



Sensitivity analysis of exposure parameters in quantitative risk assessment for substantial equivalence evaluation

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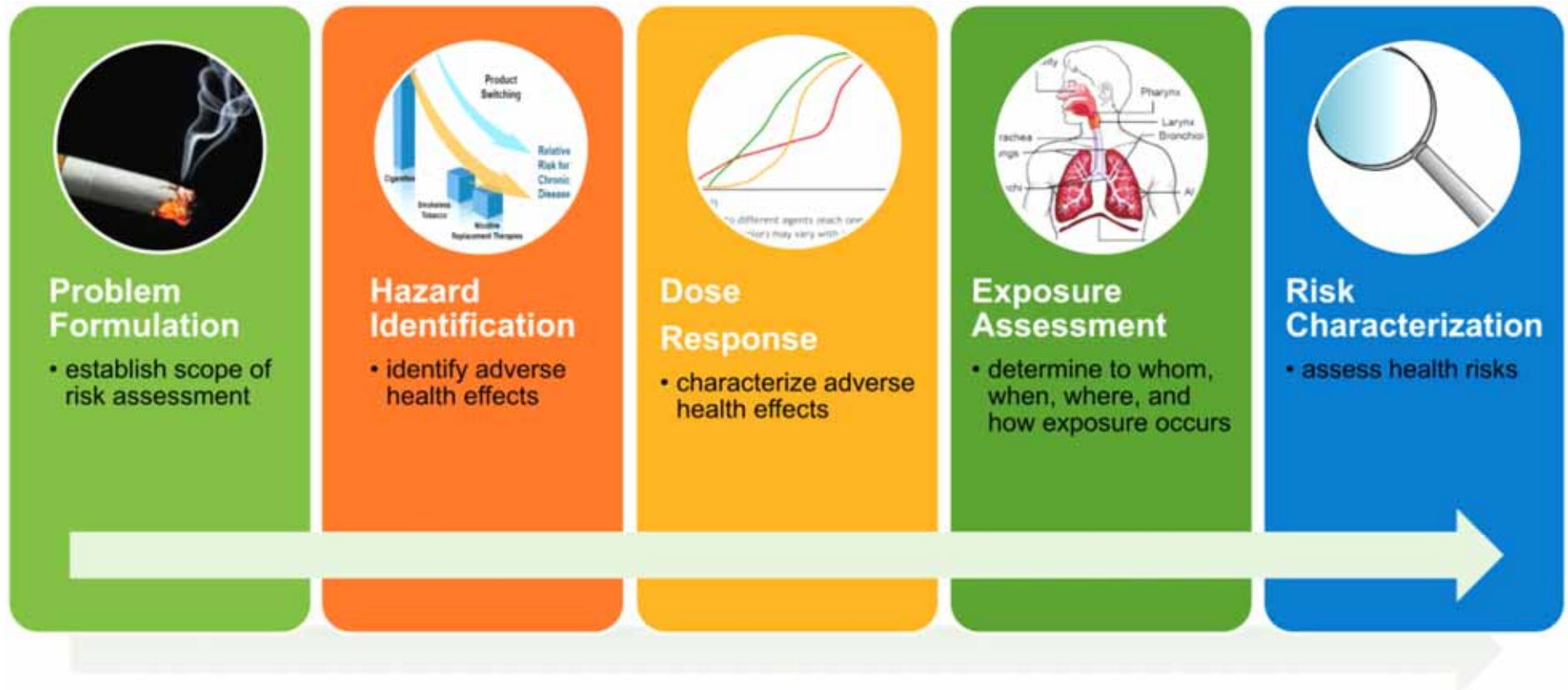
Introduction

- New tobacco products cannot be legally marketed in the US unless the Food and Drug Administration (FDA) has issued an order permitting their marketing.
- A substantially equivalent (SE) tobacco product is defined as a product that has been found by FDA to either have the same characteristics as a predicate tobacco product, or has different characteristics than the predicate but the information submitted demonstrates that the new product does not raise different questions of public health.

