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Quantitative risk assessment of tobacco products: A potentially useful component of substantial equivalence evaluations

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ABSTRACT

Quantitative risk assessment (QRA), a scientific, evidence-based analytical process that combines chemical and biological data to quantify the probability and potential impact of some defined risk, is used by regulatory agencies for decision-making. Thus, in tobacco product regulation, specifically in substantial equivalence (SE) evaluations, QRA can provide a useful, practical, and efficient approach to address questions that might arise regarding human health risk and potential influence on public health. In SE reporting, when differences in product characteristics may necessitate the determination of whether a new product raises different questions of public health, the results from QRA are a valuable metric. An approach for QRA in this context is discussed, which is modeled after the methodology for assessment of constituent mixtures by the US Environmental Protection Agency for environmental Superfund site assessment. Given the intent in both cases is an assessment of the public health impact resulting from the totality of exposure to a mixture of constituents, the application is appropriate. Although some uncertainties in the information incorporated may exist, relying on the most appropriate of the available data increases the confidence and decreases the uncertainty in the risk characterization using this data-driven methodology.

1. Introduction

1.1. Tobacco product regulation: substantial equivalence

In the United States (US), the Family Smoking Prevention and Tobacco Control Act (the Act) was enacted in June 2009 (US Congress, 2009). The Act granted the US Food and Drug Administration (USFDA) authority to regulate manufacturing, marketing, and distribution of certain tobacco products, with the intention of protecting public health. For regulated tobacco products post-February 2007, a determination of substantial equivalence (SE) is one potential premarket pathway noted in the Act. For a determination of SE, the Act states a new tobacco product must either have the same characteristics as a predicate tobacco product, or the new tobacco product may have different characteristics but the new product "does not raise different questions of public health" (US Congress, 2009). A predicate tobacco product has been defined as a tobacco product commercially marketed in the US as of February 15, 2007 or a tobacco product previously determined to be substantially equivalent (USFDA, 2011a); and characteristics have been defined as "the materials, ingredients, design, composition, heating source, or other features of a tobacco product" (US Congress, 2009, Section 910(a)(3)(B)). As of this writing, the USFDA has not provided specific guidance or regulation to define what changes constitute "different characteristics" or what changes constitute a new product raising "different questions of public health."

As indicated in USFDA (2011a), many items must be included in an SE application for both the new and predicate products under consideration, including design features, ingredients, materials, heating source, composition, and 'other features'. While each of these are recommended components of the SE application, this paper attempts to address only the incorporation of QRA into the process as an approach to address the question of whether the use of the new product in the same manner as the predicate product would potentially raise different questions of public health. The approaches presented here do not attempt to address the USFDA concerns raised in Section B of USFDA (2011a) regarding consumer perception, clinical data, or abuse liability. Additionally, it is not the intent of this paper to demonstrate SE between two specific tobacco products, but only to provide an example of the approach using non-product specific, albeit realistic, data.

1.1.1. Harmful and potentially harmful constituents in tobacco

SE reporting of a tobacco product might include chemistry and

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Table 1
Abbreviated list of harmful and potentially harmful constituents (HPHC)[†].

Cigarette Smoke	Smokeless Tobacco
Acetaldehyde[*]	Acetaldehyde
Acrolein[*]	Arsenic
Acrylonitrile[*]	Benzo[a]pyrene
4-Aminobiphenyl[*]	Cadmium
1-Aminonaphthalene	Crotonaldehyde
2-Aminonaphthalene[*]	Formaldehyde
Ammonia	Nicotine (total and free)
Benzene[*]	NNK[a]
Benzo[a]pyrene[*]	NNN[b]
1,3-Butadiene[*]	
Carbon Monoxide[*]	
Crotonaldehyde[*]	
Formaldehyde[*]	
Isoprene	
Nicotine (total)	
NNK[*a]	
NNN[*b]	
Toluene	

[†]USFDA 2012b.
[*]Identified by the World Health Organization (WHO) Study Group on Tobacco Product Regulation (TobReg) for lowering or monitoring in cigarette smoke (Burns et al., 2008).
[a] 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.
[b] N-Nitrosonornicotine.

compositional information (e.g. machine generated mainstream smoke yields for a cigarette product) as a metric to compare the new and predicate tobacco products. 2011 SE Guidance for Industry and FDA staff (USFDA, 2011a) listed harmful and potentially harmful constituents (HPHC) as "other features" of a tobacco product. In compliance with section 904(e) of the Act, in August 2011, the USFDA identified (with Request for Comments) a list of 96 HPHC in tobacco products and tobacco smoke (USFDA, 2011b). An established list of 93 HPHC was published in April 2012, and these HPHC were designated by the USFDA as having one or more of the following toxicological characteristics: carcinogen, respiratory toxicant, cardiovascular toxicant, and reproductive or developmental toxicant (USFDA, 2012a). In draft guidance in March 2012, the USFDA published an abbreviated list of HPHC to assist with reporting HPHC to USFDA under 904(e) (Table 1) (USFDA, 2012b). This abbreviated list was compiled, based on the availability of established testing and analytic methods for these HPHC, the fact that these HPHC represented different chemical classes, and the fact that these HPHC are "a representative sample of the HPHC on USFDA's established HPHC list" (USFDA, 2012b). Additionally, this abbreviated list of HPHC represents constituents present in tobacco products and tobacco smoke for which data are generally available for characterizing the potential for health effects as a result of exposure. Notably, 13 of the 18 abbreviated HPHC for cigarette smoke were identified by the World Health Organization (WHO) Study Group on Tobacco Product Regulation (TobReg) as priorities for lowering or monitoring.

Data on the constituent composition of tobacco products are widely available in the public literature (e.g. Borgerding et al., 2012; Counts et al., 2005). Not surprisingly, in a comparison of multiple HPHC between a new and predicate product, some HPHC may be numerically increased in the new product compared with the predicate product, some HPHC may be numerically decreased, and some HPHC may be no different. Thus, in an evaluation of HPHC data within the context of SE, given numerical differences in HPHC are identified, the question might arise: do these numerical differences in HPHC result in the new product raising different questions of public health?

The following presents a description and discussion of quantitative risk assessment (QRA) methodology that can be used to address numerical increases and decreases in HPHC yields between two or more tobacco products in order to make a determination of whether a new tobacco product raises different questions of public health. The available QRA approaches discussed are founded in methods commonly used by the US Environmental Protection Agency (USEPA) to address questions of public health in environmental Superfund site assessments. Applicability of the methodology to the tobacco products SE process, and how it may be used in regulatory decision-making, are addressed.

1.2. Use of quantitative risk assessment to address questions of public health

1.2.1. Regulatory agency use of risk assessment

QRA is a scientific, evidence-based analytical process that combines chemical and biological data in order to quantify the probability and potential impact of some defined risk. The risk assessment process is an essential component of regulatory and related types of decision-making (NRC, 2008), and informs decisions by describing potential threats to health using scientific evidence. Risk assessment is used by international governmental and regulatory bodies (e.g. USEPA, US Occupational Safety and Health Administration, USFDA, European Food Safety Authority) to make decisions about environmental, occupational, biological, and consumer product risks to human health. Many US federal and state regulatory agencies also use QRA to address risks posed to human health and the environment for individual constituents as well as mixtures of constituents released into the environment (e.g. USEPA, 1989; 1991a, 1991b; 1991c, 2001; 2009a, 2009b; 2017; LDEQ, 2003; TCEQ, 2013; CalEPA, 2016a; 2016b). Therefore, the following sections outline how current regulatory QRA approaches and guidelines are being used, and how these processes might be incorporated into the SE pathway for tobacco products.

1.2.2. Tobacco products risk assessment

In the risk assessment of tobacco products, QRA principles have been applied to certain cigarette mainstream smoke constituents (Burns et al., 2008; Cunningham et al., 2011; Fowles and Dybing, 2003; Marano et al., 2012a, 2012b; 2012c; Talhout et al., 2011; Watanabe et al., 2009; Xie et al., 2012), as well as smokeless tobacco product constituents (Ayo-Yusuf and Connolly, 2011; Marano et al., 2012b, 2012c). The USFDA has used QRA in the context of a proposed rule for a smokeless tobacco product constituent product standard (USFDA, 2017), as well as in the evaluation of two cigarette products in the context of an SE clearance (USFDA, 2013). Information generated from QRA has been used to prioritize cigarette smoke toxicants (Burns et al., 2008) and to assess tobacco products, including those categorized as potentially reduced exposure products (PREPs) (Pankow et al., 2007). In the absence of long-term epidemiological studies, QRA is a practical and efficient approach for the evaluation of potential human health risks associated with tobacco products, in particular in the context of an SE evaluation. That is, QRA is specifically useful in a relative or comparative assessment between two or more tobacco products. Notably, given the state of the scientific evidence to-date (e.g. limited toxicity data, limited data on constituent interactions in mixtures), absolute values associated with QRA do not necessarily align quantitatively with epidemiological data of the use of tobacco products (Fowles and Dybing, 2003).

