A Framework for Toxicological Risk Assessment of Combustible Tobacco Products in the Substantial Equivalence Pathway

Kimberly Ehman, PhD, DABT

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Objective and Overview

- Objective:
  - To provide an overview of a toxicological risk assessment approach that applies to evaluation of combustible products to demonstrate that a New Product is substantially equivalent

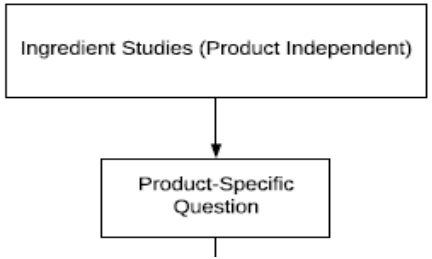
- Overview:
  - Types of product-specific questions that trigger risk assessment in the SE pathway
  - Exposure assumptions for cigarettes and cigars
  - Applicability of Occupational Exposure Limits (OELs) and a Threshold of Toxicological Concern (TTC) to evaluate potential risk
    - 2 cases studies
  - Key takeaways

Risk = Hazard x Exposure

- Hazard ≠ Risk
- Need to understand exposure

Source: Bayer/ECPA

Applicability of Risk Assessment in the Substantial Equivalence Pathway



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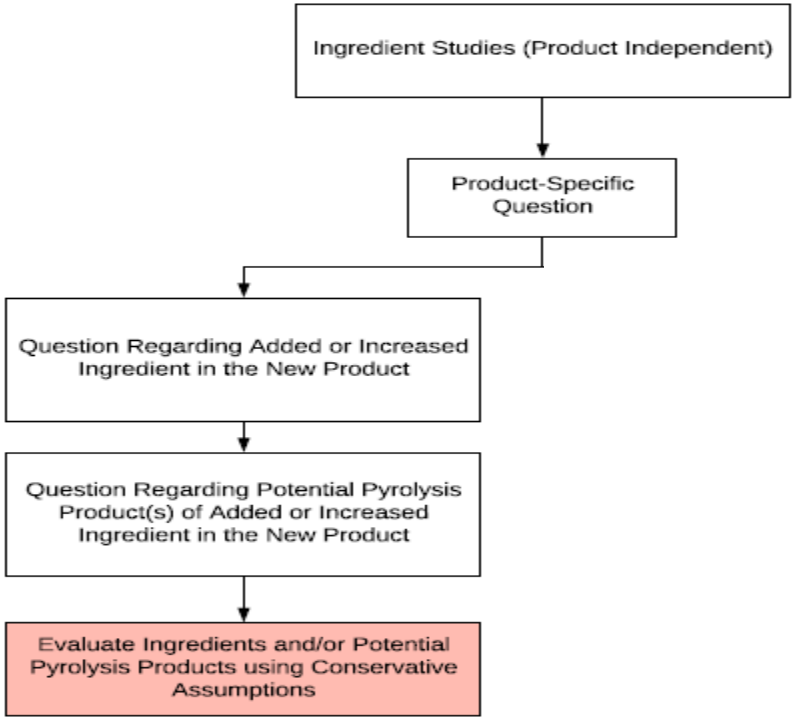

