4-hydroxy-l-(3-pyridyl)-1-but	TSNA	TSNA, Hb adduct	Blood/serum/	Can discern
16	8827356	LA Kresty, SG C CheWing tobacco	Our major go; controlled trial							Two metabolite this study has demonstrated Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	NA
17	8827356	LA Kresty, SG C CheWing tobacco	Our major go; controlled trial							Two metabolite this study has demonstrated NNAL	NNAL	TSNA	TSNA, metabolite	Urine	NA
18	9009151	N Pulerà, S Peti Cigarette, Nicotin	In the present controlled trial							Fifty heavy smo In conclusion, serum BPDE-DI DNA: Benzo(a)pyrene DNA add	DNA: Benzo(a)pyrene DNA adducts (BPDE	DNA adduct; Consider f	DNA adduct; Consider f	Blood/serum/	Cannot discern
19	9009151	N Pulerà, S Peti Cigarette, Nicotin	In the present controlled trial							Fifty heavy smo In conclusion, serum BPDE-DI Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Blood/serum/	Can discern
20	9009151	N Pulerà, S Peti Cigarette, Nicotin	In the present controlled trial							Fifty heavy smo In conclusion, serum BPDE-DI Nicotine	Nicotine	Tobacco alkaloid	Tobacco alkaloid	Blood/serum/	Can discern
21	9009151	N Pulerà, S Peti Cigarette, Nicotin	In the present controlled trial							Fifty heavy smo In conclusion, serum BPDE-DI Carbon monoxide	Carbon monoxide	Carbon monoxide	Carbon monoxide	Exhaled breath	Can discern
22	9163684	DM DeMarini, I Bidi	we evaluated observational	Cross-sectional						Urinary organic A strong associ The bidi smol Urine mutagenicity	Mutagens, unspecified	Other	Other	Urine	Can discern
23	9169167	P Suardicani, HC Chevrout, Cigar,	This study exa observational	Cohort (prospectiv						A prospective s Potentially mis snuff and che Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Blood/serum/	Can discern
24	9309261	G Roussel, D Rc Cigarette, Nicotin	To evaluate th controlled trial							125 patients w Urinary cotinine and nicotine Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	Can discern
25	9309261	G Roussel, D Rc Cigarette, Nicotin	To evaluate th controlled trial							125 patients w Urinary cotinine and nicotine Nicotine	Nicotine	Tobacco alkaloid	Tobacco alkaloid	Urine	Can discern
26	9309261	G Roussel, D Rc Cigarette, Nicotin	To evaluate th controlled trial							125 patients w Urinary cotinine and nicotine Carboxyhemoglobin	Carboxyhemoglobin	Carbon monoxide	Carbon monoxide, Hb	Blood/serum/	Can discern
27	9309261	G Roussel, D Rc Cigarette, Nicotin	To evaluate th controlled trial							125 patients w Urinary cotinine and nicotine Carbon monoxide	Carbon monoxide	Carbon monoxide	Carbon monoxide	Exhaled breath	Can discern
28	10224986	P Jacob, L Yu, A Cigar, Cigarette, f	This study (1) Other : PK study							Nicotine intake In conclusion, v No switch or Nicotine	Nicotine	Tobacco alkaloid	Tobacco alkaloid	Urine	Not address
29	10224986	P Jacob, L Yu, A Cigar, Cigarette, f	This study (1) Other : PK study							Nicotine intake In conclusion, v No switch or Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	Not address
30	10224986	P Jacob, L Yu, A Cigar, Cigarette, f	This study (1) Other : PK study							Nicotine intake In conclusion, v No switch or Nornicotine	Nornicotine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	Not address
31	10224986	P Jacob, L Yu, A Cigar, Cigarette, f	This study (1) Other : PK study							Nicotine intake In conclusion, v No switch or Anabasine	Anabasine	Tobacco alkaloid	Tobacco alkaloid	Urine	Not address
32	10224986	P Jacob, L Yu, A Cigar, Cigarette, f	This study (1) Other : PK study							Nicotine intake In conclusion, v No switch or Anatabine	Anatabine	Tobacco alkaloid	Tobacco alkaloid	Urine	Not address
33	11211244	I Cok, R Oztürk Cigarette, Maras	The aim of th observational							urine samples v A significant difference has b Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	Can discern
34	12371055	S Agewall, B Pe Cigarette, Snuff	With the hypc observational	Cohort (prospectiv						Accuracy of a q cotinine measurement subst Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	Can discern
35	12496059	P Jacob, D Hats Cigarette, Dippir	The objective controlled trial							Urine samples s Our studies have demonstrat Anabasine	Anabasine	Tobacco alkaloid	Tobacco alkaloid	Urine	Can discern
36	12496059	P Jacob, D Hats Cigarette, Dippir	The objective controlled trial							Urine samples s Our studies have demonstrat Anatabine	Anatabine	Tobacco alkaloid	Tobacco alkaloid	Urine	Can discern
37	12496059	P Jacob, D Hats Cigarette, Dippir	The objective controlled trial							Urine samples s Our studies have demonstrat Cotinine	Cotinine	Tobacco alkaloid	Tobacco alkaloid, nicotin	Urine	Can discern
38	12496059	P Jacob, D Hats Cigarette, Dippir	The objective controlled trial							Urine samples s Our studies have demonstrat Nicotine	Nicotine	Tobacco alkaloid	Tobacco alkaloid	Urine	Not address