2. Materials and methods

2.1. Risk assessment process

In general, risk assessment is a four-step process including hazard identification, exposure assessment, toxicity assessment, and risk characterization, as presented in Table 2.

Table 2
Risk assessment process (NRC, 2008).

Hazard identification	What adverse health effect(s) are associated with the constituent(s) of concern?
Exposure assessment	To how much of the constituent(s) and by what routes are individuals exposed?
Toxicity assessment	How much of the constituent(s) does it take to cause the adverse biological effect?
Risk characterization	What is the risk (probability) of toxicity occurring in the exposed population?

2.2. Proposed approach for use of QRA in SE evaluation of tobacco products

One approach for using QRA to understand the different questions of public health potentially posed by numerical differences in HPHC in the context of an SE evaluation of tobacco products is modeled after the methodology for the assessment of constituent mixtures at Superfund sites presented in the USEPA Risk Assessment Guidelines for Superfund (RAGS) (USEPA, 1989; 2009a, 2017). This approach to mixtures risk assessment is utilized by both federal and state US agencies (GAO, 2001; LDEQ, 2003; USEPA, 1989; 2017), as well as other countries and international organizations (European Commission, 2011; ISO, 2002; Staal and van der Ven, 2015), to assist in decision-making related to the need for remedial action to decrease the exposure to a specific constituent, in order to be protective of human health and/or the environment. The USEPA RAGS guidelines (USEPA, 1989; 1991a, 1991b; 1991c, 2001; 2009a, 2017) also provide a basis for determining levels of constituents that can remain available for public exposure and be adequately protective of public health (i.e. do not raise questions of public health from a toxicological perspective). These Superfund site assessment guidelines are aligned with the four-step risk assessment process of hazard identification, toxicity assessment, exposure assessment, and risk characterization (Table 2). One proposed QRA approach for SE evaluation of tobacco products applies the same four-step approach for the assessment of HPHC measured in tobacco products. Given the intent in both cases is to make an assessment regarding the public health impact of constituents in a mixture, the applicability is appropriate.

Table 3 provides a summary of the four-step risk assessment process as it relates to Superfund site evaluations and to the risk assessment of tobacco products. Each of the steps are then described in more detail below.

2.2.1. Hazard identification

The objective of the hazard identification is to determine whether exposure to a stressor can cause an increase in the incidence of specific adverse health effects (e.g. cancer and/or noncancer effects) (NRC, 2008).

In an environmental QRA, the hazard identification is an evaluation of the constituents potentially encountered in the environmental media. The initial list of constituents to be considered may be based upon the historical and/or current activity at the site (e.g. the constituent list for a gasoline refinery would be different than the constituent list for a pesticide production facility) or based upon general USEPA analytical methods (e.g. SW-846 Method 8270 for semi-volatile compounds, 8260 for volatile compounds, USEPA 6010 for specific metals). From the constituents included in the analytical analysis, constituents of potential interest (COPIs) can be identified by comparing the measured concentrations to regulatory approved screening levels (e.g. USEPA regional screening levels [RSLs] or state regulatory generated values). Constituents identified as COPIs (e.g. having measured concentrations in excess of the screening levels) would be formally evaluated in the remainder of the QRA process.

For tobacco products QRA in the context of a SE evaluation, the hazard identification is an evaluation of tobacco product constituents that are representative of the product(s). The USFDA has identified an abbreviated list of HPHC for reporting (Table 1) (USFDA, 2012b), which is considered a representative sample of the established list of HPHC (USFDA, 2011b). HPHC are considered by USFDA to be associated with certain toxicological characteristics, as presented in Table 4 (cigarette smoke) and Table 5 (smokeless tobacco). For tobacco products, no standards for screening HPHC have been developed; therefore, constituents identified as relevant to “different product characteristics” would be formally evaluated in the QRA process. Alternatively, the full abbreviated list may be retained for the QRA, given they are a representative list of USFDA 93 identified harmful and potentially harmful constituents in tobacco products and tobacco smoke.

2.2.2. Toxicity (dose-response) assessment

The objectives of the toxicity (dose-response) assessment are 1) to evaluate the inherent toxicity of the substances under investigation; and 2) to identify the level of exposure below which these toxic effects (i.e. noncancer) are not expected to occur or the risk of effects (i.e. cancer) would be negligible. The toxicity assessment would be conducted in a similar manner for environmental risk assessments and tobacco products risk assessments.

For carcinogens, carcinogenic dose-response is defined using oral cancer slope factors (CSF) for oral exposure and inhalation unit risk (IUR) factors for inhalation exposure. The CSF is an estimate of the

Table 3
Comparison of risk assessment approaches: Superfund site versus tobacco products.

Superfund Site Assessment	Assessment of Tobacco Products
Hazard Identification	
Chemicals of concern, representative of those classes of compounds expected to be at the site, with available toxicity data, defined by USEPA.	HPHC, representative of those classes of compounds expected to be in tobacco products, with available toxicity data, defined by USFDA.
Toxicity Assessment	
Identification of exposure (dose) that is considered to be acceptable. Relies upon a hierarchy of well-documented toxicity information.	Identification of exposure (dose) that is considered to be acceptable. Relies upon a hierarchy of well-documented toxicity information.
Exposure Assessment	
Quantification of the extent, frequency, and duration of exposure to the population of interest by relevant pathways. Depends on media and receptor (e.g. a resident's exposure to soil).	Quantification of the extent, frequency, and duration of exposure to the population of interest by relevant pathways. Depends on media and receptor (i.e. product and user).
Risk Characterization	
Adverse health impact due to exposure to constituents estimated based on combination of toxicity and exposure. Comparison of risks and hazard between baseline and 5-year review incorporating potential uncertainty and variability. Additivity preferred approach for summation of risk or hazard estimate.	Adverse health impact due to exposure to HPHC estimated based on combination of toxicity and exposure. Comparison of risks and hazards between new versus predicate product incorporating potential variability and uncertainty. Additivity preferred approach for summation of risk or hazard estimate.

Table 4
Toxicological characteristics of HPHC in cigarette smoke*.

HPHC	Carcinogen	Respiratory Toxicant	Cardiovascular Toxicant	Reproductive or Developmental Toxicant
Acetaldehyde	✓	✓		
Acrolein		✓	✓	
Acrylonitrile	✓	✓		
1-Aminonaphthalene	✓			
2-Aminonaphthalene	✓			
4-Aminobiphenyl	✓			
Ammonia		✓		
Benzene	✓		✓	✓
Benzo[a]pyrene	✓			
1,3-Butadiene	✓	✓		✓
Carbon Monoxide				✓
Crotonaldehyde	✓			
Formaldehyde	✓	✓		
Isoprene	✓			
NNK	✓			
NNN	✓			
Toluene		✓		✓

HPHC, harmful and potentially harmful constituent.
*Includes HPHC on the abbreviated list of HPHC (USFDA, 2012b) and the disease outcomes identified by USFDA (2012a) to be associated with each HPHC. This list of HPHCs is also considered a representative sample of the established list of HPHC (USFDA, 2012a). HPHC are characterized toxicologically without specification of relevant route of exposure.
NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.
NNN, N-Nitrosonornicotine.

Table 5
Toxicological characteristics of HPHC in smokeless tobacco*.