Introduction

- Quantitative Risk Assessment (QRA) is a five step process that can provide a useful and efficient approach to address questions regarding human health risk and potential impact of tobacco products on public health.
- QRA can be used to evaluate differences in harmful and potentially harmful constituents (HPHC) in the determination of whether a new product possibly raises different questions of public health.

Risk Assessment Process



Purpose

- Evaluate the impact of exposure parameters (e.g. consumption rate, body weight, lifespan) on estimated long-term health risks of combustible cigarettes and smokeless tobacco products in the context of SE evaluations.
- Present multiple cases comparing new and predicate products (combustible and smokeless)

US FDA Abbreviated List of Harmful and Potentially Harmful Constituents (HPHCs)¹

Constituent	Cigarette Smoke	Smokeless Tobacco	Constituent	Cigarette Smoke	Smokeless Tobacco
Acetaldehyde	√	√	1,3-butadiene	√	
Acrolein	√		Cadmium		√
Acrylonitrile	√		Carbon Monoxide	√	
1-aminonaphthalene	√		Crotonaldehyde	√	√
2-aminonaphthalene	√		Formaldehyde	√	√
4-aminobiphenyl	√		Isoprene	√	
Ammonia	√		Nicotine	√	√
Arsenic		√	NNK	√	√
Benzene	√		NNN	√	√
Benzo[a]pyrene	√	√	Toluene	√	

¹FDA. 2012. Draft Guidance for Industry Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act.

Data Sources

- US Centers for Disease Control and Prevention (CDC)
- National Health Interview Survey (NHIS)
- 1999-2016 National Health and Nutrition Examination Survey (NHANES)
- US Environmental Protection Agency (USEPA)
- US FDA recommended values
- Peer-reviewed literature