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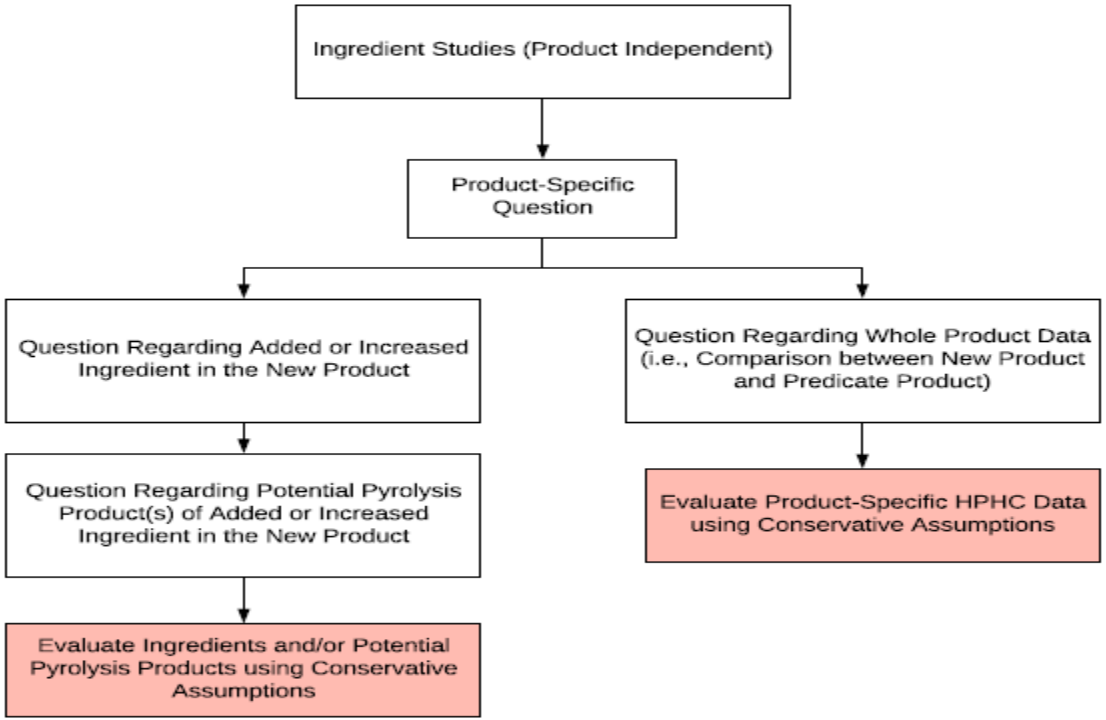

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Exposure Assumptions are Conservative

Added or Increased Ingredients or Potential Pyrolysis Products
• Assume 40 cigarettes/day[a]   • 14.1 cigarettes/day is current CDC estimate[b] • Assume 5 cigars/day[c]
• Assume 20-100% transfer of chemical into smoke[d-f]
• 100% absorption in lung

[a]Waingrow et al., 1968
[b]CDC, 2018
[c]ALCS CATTS 3.0 tracking study for current adult large mass cigar consumers and for those who report daily use (12 month average); only about 18% of consumers report daily cigar use
[d]Green et al., 1989
[e]Von Holt et al., 1999
[f]Purkis et al., 2011

Exposure Assumptions are Conservative

Added or Increased Ingredients or Potential Pyrolysis Products	Product-Specific HPHCs

• Assume 40 cigarettes/day[a]
  • 14.1 cigarettes/day is current CDC estimate[b]
• Assume 5 cigars/day[c]
	• Assume 40 cigarettes/day[a]
	  • 14.1 cigarettes/day is current CDC estimate[b]
	• Assume 5 cigars/day[c]

• Assume 20-100% transfer of chemical into smoke[d-f]	• Assume exposure to 100% of measured analyte (e.g., µg/cigarette)
• 100% absorption in lung	• 100% absorption in lung