HPHC	Carcinogen	Respiratory Toxicant	Cardiovascular Toxicant	Reproductive or Developmental Toxicant
Acetaldehyde	✓	✓		
Arsenic	✓		✓	✓
Benzo[a]pyrene	✓			
Cadmium	✓	✓		✓
Crotonaldehyde	✓			
Formaldehyde	✓	✓		
NNK	✓			
NNN	✓			

HPHC, harmful and potentially harmful constituent.
*Includes HPHC on the abbreviated list of HPHC (USFDA, 2012b) and the disease outcomes identified by USFDA (2012a) to be associated with each HPHC. This list of HPHCs is also considered a representative sample of the established list of HPHC (USFDA, 2012a). HPHC are characterized toxicologically without specification of relevant route of exposure.
NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.
NNN, N-Nitrosonornicotine.

increased cancer risk from oral exposure to a chemical at a concentration of 1 milligram per kilogram body weight per day (mg/kg/day); the IUR is an estimate of the increased cancer risk from inhalation exposure to a chemical at a concentration of 1 microgram per cubic meter (1 μg/m^3) in air (USEPA, 2018a). Given how CSF and IUR are derived (i.e. relying upon upper bound conservative estimates), the actual risks associated with exposures to potential carcinogens are unlikely to be higher than the risks calculated using CSF and IUR estimates, and the actual risks could be considerably lower.

For noncancer toxicants, toxicity refers to adverse health effects, other than cancer, that are due to undesirable alterations in the structure or function of various organ systems (USEPA, 1994). Most constituents do not cause the same degree of toxicity in all parts of the body, but instead may elicit greater toxicity in one or a few organs or biological systems, termed a “target organ” effect (USEPA, 1994). The values used to estimate the potential for noncancer toxicity are referred to by USEPA as reference doses (RfD, mg/kg/day) for oral exposure and reference concentrations (RfC, mg/m^3) for inhalation exposures. Both RfD and RfC are estimates (typically based on animal data, with an uncertainty spanning an order of magnitude or more) of a daily intake for human populations, including sensitive subpopulations, that is unlikely to result in adverse noncancer health effects during a lifetime (USEPA, 1988, 1994). RfC and RfD are derived in a manner to ensure that they are unlikely to underestimate the potential for adverse noncancer effects to occur.

Generally, the toxicity factors (i.e. CSF, IUR, RfD, and RfC) generated are based upon the most sensitive endpoint identified in the most sensitive species during the toxicity assessment analysis process. While other endpoints are reviewed, basing the toxicity factor on the most sensitive endpoint in the most sensitive species ensures that the most conservative (i.e. risk-maximizing, health protective) approach is observed.

USEPA guidance documents (USEPA, 1989; 2003, 2005; 2009b) that address the estimation of cancer risk and noncancer hazard generally provide a hierarchy of sources from which representative toxicity factors should be identified. In particular, toxicity factors generated by USEPA's Integrated Risk Information System (IRIS) are generally specified as the primary source within the hierarchy; other scientifically reasonable sources for toxicity assessment information exist (noted below).

It is recommended that the selection of toxicity factors in the QRA of tobacco products follow a similar hierarchy. This ensures that the most conservative (i.e. health protective) approach is observed. Based on guidance from USEPA (2003), the hierarchy for selection of toxicity factors includes:

- Tier 1—EPA's Integrated Risk Information System (IRIS) (USEPA, 2018a, 2018b).
- Tier 2—EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs): The Office of Research and Development/National Center for Environmental Assessment/Superfund Health Risk Technical Support Center develops PPRTVs on a chemical-specific basis when requested by USEPA's Superfund program (USEPA, 2018c).
- Tier 3—Other Toxicity Values: Tier 3 includes additional USEPA and non-USEPA sources of toxicity information, such as the California Environmental Protection Agency (CalEPA, 2018a; 2018b), Agency for Toxic Substance and Disease Registry (ATSDR, 2018), Texas Commission of Environmental Quality (TCEQ, 2017a), and the peer-reviewed literature. Priority should be given to those sources of

Table 6
Inhalation toxicity values.

HPHC	Reference Concentration (mg/m^3)	Source	Inhalation Unit Risk $(\mu g/m^3)^{-1}$	Source
Acetaldehyde	9.0E-03	USEPA (2018b)	2.2E-06	USEPA (2018b)
Acrolein	3.5E-04	CalEPA (2018b)	NA	–
Acrylonitrile	2.0E-03	USEPA (2018b)	6.8E-05	USEPA (2018b)
1-Aminonaphthalene	NA	–	5.1E-04	CalEPA (2018b)[a]
2-Aminonaphthalene	NA	–	5.1E-04	CalEPA (2018b)[a]
4-Aminobiphenyl	NA	–	6.0E-03	CalEPA (2018b)
Ammonia	5.0E-01	USEPA (2018b)	NA	–
Benzene	3.0E-02	USEPA (2018b)	2.2E-06 to 7.8E-06	USEPA (2018b)[b]
Benzo[a]pyrene	2.0E-06	USEPA (2018b)	6.0E-04	USEPA (2018b)
1,3-Butadiene	3.3E-02	TCEQ (2015, 2017a)	5.0E-07	TCEQ (2015, 2017a)
Carbon Monoxide	7.0E + 00	WHO (2010)[c]	NA	–
Crotonaldehyde	8.1E-03	TCEQ (2016)	NA	–
Formaldehyde	9.8E-03	ATSDR (1999a)	1.3E-05	USEPA (2018b)
Isoprene	NA	–	2.2E-08	TCEQ (2017b)
NNK	NA	–	5.2E-03	Naufal et al. (2009)[d]
NNN	NA	–	2.4E-04	CalEPA (2018b)[e]
Toluene	5.0E + 00	USEPA (2018b)	NA	–

[a] No IUR for 1- and 2-aminonaphthalene exist. IUR herein is converted from an oral/inhalation slope factor, assuming a body weight of 70 kg and an inhalation rate of 20 m^3/day, per USEPA guidance (USEPA, 1989).
[b] For benzene, IURs range from 2.2E-06 to 7.8E-06 per $\mu g/m^3$. To be health protective, the most stringent IUR value of 7.8E-06 per $\mu g/m^3$ is recommended (USEPA, 2018b).
[c] No chronic or subchronic RfC available. 24-hour indoor air guideline from WHO is recommended as a surrogate.
[d] No IUR for NNK exists. IUR herein is extrapolated from CSF assuming a body weight of 70 kg and an inhalation rate of 20 m^3/day per USEPA guidance (USEPA, 1989).
[e] For NNN, the IUR was adjusted to be consistent with USEPA's refined recommended approach for body weight-surface area scaling factors for animal-to-human extrapolation (USEPA, 1992, 2005).
NA, Not available. HPHC is likely not considered a carcinogen/noncancer toxicant, as relevant.
-, not applicable.
NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.
NNN, N-Nitrosonornicotine.

information that are the most current, the basis for which is transparent and publicly available, and which have been peer-reviewed.

For certain HPHC, toxicity factors associated with the relevant route of exposure (i.e. inhalation exposure for cigarettes, oral exposure for smokeless tobacco) are not available. Notable examples include no IUR for N-Nitrosonornicotine (NNN) and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), although CSFs exist. In these cases, a route-to-route extrapolation can be conducted. For example, in the absence of sufficient inhalation data to derive an IUR, it is standard risk assessment practice to conduct a route-to-route extrapolation for development of an IUR, in particular if data are available from another route of exposure. This is consistent with USEPA and CalEPA dose-response assessment practice (CalEPA, 2018b; USEPA, 2002a; 2005, 2009b). There are multiple chemicals in USEPA IRIS for which an IUR value has been extrapolated from an oral CSF (e.g. polychlorinated biphenyls) (USEPA, 2018b). Specific examples related to the toxicity assessment of tobacco products are discussed below.

Recommended inhalation toxicity factors identified per the hierarchy are presented in Table 6 and recommended oral toxicity factors identified per the hierarchy are presented in Table 7. Consistent with the proposed hierarchy, for HPHC, when toxicity factors were not available from USEPA, other sources were identified. Regardless of the toxicity value selected for HPHC and used in the QRA, given the comparative assessment of risk between the new and corresponding predicate products, the same value would be applied for both products. Thus, the resulting difference between the estimated risk for each product (i.e. the results and conclusions) would generally not be affected. The notable difference would be in the evaluation of which HPHC contribute the most to the overall risk (e.g. the use of the most sensitive endpoint would indicate that the constituent is a greater contributor at lower concentrations).