Exposure Parameters Change over Time

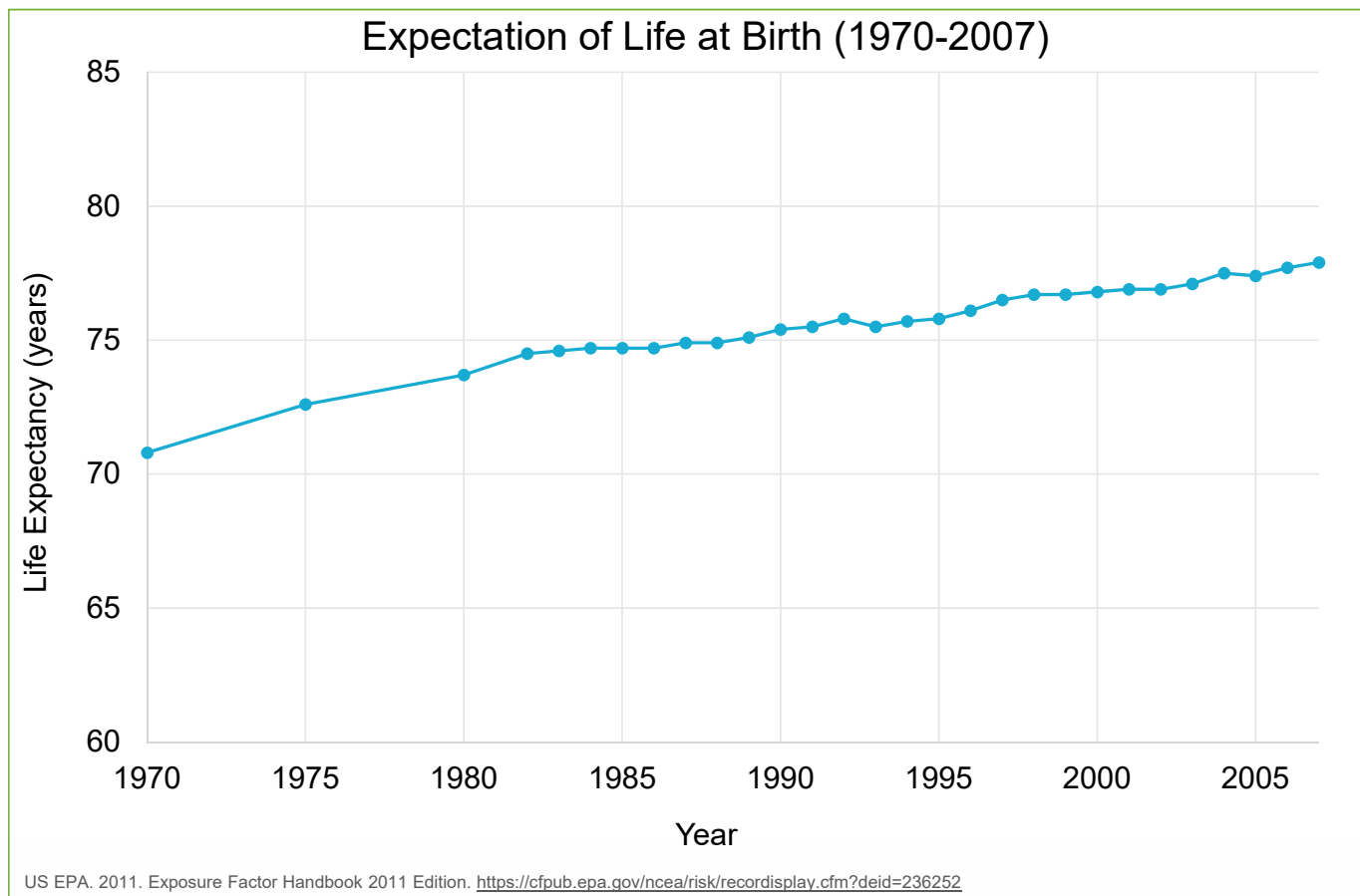
- Consumption Rate (cigarettes per day^a; smokeless tobacco, g/day^b)
- Body Weight (kg) ^{a,c}
- Lifespan (years) ^c