Characterizations of the Evidence Base for Biomarkers of Exposure Related to Articles *Without* Alternative Products

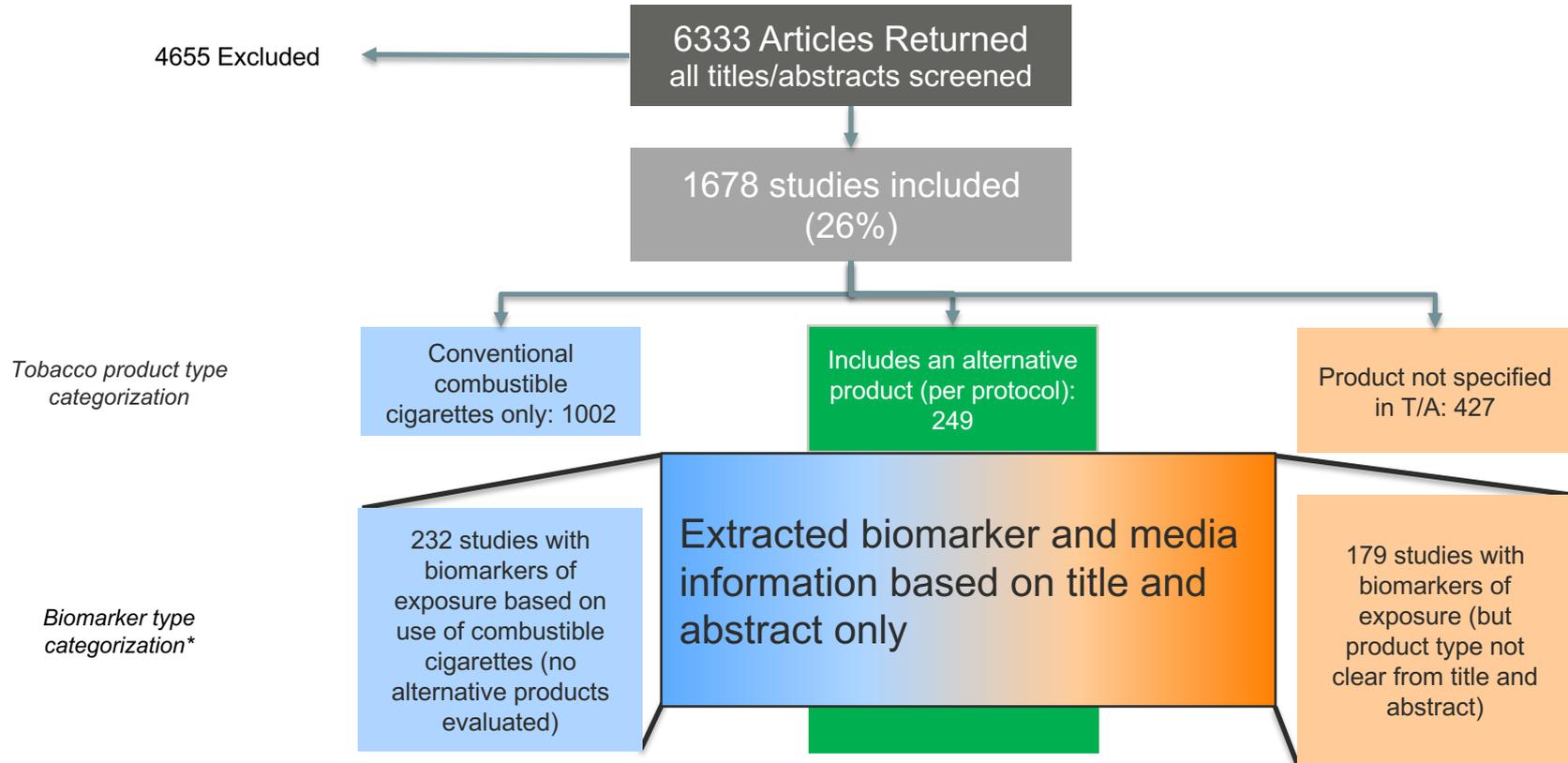
Extraction of Data from Titles and Abstracts

The abstracts were further reviewed for all articles that included data for conventional combustible cigarettes only, or data for users of unspecified nicotine products (e.g., reported as “smokers” or “tobacco users”, etc.)