2.2.3. Exposure assessment

Exposure assessment is defined as the process of measuring or estimating concentration (or intensity), duration, and frequency of exposures to a constituent. Three steps are considered in the exposure assessment: 1) the exposure setting must be characterized (e.g. what is the source of the potential contact); 2) the potential exposure pathways must be identified (e.g. from what media does the exposure occur); and, 3) to what quantity of constituent does exposure occur. During the exposure assessment, the potentially affected population and route of exposure are identified and, where possible, the amount, frequency, and length of time are estimated. The exposure assessment is a key step in the risk assessment process because without the determination of how much and by what route exposure occurs, even the most toxic constituent may not present a threat. In the exposure assessment for an environmental QRA, it must be considered that constituents may be transported away from the initial point source. Thus, the exposure pathway must assess fate and movement of the constituent relative to its exposure point location. During the exposure assessment, measured concentrations, obtained from actual samples of the source of the exposure, and estimated concentrations, based on mathematical fate and transport models, may be used. While the guidance for exposure assessment reported in USEPA RAGS (USEPA, 1989; 2009a) focuses on exposures from constituents present at a site, the methodology is applicable to the performance of exposure assessments for almost any exposure, including from the use of tobacco products.

In 2009, the USEPA (2009a) provided an update to the Superfund Program's approach for determining risk from inhaled constituents. This guidance updates the original approach (USEPA, 1989), established in 1989, which typically derived estimates of exposure in terms of a chronic, daily “air intake” (i.e. mg/kg/day). As can be seen in Equation (1), the updated approach (USEPA, 2009a) recommends that estimates of risk via inhalation use the concentration of the constituent in air as the exposure metric (e.g. mg/m^3), rather than estimated intake

Table 7
Oral toxicity values.

Constituent	Reference Dose (mg/kg/day)	Source	Oral Cancer Slope Factor $(mg/kg/day)^{-1}$	Source
Acetaldehyde	1.0E-01	TCEQ (2017a)	NA	–
Arsenic	3.0E-04	USEPA (2018b)	1.5E+00	USEPA (2018b)
Benzo[a]pyrene	3.0E-04	USEPA (2018b)	1E+00	USEPA (2018b)
Cadmium	1.0E-03	USEPA (2018b)[a]	NA	–
Crotonaldehyde[b]	1.0E-03	USEPA (2018c)	1.9E+00	USEPA (1997)
Formaldehyde	2.0E-01	USEPA (2018b)	2.1E-02	CalEPA (2018a)
NNK	NA	–	1.8E+01	Naufal et al. (2009)
NNN	NA	–	8.3E-01	CalEPA (2018a)[c]

[a] Based on RfD for cadmium in food.
[b] Based on toxicity values for trans-crotonaldehyde.
[c] For NNN, the CSF from CalEPA was adjusted to be consistent with USEPA's refined recommended approach for body weight-surface area scaling factors for animal-to-human extrapolation (USEPA, 1992, 2005).
NA, not available. HPHC is likely not considered a carcinogen/noncancer toxicant, as relevant.
-, not applicable.
NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.
NNN, N-Nitrosonornicotine.

of a contaminant from air based on an inhalation rate and body weight (e.g. mg/kg/day) (see also USEPA, 1994).

For an exposure assessment relevant to cigarettes, the equations specified in the USEPA's RAGS Supplemental Guidance for Inhalation Risk Assessment (USEPA, 2009a) can be used (Equation (1)), with slight modifications (Equation (2)).

$$EC\ (\mu g/m^3) = \frac{C_a \times ET \times EF \times ED}{AT} \quad (1)$$

where:

EC – exposure concentration (μg/m^3)
C_a – air concentration (μg/m^3)
ET – exposure time (hours/day)
EF – exposure frequency (days/year)
ED – exposure duration (years)
AT – averaging time (hours)

As indicated previously, the concentration in air (C_a) evaluated in an environmental QRA is a measured concentration or is an estimate from a medium other than air using mathematical models. For exposure to cigarette smoke, C_a can be estimated by using the measured machine generated mainstream smoke yield (C) of the HPHC in terms of microgram per cigarette (μg/cigarette) multiplied by the number of cigarettes smoked during the day (CpD) divided by the inhalation rate (IR) in m^3/day (Equation (2)). Cigarette smokers are assumed to be lifetime receptors; thus, exposure estimates throughout a lifetime are estimated. It is noted that machine-measured HPHC yields do not represent, and are not intended to be representative of, actual human smoker exposure (Borgerding and Klus, 2005; Peeler, 1996), however are recommended herein as a surrogate. Notably, the International Organization for Standardization (ISO) has stated, "smoke emission data from machine measurements may be used as inputs for product hazard assessment, but they are not intended to be nor are they valid as measures of human exposure or risks (ISO, 2008)."

$$EC\ (\mu g/m)^3 = \frac{C \times CpD \times ED \times EF}{IR \times AT} \quad (2)$$

where:

EC – exposure concentration (μg/m^3)
C – HPHC measured yield (μg/cigarette)
CpD – number of cigarettes per day
ED – exposure duration (years)
EF – exposure frequency (days/year)
IR – inhalation rate (m^3/day)
AT – averaging time (days)

For an exposure assessment relevant to smokeless tobacco, in accordance with USEPA guidance (USEPA, 1989), exposure to constituents in a medium is expressed as chronic daily intake (CDI), which is the estimated daily chemical dose for an individual averaged over the exposure duration (Equation (3)). Similar to cigarette smokers, smokeless tobacco product users are assumed to be lifetime receptors. Exposure estimates throughout a lifetime are estimated. It is noted that measured constituent concentrations in smokeless tobacco products are not likely to be representative of actual human smokeless tobacco user exposure (Caraway and Chen, 2012), however are recommended herein as a surrogate.

$$CDI = \frac{C \times CF \times TC \times ABS \times EF \times ED}{BW \times AT} \quad (3)$$

where:

CDI – chronic daily intake (mg/kg/day)
C – HPHC concentration (nanogram per gram [ng/g] tobacco)
CF – conversion factor (10^{-6} mg/ng)
TC – tobacco consumption rate (gram per day [g/day])
ABS – HPHC absorption rate (unitless)
EF – exposure frequency (days/year)
ED – exposure duration (years)
BW – body weight (kg)
AT – averaging time (days)

Recommended input assumptions for the exposure assessments for cigarettes and smokeless tobacco products are presented in Table 8. As noted, per USEPA, the averaging time (AT) depends on the type of toxic effects assessed (i.e. cancer or noncancer) (USEPA, 1989). That is, for long term exposure to non-carcinogens, exposure concentrations are calculated by averaging intakes over the period of exposure (USEPA, 1989). For carcinogens, exposure concentrations are calculated by prorating the total cumulative intake over a lifetime (USEPA, 1989). Thus, the averaging time for noncancer effects (AT_{NC}) is equal to the exposure duration, i.e. 20987.5 days (57.5 years × 365 days/year) for cigarette smokers and 18615 days (51 years × 365 days/year) for smokeless tobacco product users (USEPA, 1989). In accordance with the most updated USEPA guidance (USEPA, 2014), the default life expectancy of 70 years is used as the averaging time for assessing carcinogens (AT_C), i.e. 25550 days (70 years × 365 days/year) for both cigarette smokers and smokeless tobacco product users (USEPA, 1989,

Table 8
Exposure parameters and assumptions.

Parameter	Symbol	Value	Unit	Source
Cigarette consumption	CpD	20	cigarettes/day	USFDA (2013)
Smokeless tobacco consumption	TC	12	grams/day	USFDA (2017)
Absorption rate	ABS	10%–100%	unitless	HPHC-specific, literature
Exposure frequency	EF	365	days/year	Maximum value
Exposure duration, cigarettes	ED	57.5	years	USFDA (2013) [a]
Exposure duration, smokeless tobacco	ED	51	years	USEPA (1989, 2014); USFDA (2017) [b]
Inhalation rate	IR	20	m^3/day	USEPA (1991c, 2011)
Body weight	BW	80	kg	USEPA (2011, 2014)
Averaging time, noncancer, cigarettes	AT_{NC}	20,988	days	USEPA (1989, 2009a, 2014)
Averaging time, noncancer, smokeless tobacco	AT_{NC}	18,615	days	USEPA (1989, 2009a, 2014)
Averaging time, cancer	AT_C	25,550	days	USEPA (1989, 2009a, 2014)

[a] Assumes average lifespan of 70 years, as recommended by USEPA (1989, 2014) and per USFDA (2013), and user initiation at 12.5 years, per USFDA (2013).
[b] Assumes average lifespan of 70 years, as recommended by USEPA (1989, 2014), and tobacco use initiation at or near 19 years of age, as recommended by USFDA (2017).

2014).

Regardless of the exposure assessment methodology and input assumptions, given the comparative assessment of risk between the new and corresponding predicate products in the context of an SE evaluation, the same methods and input values would be applied for both products. Thus, the resulting difference between the estimated risk for each product (i.e. the results and conclusions) would not be affected.