^aNHANES 1999-2016

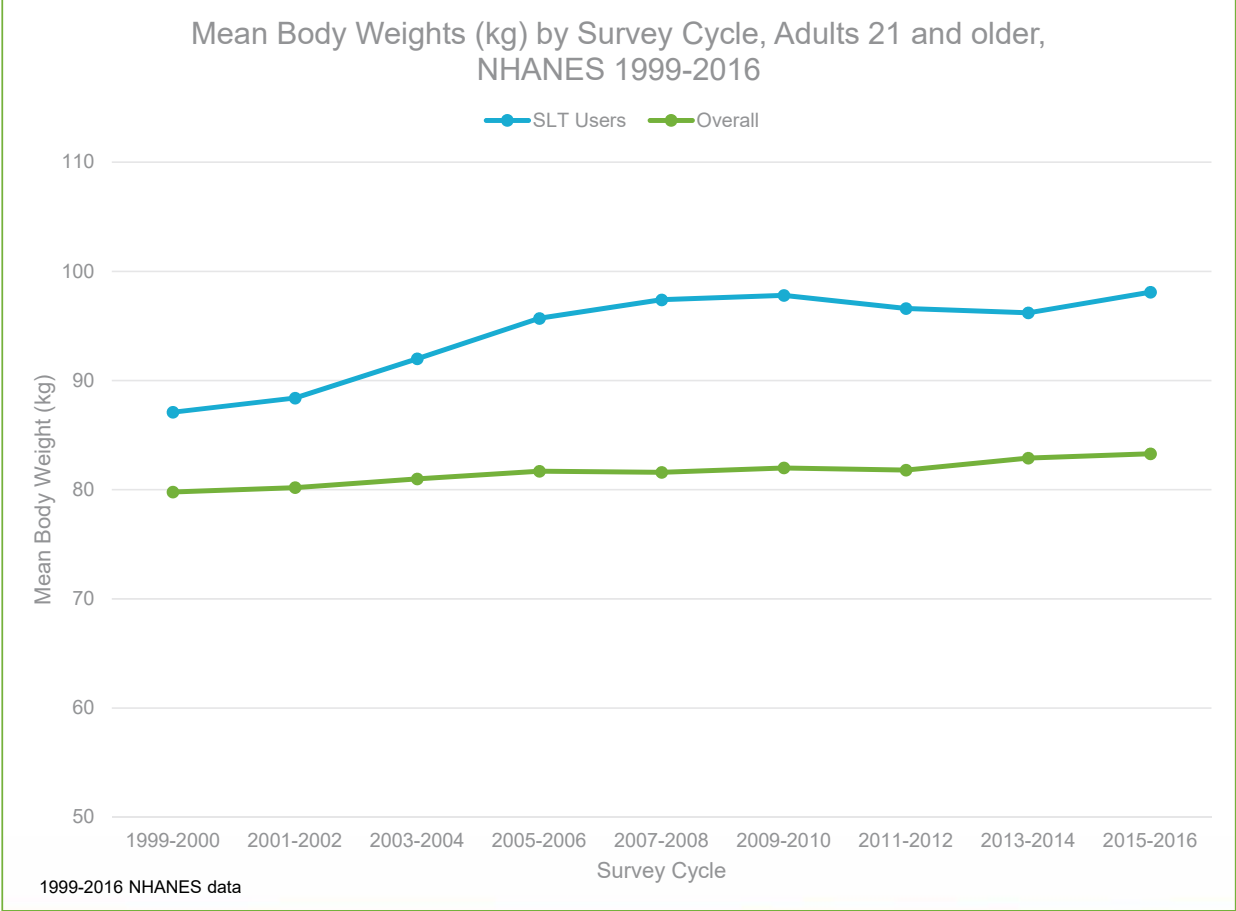
^bDigard 2009; Hatsukami 1988; FDA 2014, 2017

^cUSEPA Exposure Handbook, 2011

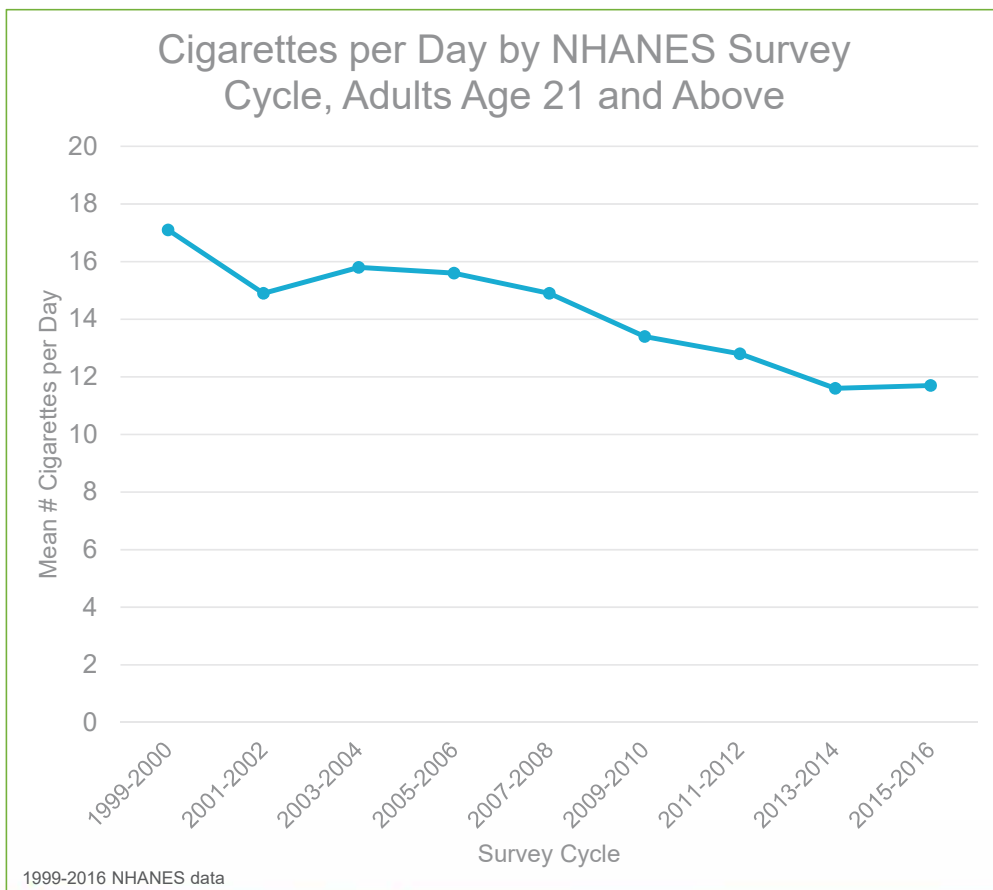
Changes in Exposure Assumptions - Lifespan