[a]Waingrow et al., 1968
[b]CDC, 2018
[c]ALCS CATTS 3.0 tracking study for current adult large mass cigar consumers and for those who report daily use (12 month average); only about 18% of consumers report daily cigar use
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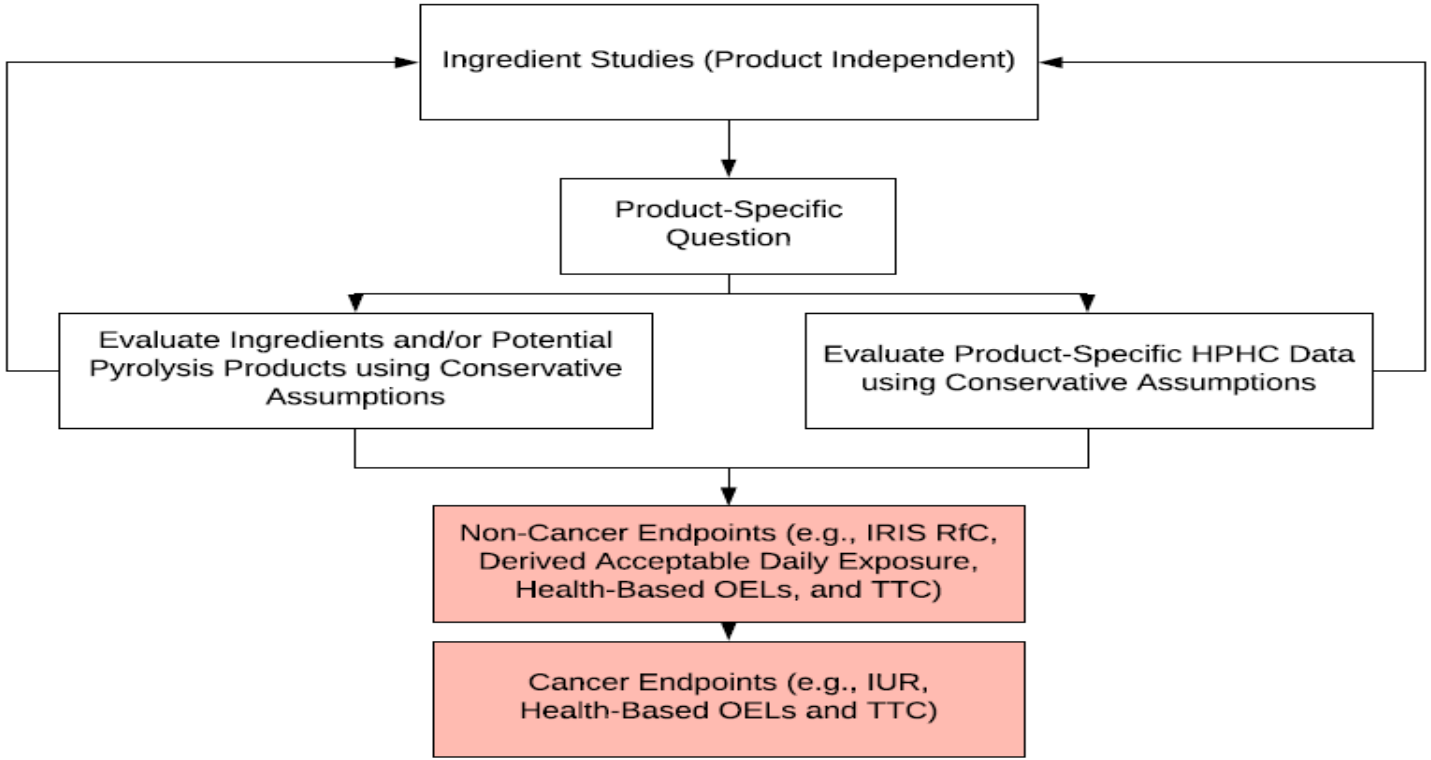
Risk Characterization

- Integration of hazard assessment, dose-response data and exposure assessment to determine likelihood that an identified chemical is going to introduce risk into the exposed population

- Identification of acceptable daily exposures
  - Literature search (e.g., IRIS, NTP, ECHA, OECD SIDS, ACGIH)
    - IRIS values (RfC and IUR)
    - Derived acceptable daily exposures
    - Health-based Occupational Exposure Limits (OELs)
    - Threshold of Toxicological Concern (TTC)
      - Widely accepted across regulated industries: food/beverage, cosmetics, personal care products, medical devices, pharmaceutical impurities

Risk Characterization – Overview of Process



Risk Characterization – Application of Health-Based OELs

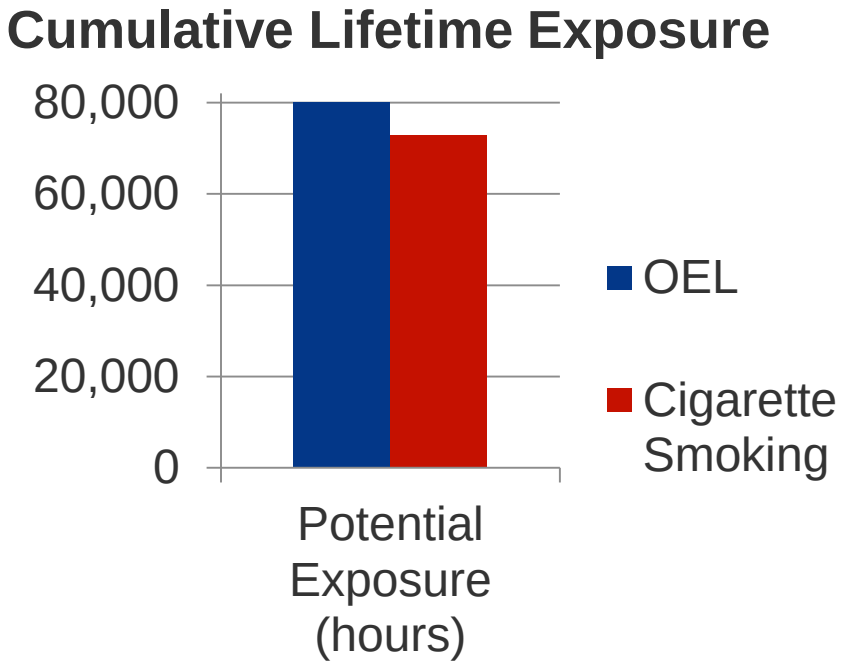
- Risk assessments performed by external organizations that take into account all available toxicological, medical, biological and chemical information
- Not based on economic or technical feasibility
- Specific to the inhalation route of exposure
- Assumes 8 hours of continuous exposure daily (5 days/week) for a working lifetime of 40 years
  - Time-weighted average reflective of episodic exposure
  - Inhalation rate assumption is higher (10 m^3 per 8 hrs) compared to EPA assumptions of 20 m^3 for 24 hours
- Represents a lifetime exposure without adverse health effects