2.2.4. Risk characterization

The objectives of the risk characterization are 1) to provide estimates of excess lifetime cancer risk and/or noncancer hazard (e.g. predict the frequency and severity of effects in exposed populations) from exposure to constituents classified as carcinogens or non-carcinogens, respectively; and 2) to provide scientifically-based interpretation of those estimates such that informed risk management decisions can be made.

2.2.4.1. Environmental assessment. For an environmental site assessment, the risk characterization is intended to provide estimates of the potential for an adverse health effect from exposure to constituents present at the site by combining the estimate of intake (i.e. the exposure concentration), calculated in the exposure assessment, with constituent specific toxicity factors presented in the toxicity (dose-response) assessment.

2.2.4.1.1. Cancer assessment. Cancer risk is estimated as excess lifetime cancer risk (ELCR), defined as the incremental probability of an individual developing cancer over a lifetime under the specified exposure conditions. ELCR are calculated for each constituent associated with cancer health effects using Equation (4) (USEPA, 1989; 2009a). If multiple constituents are considered, ELCR for each are summed (USEPA, 1989; 2009a). That is, to assess the exposure to multiple constituents, the use of dose additivity in the absence of information on the specific mixture of constituents being considered is recommended by USEPA (1989, 2009b). For constituents considered to be carcinogens, the range of acceptable risk is typically 10^{-6} to 10^{-4} (one in a million to one in ten thousand), as defined by the USEPA under Section 300.430 of the National Oil and Hazardous Substances Pollution Contingency Plan (LII, 2018; USEPA, 1991b; 1991c, 1996; 2017). Explanations of why remediation is needed must be provided if summed risk falls within this range. In addition, exceedance of this risk level does not necessarily warrant any remedial action. Total risk estimates exceeding 10^{-4} may be considered acceptable with justification.

$$ELCR = EC\ (or\ CDI) \times IUR\ (or\ CSF) \quad (4)$$

where:

ELCR – excess lifetime cancer risk (unitless)
EC – exposure concentration (μg/m^3)
CDI – chronic daily intake (mg/kg/day)
IUR – inhalation unit risk factor (per μg/m^3)
CSF – cancer (oral) slope factor (per mg/kg/day)

2.2.4.1.2. Noncancer assessment. Metrics of noncancer effects are calculated via hazard quotients (HQ, for individual constituents) or a hazard index (HI, for multiple constituents). HQ, representing the ratio of estimated exposure to the toxicity value, are calculated for each constituent associated with noncancer health effects using Equation (5) (USEPA, 1989; 2009a). When performing an environmental site-related risk assessment for multiple constituents considered as non-carcinogens, summing all of the HQ is considered a conservative approach (i.e. generally resulting in an overestimation of hazard); to assess the exposure to multiple constituents, the use of dose additivity in the absence of information on the specific mixture of constituents being considered is recommended by USEPA (1989, 2009a). Only if the HI, e.g. the sum of the HQs, is greater than 1, are additional analyses considered. USEPA guidance (USEPA, 1989; 2000, 2009a) suggests that if the HI is greater than unity as a consequence of summing several HQs of similar value, it would be appropriate to segregate the compounds by effect and by mechanism of action and to derive separate HIs for each group.

$$HQ = \frac{EC\ (or\ CDI)}{RfC\ (or\ RfD)} \quad (5)$$

where:

HQ – hazard quotient (unitless)
EC – exposure concentration (μg/m^3)
CDI – chronic daily intake (mg/kg/day)
RfC – reference concentration (μg/m^3)
RfD – reference dose (mg/kg/day)

2.2.4.2. Tobacco product assessment. The approach for tobacco product SE applications compares the estimated risk and/or hazard resulting from exposure to HPHC in a new and predicate product. As the value used for many of the parameters presented in Equations (2) and (3) would be expected to be the same for both the new and predicate products, the equations could be reduced to those parameters that are different (i.e. HPHC exposure concentration and toxicity). For example given two products, with n representing the new product and p representing the predicate product and i representing an HPHC of interest, the ELCR equation (combining Equations (2) and (4)) for each product would be:

$$ELCR_{n,i} = \frac{C_{n,i} \times CpD \times ED \times EF \times IUR_i}{IR \times AT}$$

$$ELCR_{p,i} = \frac{C_{p,i} \times CpD \times ED \times EF \times IUR_i}{IR \times AT}$$

Note that similar equations can be developed for the noncancer evaluation. As demonstrated in these two ELCR equations, the means and distributions or single point values for the parameters CpD, ED, EF, IR, and AT would be identical for the new and predicate product. Therefore, the change in the two parameters, C_i (representing the constituent yield from the product) and IUR_i (the toxicity factor for the constituent being evaluated) can be used to estimate the difference in risk or hazard for each constituent. This would also be true for the summed ELCR and HQ.

3. Example: comparison of environmental site risk assessment to tobacco product risk assessment

As described above, the evaluation of risk and hazard associated with exposure to constituents in the environment and the use of tobacco products can be addressed in a similar manner. An example to demonstrate these similarities is provided in the following sections.

3.1. Environmental site risk assessment

Consider a risk assessment conducted for a current or former gas refinery, which has experienced leaks from underground gasoline or diesel storage tanks. Thus, in this example, the list of constituents initially considered for evaluation could include benzene, toluene, ethylbenzene, and xylenes (BTEX); certain heavy metals; and possibly polycyclic aromatic hydrocarbons (PAHs) and total petroleum hydrocarbons (TPHs). Certain additives, such as lead and methyl *tert*-butyl ether (MTBE), might also be evaluated. A sampling plan would be developed and executed, with the collected samples analyzed by a laboratory for the initial list of constituents. These sampling results would then be evaluated in a QRA using the following steps:

3.1.1. Hazard identification

The concentrations of the constituents from the sampling and analysis are compared to applicable screening levels, such as the USEPA RSLs, state-specific standards, or other appropriate standards. Those constituents with concentrations exceeding the screening level, identified as constituents of potential interest (COPIs), would be retained for further assessment. For this illustration, the following constituents were identified as COPIs: benzene, ethylbenzene, arsenic, cadmium, benz[a] anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, and naphthalene.

3.1.2. Toxicity (dose-response) assessment

For the identified COPIs, a review of the available toxicity information is conducted and appropriate values selected. A hierarchical selection process for the toxicity factors is followed.

3.1.3. Exposure assessment

Considering the relevant population, the potential exposure pathways are identified. This could include any number of pathways such as: incidental ingestion of soil, dermal contact with soil or groundwater, ingestion of groundwater as a potable source, and inhalation of particulates or volatiles. Intakes to the exposed population are estimated.

3.1.4. Risk characterization

Cancer risks and noncancer hazards are estimated for each identified COPI and the relevant exposure pathway(s), incorporating toxicity information identified in the toxicity assessment and exposure information identified in the exposure assessment. Baseline and follow-up assessments are compared.

As illustrated in Table 9 using hypothetical data, cancer risks for each COPI are estimated individually and then summed. Five-year review estimates and baseline estimates are compared to evaluate the performance of the remedy at the site and whether it remains protective of human health and the environment. Similar calculations could be conducted for noncancer hazard. Additionally, similar calculations could be conducted for a different exposure pathway(s) and/or a different environmental site.

Table 9
Example of results for an environmental QRA[a].

	Excess Lifetime Cancer Risk (ELCR)					
	Baseline		5-year Review		ELCR Change (5-Year/Baseline)	
Constituent	Mean	Upper Bound	Mean	Upper Bound	Mean	Upper Bound
Benzene	2.4E-06	6.7E-06	1.0E-06	3.8E-06	0.4	0.6
Ethylbenzene	6.9E-07	1.1E-06	3.0E-07	4.6E-07	0.4	0.4
Arsenic	4.1E-06	8.8E-06	1.9E-06	2.9E-06	0.5	0.3
Cadmium	2.7E-10	3.8E-10	1.3E-10	1.6E-10	0.5	0.4
Benz[a] anthracene	6.1E-08	6.3E-08	6.1E-08	6.3E-08	1.0	1.0
Benzo[a]pyrene	6.1E-07	6.3E-07	6.1E-07	6.3E-07	1.0	1.0
Benzo[b] fluoranthene	6.1E-08	6.3E-08	6.1E-08	6.3E-08	1.0	1.0
Benzo[k] fluoranthene	6.1E-09	6.3E-09	6.1E-09	6.3E-09	1.0	1.0
Dibenz[a,h] anthracene	6.1E-07	6.3E-07	6.1E-07	6.3E-07	1.0	1.0
Naphthalene	3.2E-07	6.6E-07	2.4E-07	5.6E-07	0.7	0.9
Total Estimated Risk	**9E-06**	**2E-05**	**5E-06**	**9E-06**	**0.5**	**0.5**

Data presented in the table were randomly generated.
[a] Average of constituent analytical data used to estimate the mean ELCR and 95% upper confidence level of the arithmetic mean used to estimate the upper bound ELCR, respectively.