Changes in Exposure Assumptions – Body Weight



Changes in Exposure Assumptions – Consumption Rate

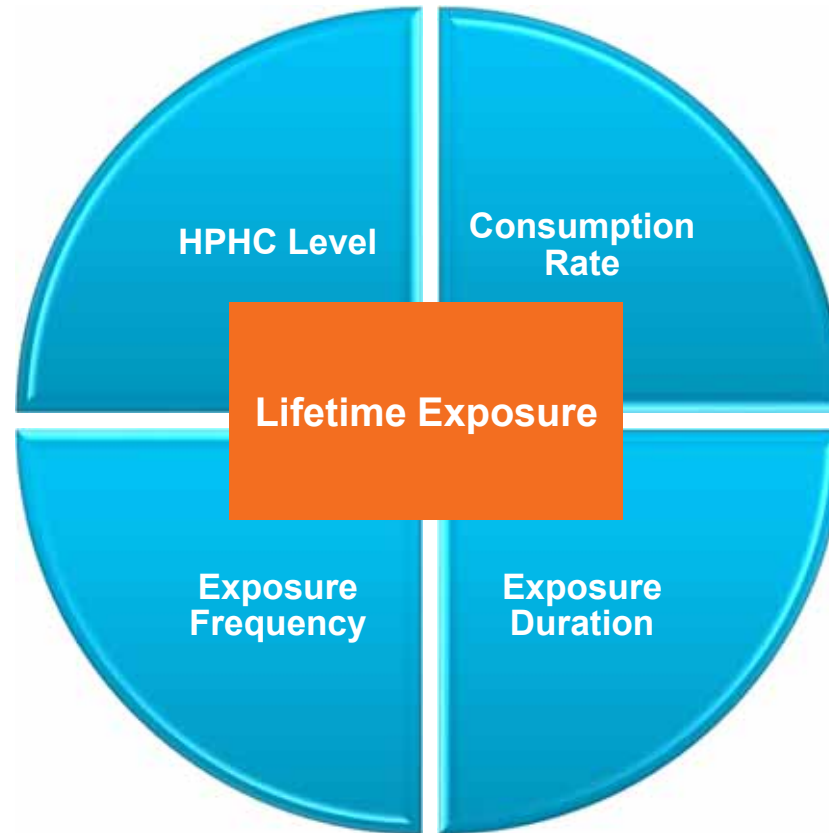


Smokeless Tobacco Consumption

Mean 12 g/day, 95th percentile 24 g/day*

*Digard 2009; Hatsukami 1988; FDA 2017

Exposure Assessment



Exposure Estimates

- Exposure Concentration (EC) for Cigarettes

$$EC\left(\frac{\mu g}{m^3}\right) = \frac{C \times \mathbf{CpD} \times EF \times ED}{AT \times Inh}$$