Chebekoue and Krishnana, 2017; Dankovic et al., 2015

Risk Characterization – OELs Provide a Conservative Comparison

OEL: Assume 50 wks/year

Smoking: Assume 40 cigarettes/day, 5 min/cigarette, 7 days/wk, 52 wks/yr for 60 yrs



TTC Overview: Two Categories

- Non-genotoxic chemicals
  - TTCs based on frequency distributions (5th percentile) of NOEL or NOAEL divided by an uncertainty factor of 100 (Kroes et al., 2000, 2004)
    - Cramer Classes:
      - Class I: 1800 µg/day
      - Class II: 540 µg/day
      - Class III: 90 µg/day

- Genotoxic chemicals
  - TTC based on predicted tumor risk derived through an analysis of genotoxic chemicals in Carcinogenic Potency Database (CPDB; Gold et al., 1989)
  - 1.5 µg/day corresponds to 1 in 100,000 excess lifetime risk of cancer (ICH, 2014)
    - Represents a small theoretical increase in risk when compared to human overall lifetime incidence of developing any type of cancer, which is greater than 30%
      - 0.30000 vs 0.30001

Risk Characterization – Application of an Inhalation TTC

- TTC is a risk assessment tool based on the principle of establishing a human exposure threshold below which there is a very low probability of appreciable risk to human health (Kroes et al., 2000 and 2004)

- **1.5 µg/day** is used across regulated industries as an acceptable level for lifetime exposures (70 years) to chemicals, including mutagenic compounds (Kroes et al., 2004; Munro et al., 2008; ICH, 2014; ISO, 2017)

- 1.5 µg/day is applicable to **all routes of exposure**, including inhalation (ICH, 2014; ISO, 2017)

Risk Characterization – Application of an Inhalation TTC

Summary of Derived TTC Values Applicable to Inhalation

Publication	Route of Exposure	Type	Unit	Derived TTC for Cramer Class		TTC for Chemicals with a Structural Alert for Genotoxicity
				1	3	
Munro et al. 1996	Oral	Systemic	µg/person/day	1800	90	TTC for carcinogenicity not derived; however, dataset did include both genotoxic and non-genotoxic compounds
Carthew et al. 2009	Inhalation	Systemic	µg/person/day	980	170	Genotoxic carcinogens and *in vivo* mutagens excluded from derivation
Carthew et al. 2009	Inhalation	Local	µg/person/day	1400	470[A]	
Escher et al. 2010[B]	Inhalation	Systemic	µg/person/day	180 (71)	4 (4)	Lower TTC values in ( ) reflect inclusion of genotoxic chemicals in dataset used to derive TTC
ICH, 2014	All routes, including inhalation	Systemic	µg/person/day	NA	NA	1.5[C]
Tluczkiewicz et al., 2016	Inhalation	Systemic	µg/person/day	4260	2	Dataset included compounds with structural alerts for genotoxicity
ISO 18562-1, 2017	Inhalation	Systemic	µg/person/day	NA	NA	1.5[D]

[A] This reflects a TTC for local effects using a human lung weight of 650 g.
[B] Assuming 24h/d and 7d/week exposure; ( ) indicates TTC derived with genotoxic compounds included.
[C] Exposure limit for chemicals with structural alerts for genotoxicity and assuming daily exposure over a lifetime; regulatory value accepted for mutagenic impurities in pharmaceuticals.
[D] Exposure limit for leachable chemicals from medical devices that will contact a patient via the inhalation pathway; regulatory value accepted for medical devices with a breathing gas pathway exposure.