3.2. Tobacco product risk assessment

An evaluation of cancer risk and noncancer hazard due to exposure to tobacco smoke or through the use of smokeless tobacco can be conducted in a similar manner. Analysis of tobacco products under consideration are conducted to estimate the concentration of certain HPHC in the product. These results would then be evaluated in a QRA using the following steps:

3.2.1. Hazard identification

Unlike the environmental analysis, no screening levels have been developed for tobacco products; no tobacco products are safe. Therefore, HPHC relevant to the new and predicate products would be considered COPIs and assessed.

3.2.2. Toxicity (dose-response) assessment

For the identified COPI, a review of the available toxicity information would be conducted and appropriate values selected. A hierarchical selection process for the toxicity factors is followed.

3.2.3. Exposure assessment

For cigarettes, the most applicable pathway would be inhalation exposure; for smokeless tobacco use, the most applicable pathway would be oral exposure. Exposure to the population of interest is evaluated. The QRA utilizes standard default exposure factors recommended by USEPA (1989, 2009a, 2011, 2014, 2017), USFDA (2017), and documentation from well-respected scientific organizations to derive an upper-bound lifetime exposure to HPHC. The purpose of using USEPA and USFDA recommended standard default exposure factors and USEPA preferred toxicity values in the QRA is to estimate a conservative exposure case (i.e. well above the average) and to reduce variability and uncertainty in the risk assessment.

3.2.4. Risk characterization

Cancer risks and noncancer hazards are estimated for each HPHC and the relevant exposure pathway, incorporating toxicity information identified in the toxicity assessment and exposure information identified in the exposure assessment. New and predicate product estimates are compared.

Sample calculations of the exposure concentration, ELCR (IUR of 2.2E-06 per μg/m^3), and HQ (RfC of 9E-03 mg/m^3) for acetaldehyde with an estimated yield of 592.2 μg/cigarette, under the ISO smoking regimen, and using the inputs indicated in Table 8 is provided below:

$$EC_{cancer}\left(\frac{\mu g}{m^3}\right) = \frac{C \times CpD \times ED \times EF}{IR \times AT} = \left[592.2\frac{\mu g}{cig} \times 20\frac{cigs}{day} \times 57.5\ yrs \times 365\frac{days}{yr}\right] / \left[20\frac{m^3}{day} \times 25550\ days\right] = 486.4\frac{\mu g}{m^3}$$

$$EC_{noncancer}\left(\frac{\mu g}{m^3}\right) = \frac{C \times CpD \times ED \times EF}{IR \times AT} = \left[592.2\frac{\mu g}{cig} \times 20\frac{cigs}{day} \times 57.5\ yrs \times 365\frac{days}{yr}\right] / \left[20\frac{m^3}{day} \times 20988\ days\right] = 592.1\frac{\mu g}{m^3}$$

$$ELCR = EC_{cancer} \times IUR = 486.4\frac{\mu g}{m^3} \times 2.2E-06\ per\frac{\mu g}{m^3} = 1.1E-03$$

$$HQ = \frac{EC_{noncancer}}{RfC} = \frac{592.1\frac{\mu g}{m^3}}{9E{-}03\frac{mg}{m^3} \times 1000\frac{\mu g}{mg}} = 65.8$$

Calculations for the other HPHCs are presented in the supplemental information workbook "Additivity Manuscript Risk_Hazard Example Calculations.xlsx".

As illustrated in Table 10, using hypothetical data, cancer risks following inhalation exposure to the abbreviated list of HPHC in tobacco smoke (i.e. COPI in this example) are estimated individually and then summed. The new and predicate product estimates are compared. The resulting HQs for the HPHC identified as having non-carcinogenic effects are presented in Table 11 with the HQs for each of the HPHC summed to obtain a total estimated hazard (the HI). While not shown, it would be appropriate to segregate the HPHCs by effect and by mechanism of action and to derive separate HIs for each group. Similar calculations could be conducted for a smokeless tobacco product.

Tables 10 and 11 present an example comparison of the means and upper bounds for the predicate and new products demonstrating that their resulting risks and non-carcinogenic hazard effects are similar. For a determination of SE, the variability around the mean (ISO data) and upper bound (HCI data) for both the predicate and new products would be considered and some form of statistical comparison, such as a *t*-test, used to evaluate whether their differences are statistically significant. This statistical comparison would be performed on the cigarette yields. If differences are within an acceptable margin of safety, then the new product is considered to not raise different questions of public health, and the new and predicate products are determined to be SE.

4. Result

4.1. Uncertainty and variability

In any risk assessment, the estimates of potential health effects (i.e. cancer risks and noncancer hazards) have various associated uncertainties. The primary areas of uncertainty and variability include the constituent (chemistry) data (i.e. COPI/HPHC), the exposure assessment, the dose-response (toxicity) assessment, and the risk characterization. Generally, similar uncertainty and variability exist in both an environmental site risk assessment and a tobacco product risk assessment.

4.1.1. Constituents

Uncertainty is often associated with the estimation of constituent concentrations. Uncertainty in the analytical data may stem from errors inherent in sampling and/or laboratory procedures. One of the most effective methods to minimize procedural or systematic error is to subject the data to a strict quality control (QC) review. The QC review procedures help to eliminate or minimize laboratory errors. However, even with all data rigorously validated, it must be realized that error is inherent in all laboratory procedures. Samples of constituents are dependent upon a sampling analysis; for an environmental site assessment, samples from certain media (e.g. soil, groundwater) are collected and analyzed; for tobacco products, product samples are collected, and the amount of an HPHC in tobacco and/or tobacco smoke is measured. Uncertainties can exist in how these samples are collected, and results can vary across different samples, products, and over the time period the samples were collected.

Oldham et al. (2014) evaluated the replicate-to-replicate (sample-to-sample) variability in the HPHCs measured for both ISO and HCI by calculating percent relative standard deviations for each HPHC

Table 10
Substantial equivalence comparison example for tobacco smoke for cancer risk[a].

	Excess Lifetime Cancer Risk (ELCR) Predicate Product		New Product		ELCR Change (New/Predicate)	
HPHC	Mean	Upper Bound	Mean	Upper Bound	Mean	Upper Bound
1,3-Butadiene	2.2E-05	5.2E-05	2.2E-05	5.7E-05	1.0	1.1
1-Aminonaphthalene	1.1E-05	2.0E-05	1.2E-05	2.2E-05	1.1	1.1
2-Aminonaphthalene	5.6E-06	9.4E-06	6.0E-06	7.7E-06	1.1	0.8
4-Aminobiphenyl	1.6E-06	1.8E-06	1.5E-06	1.5E-06	1.0	0.9
Acetaldehyde	1.1E-03	2.7E-03	7.5E-04	2.1E-03	0.7	0.8
Acrylonitrile	5.1E-04	1.4E-03	5.1E-04	1.5E-03	1.0	1.1
Benzene	7.4E-05	1.6E-04	6.3E-05	1.1E-04	0.9	0.7
Benzo[a]pyrene	4.0E-06	7.6E-06	3.5E-06	1.0E-05	0.9	1.4
Formaldehyde	3.4E-04	9.3E-04	2.5E-04	1.2E-03	0.8	1.3
Isoprene	7.7E-06	1.9E-05	9.3E-06	1.4E-05	1.2	0.7
NNK	2.3E-04	5.5E-04	1.9E-04	7.4E-04	0.9	1.4
NNN	1.6E-05	3.9E-05	1.2E-05	2.9E-05	0.7	0.7
Total Estimated Risk[b]	**2.3E-03**	**5.8E-03**	**1.8E-03**	**5.9E-03**	**0.8**	**1.0**

Data presented in the table were randomly generated.

[a] Analytical data from ISO and HCI smoking regimens used to estimate mean and upper bound ELCRs, respectively.

[b] Summed risk of individual constituent risks is generally reported to one significant digit; reported at two significant digits to show change. HPHC, harmful and potentially harmful constituent; NNN, N-Nitrosonornicotine; NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.