- Estimated Daily Intake (DI) for Smokeless Tobacco Products

$$DI\left(\frac{\mu g}{kg-day}\right) = \frac{C \times TC \times EF \times ED}{AT \times BW}$$

C – constituent concentration
CpD – cigarettes per day
EF – exposure frequency
ED – exposure duration
AT – averaging time
Inh – inhalation rate
TC – tobacco consumption rate
BW – body weight



Results

Impact of Cigarettes per Day on Risk Estimates

Cigarettes per Day ^a	Noncancer Hazard Index		Excess Lifetime Cancer Risk	
	New Product	Predicate Product	New Product	Predicate Product
14	60	60	4E-03	4E-03
20	100	100	7E-03	7E-03
40	200	200	1E-02	1E-02

^aCDC. 2014. Morbidity and Mortality Weekly Report. 63(47), 1108-1112.

Impact of Smokeless Tobacco Consumption Rate on Risk Estimates

Consumption Rate ^a (gram/day)	Noncancer Hazard Index		Excess Lifetime Cancer Risk	
	New Product	Predicate Product	New Product	Predicate Product
12 (Mean)	2E-01	2E-01	1E-03	1E-03
24 (95th Percentile)	4E-01	4E-01	3E-03	3E-03

^aDigard H. et al. 2009. Patterns and behaviors of snus consumption in Sweden. *Nicotine Tob Res.* 11(10):1175-81.

Impact of Body Weight on Smokeless Tobacco Risk Estimates

Body Weight (kilogram)	Noncancer Hazard Index		Excess Lifetime Cancer Risk	
	New Product	Predicate Product	New Product	Predicate Product
70 ^a	4E-01	3E-01	2E-03	2E-03
80 ^b	4E-01	3E-01	2E-03	2E-03
97 ^c	3E-01	2E-01	2E-03	2E-03

^aEPA. 1997. Exposure Factor Handbook

^bEPA. 2014. OSWER Directive 9200.1-120. Memorandum, Human Health Evaluation Manual, Supplemental Guidance, Update of Standard Default Exposure Factors.

^c1999-2016 National Health and Nutrition Examination Survey (NHANES) data.

Impact of Lifespan on Risk Estimates

Life Span (years)	Noncancer Hazard Index		Excess Lifetime Cancer Risk	
	New Product	Predicate Product	New Product	Predicate Product
70 ^{a,b}	100	100	7E-03	7E-03
78 ^c	100	100	7E-03	7E-03

^aEPA. 1997. Exposure Factor Handbook

^bEPA. 2014. OSWER Directive 9200.1-120. Memorandum, Human Health Evaluation Manual, Supplemental Guidance, Update of Standard Default Exposure Factors.

^cEPA. 2011. Exposure Factor Handbook, 2011 Edition.

Conclusions

- Tobacco consumption rates exert the most influence on estimated long-term health risks from exposure to HPHCs in tobacco products. However, the impact from consumption rate affects both new and predicate products equally.
- Recent updates of body weight (i.e. 80 vs. 70 kg) and lifespan values (78 vs. 70 years) have minimal impact on predicted long-term health risks of tobacco users compared to previously recommended values.

Conclusions

- Given the comparative assessment of risk between the new and corresponding predicate products in the context of an SE evaluation, use of various values for parameters such as product use rate, body weight, and lifespan when used uniformly for product comparisons will not affect the final comparison between the new and predicate products

Strengths

- QRA provides a practical approach to address public health questions in the context of Substantial Equivalence of tobacco products.
- These data sources are publically available, study can be replicated.
- Survey data are representative of the non-institutionalized, civilian US population.

Limitations

- Survey data (i.e. CpD estimates) are self-reported and may be subject to recall bias.
- Body weight and lifespan data are limited to general population. Lack of user-specific data.
- Further studies and analyses of smokeless tobacco consumption measures are warranted.

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