Individual biomarker details were recorded:

1. Biomarker name/identity
2. Biological matrix in which each biomarker was measured

Focus: studies with biomarkers of exposure *not* associated with use of an alternative nicotine product



*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. This slide deck focuses on biomarkers of exposure only.

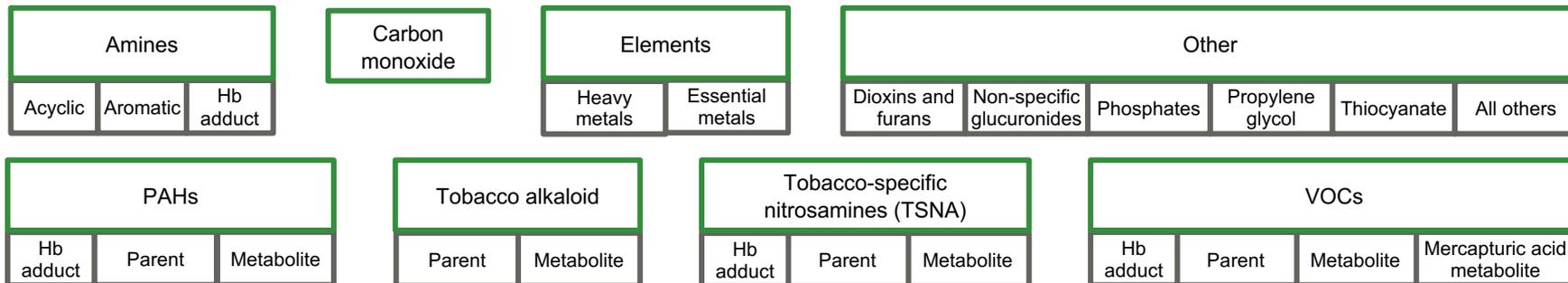
Summary of Biomarkers of Exposure Reported for Conventional Cigarettes

Articles that reported on conventional cigarettes only: 1002

Biomarkers of exposure: 232 articles

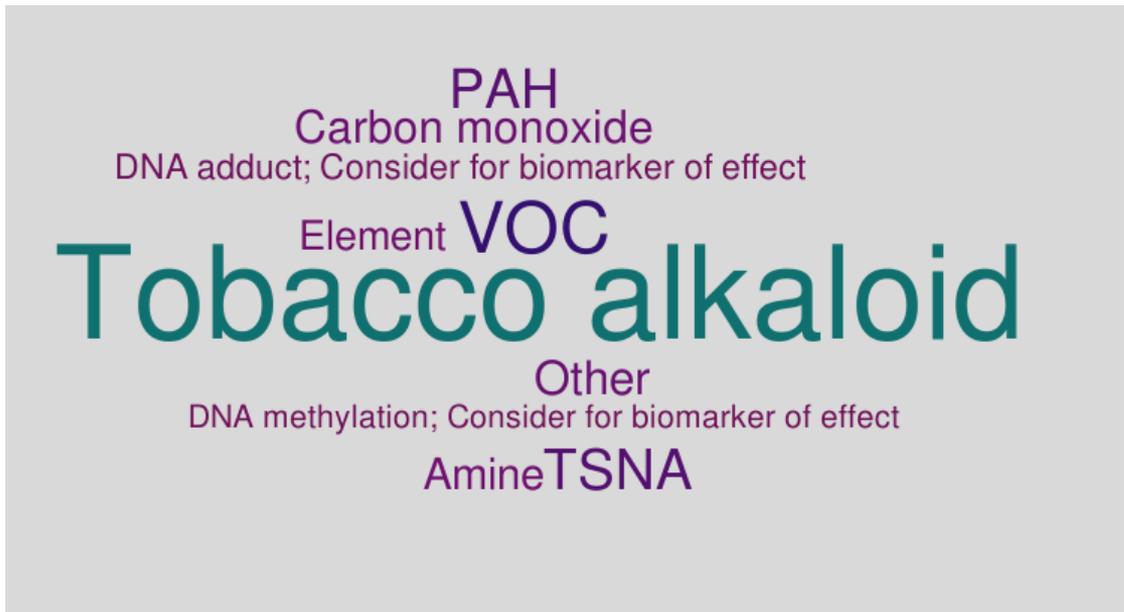
512 individual measurements reported

A total of 116 individual biomarkers were reported, which can be sorted into the following biomarker “groups”



An additional group not represented here is DNA adducts; in some cases, the authors report DNA adducts as a means of measuring exposure; however, these should also always be considered for a biomarker of effect.