Table 11
Substantial equivalence comparison example for tobacco smoke for noncancer hazards[a].

HPHC	Hazard Quotients (HQ) Predicate Product		New Product		HQ Change (New/Predicate)	
	Mean	Upper Bound	Mean	Upper Bound	Mean	Upper Bound
Acetaldehyde	6.6E+01	1.6E+02	4.6E+01	1.3E+02	0.7	0.8
Acrolein	1.6E+02	4.5E+02	1.7E+02	4.1E+02	1.1	0.9
Acrylonitrile	4.6E+00	1.2E+01	4.6E+00	1.4E+01	1.0	1.1
Ammonia	1.9E-02	6.5E-02	2.2E-02	5.4E-02	1.2	0.8
Benzene	1.4E+00	2.9E+00	1.2E+00	2.0E+00	0.9	0.7
Benzo[a]pyrene	4.1E+00	7.8E+00	3.6E+00	1.1E+01	0.9	1.4
1,3-Butadiene	1.6E+00	3.9E+00	1.6E+00	4.2E+00	1.0	1.1
Carbon Monoxide	1.6E+00	4.2E+00	1.5E+00	5.35E+00	1.0	1.3
Crotonaldehyde	1.4E+00	6.3E+00	1.2E+00	5.9E+00	0.9	0.9
Formaldehyde	3.2E+00	8.9E+00	2.4E+00	1.2E+01	0.8	1.3
Toluene	1.2E-02	3.0E-02	8.4E-03	3.3E-02	0.7	1.1
Total Estimated Hazards[b]	**2.4E+02**	**6.6E+02**	**2.3E+02**	**5.9E+02**	**1.0**	**0.9**

Data presented in the table were randomly generated.

[a] Analytical data from ISO and HCI smoking regimens used to estimate mean and upper bound ELCRs, respectively.

[b] Summed risk of individual constituent risks is generally reported to one significant digit; reported at two significant digits to show change. HPHC, harmful and potentially harmful constituent; NNN, N-Nitrosonornicotine; NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone.

considered. Oldham et al. (2014) indicate that the relative standard deviations for HPHC in the smoking regimen ranged from 0% to more than 40%. For those HPHCs on the FDA abbreviated list, the range of standard deviations was narrower (4.7%–10.3%). This represents the short-term variation, as the tobacco products evaluated were from a single lot. Expected long-term variation would be greater due to temporal changes to the product (e.g., natural changes in the tobacco) and evaluations being conducted via different laboratories or different equipment. These types of variability, along with changes in how the user of the product consumes the product, could be incorporated into the QRA, if the appropriate data are available, when determining if the new product is substantially equivalent to the predicate product.

4.1.2. Exposure assessment

The exposure parameters used in estimating the dose or intake from exposure to constituents in the environment or a tobacco product also contain uncertainty and variability. The goal is to estimate a reasonable maximum exposure or “upper bound” (i.e. the highest exposure that is reasonably expected to occur) in conjunction with an understanding of the range or distribution of exposures. The exposure parameters (e.g. inhalation rate) vary over the population of interest with an upper bound value selected to ensure that the resultant risk/hazard is not underestimated. The variability in these parameters can be assessed by viewing the distribution of the entire population of interest. Certain probabilistic evaluations (e.g. Monte Carlo analysis) can be conducted; however, these approaches are not typically applied due to their complexity. Simplistic approaches that capture the range of values for each exposure parameter can be incorporated into the estimate of exposure to provide a general indication of the overall variability in the exposure estimates. In relative comparisons, e.g. comparisons between the new and predicate tobacco product and/or comparisons between an environmental site at baseline and at five years post baseline, the uncertainty and variability in exposure would be of less concern. This is because changes in exposure parameters would be the same in the scenarios being compared, resulting in similar increases or decreases. Therefore, while the reported magnitude of risk or hazard might change, the difference between the risk and hazard presented by the predicate and new products (or baseline and five years post baseline) would remain the same.

Risk assessments typically utilize average concentrations, or an upper bound on the average concentration of constituents, and a mixture of average and upper bound exposure parameters to quantify exposure to constituents. These values are used because cancer and noncancer toxicity criteria and resulting risks are based on a lifetime of exposure. For tobacco products, consumers use products in a random fashion (i.e. within an individual consumer and between consumers) (Borgerding and Klus, 2005; Peeler, 1996; US Federal Trade Commission, 1967), and therefore, average values are reasonably representative of potential exposure. Additionally for tobacco products, it is widely recognized that HPHC yield data generated under the Health Canada Intense (HCI) smoking regimen are representative of an intense smoking scenario and thus can be considered as upper percentile yields of HPHC, relative to the ISO smoking regimen. Notably, due to limitations of sample size, and uncertainty and variability in estimating the true average values, average values may not be representative of extreme conditions, e.g. people who rarely smoke and/or heavy smokers.

In this QRA methodology, the default assumption in estimating exposure is that 100% of the constituent is absorbed into the systemic circulation and can reach the target organ of interest. The choices made for these assumptions are protective and are unlikely to underestimate risks. Cancer risks and noncancer hazards could be overestimated based on the use of conservative exposure parameters in estimating risks. Certainly, the goal of estimating risks well above the average and at the upper end of possible risks is likely achieved. These limitations apply equally to the scenarios being compared. Thus, for a comparative assessment, it will not affect the final comparison between the products or the ultimate conclusions.

In the example provided herein, the QRA treats exposure to an HPHC in smoke as a continuous process and estimates an exposure concentration by averaging the yields of the HPHC from cigarettes consumed over the average daily volume of air inhaled by a user. The QRA utilizes standard default exposure factors recommended by USEPA (1989, 2011, 2014) and USFDA (2013) to derive an upper-bound lifetime exposure to HPHC. For example, the QRA assumes a user smokes one pack of cigarettes per day, i.e. 20 cigarettes per day, a value consistently above the US average adult daily smoking frequency reported by several surveys from the Centers for Disease Control and Prevention (CDC, 2014a, 2014b, 2014c). Exposure frequency for a smoker is assumed to be 365 days per year (maximum value possible) and exposure duration is assumed be 57.5 years (an upper percentile value; USFDA, 2013). Mean HPHC yield data generated under the HCI smoking regimen are representative of an intense smoking scenario and thus, can be considered as upper percentile yields of HPHC, relative to the ISO smoking regimen. The purpose of using USEPA and USFDA recommended standard default exposure factors is to estimate a conservative exposure case (well above the average) and reduce variability and uncertainty in the risk assessment.

One aspect that is not captured in the QRA, is whether a change

from using the predicate product to the new product results in any changes in smoking behavior (e.g., longer or more intense puffs, smoking more frequently). However, these types of data cannot be obtained prior to the availability of the new product on the market. Notably, smoking behavior has long been demonstrated to be quite variable both between and among individuals (e.g., Bradford et al., 1936; FTC, 1967; Zacny and Stitzer, 1996). Yield data for the HPHCs evaluated in the QRA are representative of a specific machine smoking scenario (i.e., ISO and HCI) used for both the predicate and new products under the same conditions and are considered to include more intense smoking behaviors (e.g., HCI).

4.1.3. Toxicity (dose-response) assessment

A potentially large source of uncertainty is inherent in the toxicity values (e.g. RfCs and IURs) derived by the USEPA and others. Uncertainty can be the result of a variety of factors. For example, some constituents lack a well-defined dose-response relationship, and in many cases, data are extrapolated from animal studies to sensitive humans by the application of uncertainty factors to an estimated no-observed-adverse effect level or lowest-observed-adverse-effect level for noncancer health effects. While designed to be health protective, it is likely in many cases that the uncertainty factors applied overestimate the magnitude of differences that may exist both between humans and animals and among humans. Additional factors associated with uncertainty in the toxicity assessment include the fact that when using publicly available values, it is assumed they have been appropriately derived by the source, including the application of dosimetric adjustment factors. Further, it is also assumed that animal dose-response data are appropriate, and the animal toxicity endpoints are relevant to human health. In addition, both cancer and noncancer dose-response assessments are often conducted assuming that the critical or most sensitive toxic effect is of primary concern, and the prevention of the critical or most sensitive toxic effect is protective of other toxic effects that may occur following exposure to higher concentrations. With the goal of protecting the public health, noncancer toxicity values developed by USEPA and other scientific organizations are based on the most sensitive endpoints observed, typically in laboratory animals.