Case Studies

- Example 1
  - **Multiple compounds**
    - Product-specific question related to components of an adhesive added to the New Product
    - Applied conservative exposure assumptions
    - Compared to TTC of 1.5 µg/day

- Example 2
  - **Propylene Oxide**
    - Product-specific question related to potential pyrolysis product of propylene glycol
    - Applied conservative exposure assumptions to product-specific HPHC yield
    - Compared yield in New Product and Predicate Product to a health-based OEL

Example 1 - Application of TTC

- Specific questions related to components of an adhesive in a New Product

Chemical	Weight in Product (mg/product)	Estimated Daily Exposure (µg/day)[a]
(benzyloxy)methanol	0.00002	0.16
2-butylaminoethanol	0.0000008	0.0064
Ethanolamine	0.00005	0.4

[a]Hypothetical data not representative of an actual product

Estimated Daily Exposure (µg/day) = mg/product x 1000 µg/mg x 40 cigarettes/day x 20% transfer to smoke x 100% absorption in lung

- If estimated daily exposure to ingredient is < 1.5 µg/day, then no further evaluation is necessary for component or its potential pyrolysis products
- The TTC of 1.5 µg/day is applicable to the inhalation route of exposure and protective for lifetime exposure to mutagenic compounds
- **Conclusion**: The presence of these ingredients does not increase the toxicity of the New Product compared to the inherent toxicity of combustible tobacco products, including the Predicate Product

Product-Specific HPHC Data

ISO and CI HPHC Yields for the New Product and the Predicate Product

Smoke Constituent	Unit of Measure	ISO Smoking Regimen				CI Smoking Regimen			
		New Product		Predicate Product		New Product		Predicate Product	
		Average	StdDev	Average	StdDev	Average	StdDev	Average	StdDev
Acetaldehyde	µg/cig	680	86	730	668	1476	87	1637	76
Acrolein	µg/cig	78.9	8.9	81.5	10.9	174	14.3	190	7.7
Benzene	µg/cig	49.4	1.6	52.2	1.6	109	2.2	108	5.1
1,3-Butadiene	µg/cig	50.2	2.2	51.6	2.4	110	4.5	115	5.3
Propylene Oxide	ng/cig	776	136	749	145	2686	344	2020	302

[a]Hypothetical data not representative of an actual product

- HPHC data are reviewed in conjunction with analytical variability information (e.g., reproducibility and repeatability for the smoke constituent), literature, and reference cigarette data to determine if values are within the analytical variability for the method

Example 2: Propylene Oxide - Application of Health-Based OEL

- Potential daily exposure to Propylene Oxide
  - New product (2.69 µg/cigarette x 40 cigarettes = 107.6 µg/day)
  - Predicate product (2.02 µg/day x 40 cigarettes = 80.8 µg/day)

- OEL = $\frac{4.8\ mg}{m^3}$
  - Equal to 48 mg/day (convert using 10 m^3 for 8-hr exposure)
  - OEL is protective for increases in cell proliferation and carcinogenic risk

	Estimated Daily Exposure to Propylene Oxide (mg/day)	Comparison to OEL (48 mg/day) for Daily Lifetime Exposure
New Product	0.11 mg/day	436x lower
Predicate Product	0.08 mg/day	600x lower

- **Conclusion**: The small increase in propylene oxide detected in HPHC testing for in the New Product would not increase the toxicity of the New Product compared to the inherent toxicity of combustible tobacco products, including the Predicate Product

Considerations with Product-Specific HPHC Data

- Variability
  - Analytical and manufacturing
  - Cigar variability is expected to be even greater than cigarettes

- HPHC difference should not be attributed to a change in a single ingredient
  - Predicate Product versus New Product comparisons are not designed to isolate contribution of single ingredient on overall smoke yields

Key Takeaways

- Combustible tobacco products are inherently toxic
- Ingredient studies in the literature demonstrate that ingredients do not significantly impact the chemical or toxicological nature of smoke
- Standard toxicological approaches are appropriate to evaluate product-specific questions, including health-based OELs and TTC
- Taken together, these methodologies provide a conservative approach to evaluating new or added ingredients in combustible tobacco products

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