Biomarker Reporting – Frequency



Tobacco alkaloids (and their respective metabolites) were the most frequently measured biomarkers of exposure among articles that focused specifically on combustible cigarettes. VOCs, PAHs, and TSNAs followed, similar to the biomarker types that were most frequently reported in the articles that evaluated use of nicotine product other than, or in addition to, conventional cigarettes.

Word cloud depicts the biomarker families according to the frequency of their appearance in the extraction table. Large size and green color represents more frequent biomarkers, small size and purple color represents lower frequency.

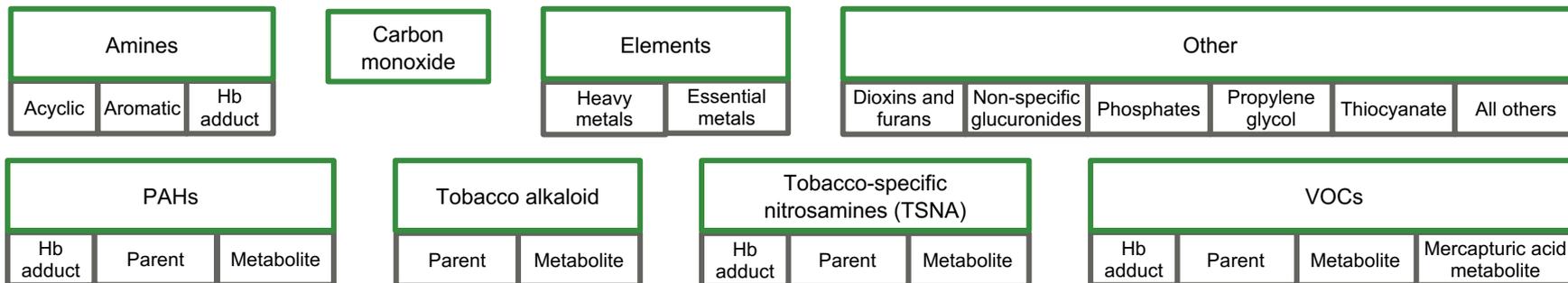
Summary of Biomarkers of Exposure Reported for Unspecified Products

Articles that reported unspecified products:
427

Biomarkers of exposure:
179 articles

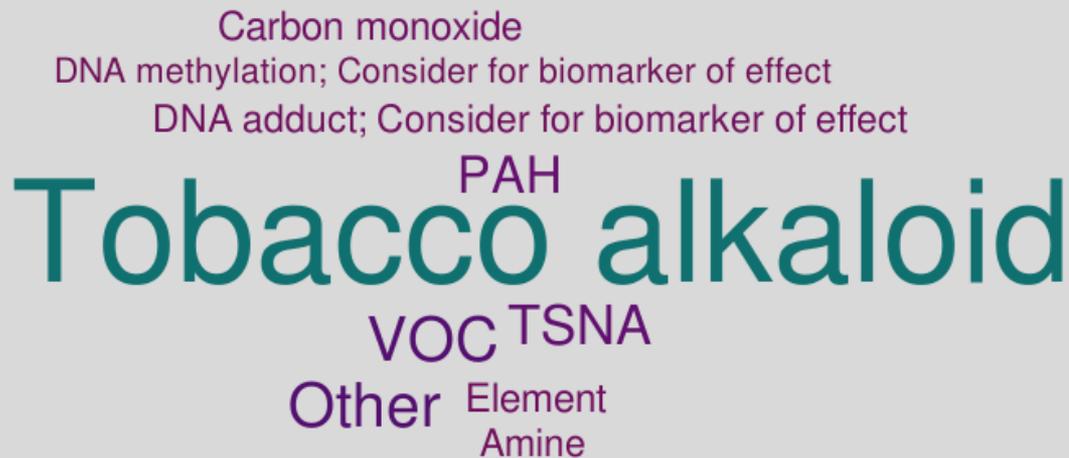
362 individual measurements reported

A total of 116 individual biomarkers were reported, which can be sorted into the following biomarker “families”



An additional group not represented here is DNA adducts; in some cases, the authors report DNA adducts as a means of measuring exposure; however, these should also always be considered for a biomarker of effect.

Biomarker Reporting – Frequency



Tobacco alkaloids (and their respective metabolites) were by far the most frequently measured biomarkers of exposure among articles for which the product was not specified in the abstract. VOCs, PAHs, TSNAs, and those biomarkers that fell into the “other” category were the biomarker types that were the next most frequently reported.

Word cloud depicts the biomarker families according to the frequency of their appearance in the extraction table. Large size and green color represents more frequent biomarkers, small size and purple color represents lower frequency.