Derivation of cancer potency factors often involves linear extrapolation of effects at high doses to potential effects at lower doses that commonly occur in environmental exposure settings. Thus, cancer is assumed to be a non-threshold event, although currently, it is not known whether linear extrapolation is appropriate for most constituents. This assumption of linearity (i.e. non-threshold) could overestimate the cancer risk (USEPA, 2005). It is probable that the shape of the dose response curve for carcinogenesis varies with different chemicals and mechanisms of action. It is not possible at this time, however, to describe such differences in quantitative terms. As noted, it is likely that the assumption of linearity is conservative and yields potency factors that are unlikely to lead to underestimation of risks. Yet, for specific chemicals, current methodology could cause the potency factors, and hence risks, to be overestimated.

In some instances, toxicity values are not available from one route of exposure (e.g. inhalation) although data are available from a different route of exposure (e.g. oral). In such instances, there is regulatory precedent to conduct route-to route extrapolation in order to quantify toxicity via the relevant route of exposure (USEPA, 2002b; 2005, 2009a; 2018b). Conducting route-to-route extrapolation is an additional area of uncertainty in the dose-response assessment; however, in the absence of route-specific data, extrapolation is a useful and appropriate alternative.

Finally, dose-response data for some constituents are not available. Although no strong conclusions can be reached regarding the potential for risk for a constituent without the appropriate toxicity factors, it is suspected that the magnitude of the error that results is likely to be low. The absence of toxicity information for a chemical is most often because toxicological concern over that chemical is low. That is, chemicals that lack toxicity values have not been well studied because they are not frequently used or detected and/or existing data suggest relatively low toxicity to humans. Thus, researchers have focused on chemicals with a higher potential for toxicity. This would be true for both an environmental site assessment as well as a tobacco product assessment.

4.1.4. Risk characterization

This proposed risk assessment methodology should not be construed as presenting absolute risks or hazards. Rather, results provide a conservative analysis intended to indicate the potential for adverse impacts to occur based on the specified exposure condition. Any uncertainties would be applicable to the risk and hazard estimates being compared across scenarios (i.e. products or sites). Accordingly, these QRA metrics are useful for the comparison of the potential for health effects across scenarios based on the specified exposure condition. While there may be some uncertainties in the approaches or data used, the proposed method is data-driven and relies upon the most appropriate information for the population of interest; using all of the available data to characterize the potential for exposure and toxicity will increase the confidence and decrease the uncertainty in the resulting risk characterization.

Specific to tobacco products, there are tens of thousands of constituents, and it is not practical to measure each one separately. Additionally, only a relatively small number of the constituents are well characterized with respect to toxicity. The HPHC evaluated in a QRA for SE submissions would be those identified by USFDA and considered to be representative of different chemical classes with potential for different adverse health effects (i.e. both cancer and noncancer) in tobacco products. This is consistent with Superfund site assessment where chemicals of concern, representative of those classes expected to be present and with available toxicity data, are evaluated (Table 3, hazard identification). The approach to evaluating complex mixtures using those constituents designated as the most toxic or carcinogenic chemicals, as was employed in the examples herein, has been used by USEPA and WHO for polychlorinated biphenyls (PCB) (USEPA, 2010; Van den Berg et al., 2006), total petroleum hydrocarbons (TPHCWG, 1997; ATSDR, 1999b; MDEP, 2002; USEPA, 2009b), and dioxin-furans (USEPA, 2010; Van den Berg et al., 2006) in risk assessment. For example, PCBs belong to a broad family of man-made organic chemicals known as chlorinated hydrocarbons. PCBs have a range of toxicity, and vary in consistency from thin, light-colored liquids to yellow or black waxy solids (USEPA, 2018d). Among the 209 PCB congeners, toxicity equivalence factors (TEFs) are only available for 12 dioxin-like congeners. These 12 congeners have been used as index chemicals and surrogates in human health and ecological risk assessment of PCBs (USEPA, 2010; Van den Berg et al., 2006). The approach to evaluating complex mixtures using those designated as the most toxic or carcinogenic index chemicals enables manufacturers to begin testing and reporting, and USFDA to begin analyzing HPHC information, in a relatively expedient manner (USFDA, 2012b). Evaluation of a representative list of constituents is also consistent with a previous QRA conducted by USFDA in the context of substantial equivalence evaluation and clearance of cigarette products (USFDA, 2013).

There is uncertainty in assessing risks associated with a mixture of constituents. These substances occur together in tobacco products and the environment, and individuals are exposed to mixtures of the constituents. Predictions of how mixtures of constituents will interact should be based on an understanding of the mechanisms of such interactions. However, suitable data are not currently available to rigorously characterize the effects of all chemical mixtures that may be present in the environment or in tobacco products and any interactions between chemicals or HPHC. Consequently, as recommended by the USEPA (1986), in the environment, constituents are assumed to act additively, and potential health risks are evaluated by summing excess lifetime cancer risks and noncancer hazards. This approach to assessing risk associated with mixtures assumes that there are no synergistic or

antagonistic interactions among their constituents, and that all constituents have the same toxic endpoint and mechanisms of action. Thus, cancer risk and noncancer hazard for individual constituents are assumed to be independent and additive. To the extent that these assumptions are correct, the actual risks could be either underestimated or overestimated; however, this, for the most part, applies equally to both scenarios being compared in the QRA (i.e. products or sites).

4.2. Additional discussion regarding additivity

USEPA has noted that the simple addition, i.e. "combining risks which accounts for the joint probability of the same individual developing cancer as a consequence of exposure to two or more carcinogens" is considered appropriate for most Superfund risk assessments. Additionally, "when evaluating predicted cancer risks from multiple contaminants, risk assessors should estimate the cancer risk for each substance and then sum these risks" (USEPA, 2009a) and "use of dose addition for determining the combined risk of the CAG [cumulative assessment group]" (USEPA, 2002b) is recommended. Other well-respected scientific organizations also advocate summing constituent risks in the risk characterization step. For example, ATSDR (2004) has noted that the "[u]se of the dose-additivity assumption is likely to produce estimates of health hazard that range from appropriate to somewhat conservative, and which are therefore protective of public health." As previously noted, in the majority of cases, results generated using the simple additive mixture approach are not intended to be benchmarks of absolute risk or hazard, but rather to be illustrative of the relation between the different constituents and/or constituent classes in terms of priorities for cancer risk and noncancer hazard assessments (USEPA, 1987; 1989, 2000; 2018b; Fowles and Dybing, 2003).

As noted, to assess the exposure to multiple constituents, the use of dose additivity, in the absence of information on the specific mixture of constituents being considered, is recommended by USEPA (1989, 2009a). Dose additivity assumes "independence of action by the compounds involved," i.e. that there are no synergistic or antagonistic constituent interactions, and that all constituents produce the same effect, e.g. cancer. Toxicity information is generally available for individual constituents, although generally not available for mixtures of constituents. In the case of tobacco products specifically, as no toxicity information is available for the new or predicate products as a whole (nor a known suitable surrogate), nor are the potential interactions between the HPHC in the new and predicate products known, a constituent-based additive approach can be applied. This is consistent with the available guidance for the risk assessment of constituent mixtures available from US and international scientific bodies and regulatory agencies and is likewise consistent with the approach for environmental site assessments.

5. Conclusions

In this evaluation, application of QRA approaches used in the environmental setting for regulatory decision making has been demonstrated for use with tobacco products in the context of SE evaluations. The information presented herein has demonstrated how the available methodology and equations recommended by USEPA for environmental site risk assessment, with some minor adjustments, can be utilized for performing a QRA for tobacco products. Further, this has demonstrated the application of this methodology in the context of an SE evaluation of tobacco products. While certain steps involved in the process are slightly different due to differences in the media/product being evaluated, the overall methodology is similar. The consideration of these guidelines and the application of QRA into the tobacco submission process is important in an attempt to determine what changes constitute "different characteristics" or what changes constitute a new product raising different questions of public health. This information is of particular utility given, to date, the USFDA has not provided guidance on the use of QRA for the assessment of tobacco products, even though it has conducted a QRA in the context of an SE (USFDA, 2013) using similar methods and guidelines discussed.

QRA should be considered one useful component of the SE application which can play a role in addressing the question of whether the new product potentially raises different questions of public health. As described in USFDA (2011a), additional information related to the design features, ingredients, materials, heating source, composition, and "other features" of the products is also recommended, as well as, the USFDA concerns raised in Section B of USFDA (2011a) regarding consumer perception studies, clinical data, and abuse liability.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2018.03.026.

Transparency document

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