# QUANTITATIVE RISK ASSESSMENT OF TOBACCO PRODUCTS IN SUBSTANTIAL EQUIVALENCE EVALUATIONS

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# OUTLINE

- Discuss Quantitative Risk Assessment (QRA) approach used to assess public health impact from constituents present in the environment and consumer products
- Demonstrate similarity and applicability of QRA approach for environmental and tobacco products assessment via comparison
- Demonstrate acceptance of QRA approach across regulatory agencies/authoritative bodies for use in decision making

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# WHAT IS QUANTITATIVE RISK ASSESSMENT (QRA)?

- 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.
- QRA has been noted by the National Research Council (NRC 2008) as an essential component for regulatory decision-making.
- Used by governmental and regulatory bodies (e.g., US Environmental Protection Agency, US Occupational Safety and Health Administration, US Food and Drug Administration) to inform decisions about environmental, occupational, biological, and consumer product risks to human health.

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# SUBSTANTIAL EQUIVALENCE (SE) EVALUATIONS

- One of the pathways per Family Smoking Prevention and Tobacco Control Act of 2009 for marketing new tobacco products
- Evaluate if new product is substantially equivalent to predicate product (i.e., was commercially marketed in US as of Feb. 15, 2007)
  - new product has same characteristics as predicate product
  - new product has different characteristics as predicate product but does not raise different questions of public health

Concentration of Harmful or Potentially Harmful Constituent (HPHC) in new product may increase or decrease in comparison to the predicate product.

Can QRA be used to address differences in HPHC and different questions of public health?

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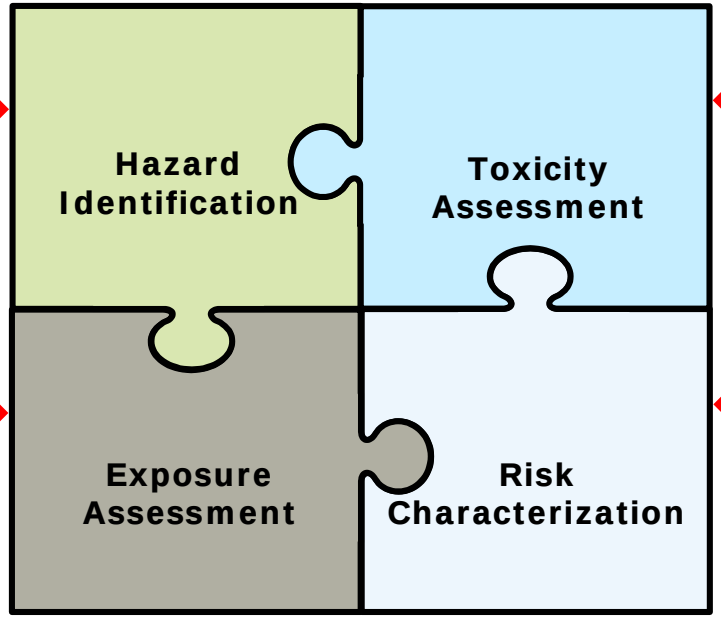
# QRA PROCESS

What adverse health effect(s) are associated with the chemical(s) of concern?




How much of the chemical(s) does it take to cause the adverse biological effect?

To how much of the chemical(s) and by what routes are individuals exposed?

What is the risk (probability) of toxicity occurring in the exposed population?

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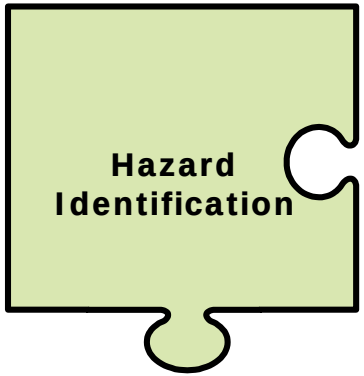
# QRA PROCESS

## Environmental

- Potential chemicals of concern (COC) defined by USEPA
- List of COCs that are representative of classes of compounds expected to be present and that have appropriate toxicity data




## Tobacco Products

- Harmful and Potentially Harmful Constituents (HPHCs) defined by USFDA
- List of HPHCs that are representative of classes of compounds present and that have appropriate toxicity data

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# HAZARD IDENTIFICATION

- Environmental – US EPA
  - List of COC driven by chemicals expected to be present based on activities and/or operations at site of interest
- Tobacco products – US FDA
  - List of 93 HPHCs in tobacco products and tobacco smoke, established 2012
  - Each HPHC characterized as carcinogen, cardiovascular toxicant, respiratory toxicant, or reproductive/developmental toxicant
  - Abbreviated list focused on those for which testing and analytic methods are well established and widely available, that represent several different chemical classes, and constitute a representative sample of the established list of 93

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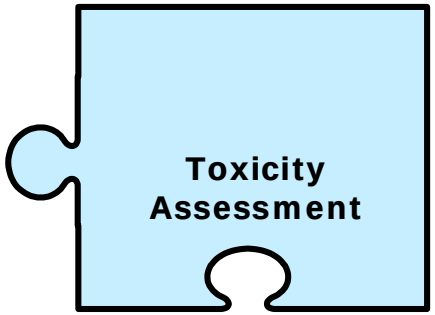
# QRA PROCESS

## Environmental

- Identification of safe exposure dose for COC
- Based on a hierarchy of toxicity information
- Use toxicity for most sensitive endpoint




## Tobacco Products

- Identification of safe exposure dose for HPHC
- Based on a hierarchy of well-documented toxicity information
- Use toxicity for most sensitive endpoint

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# TOXICITY ASSESSMENT

- Factors developed based on most sensitive endpoint
- Cancer
  - US EPA provides estimates of extra lifetime cancer risk, defined as the probability of developing cancer after a lifetime of continuous exposure at a specified intake
  - Inhalation – Inhalation Unit Risk (IUR) in per µg/$m^3$
  - Oral – Cancer Slope Factor (CSF) in per mg/kg/day
- Noncancer
  - US EPA provides estimates (typically based on animal data, with an uncertainty spanning an order of magnitude) of a daily intake for human populations, including sensitive subpopulations, that is unlikely to result in adverse noncancer health effects
  - Inhalation – Reference Concentration (RfC) in mg/$m^3$
  - Oral – Reference Dose (RfD) in mg/kg/day

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# POTENTIAL SOURCES OF TOXICITY INFORMATION

- USEPA's Integrated Risk Information System (IRIS)
- Other regulatory agencies [e.g. California Environmental Protection Agency (CalEPA), Texas Commission for Environmental Quality (TCEQ), Agency for Toxic Substances and Disease Registry (ATSDR)]
- Peer-reviewed literature
- Use surrogate or develop toxicity values when appropriate

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# QRA PROCESS

## Environmental

- Quantify extent, frequency, and duration of exposure
- Depends upon media and receptor (e.g., a resident's exposure to soil)


## Tobacco Products

- Quantify extent, frequency, and duration of exposure
- Depends upon media and receptor (i.e., product use and user)

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# EXPOSURE EQUATIONS

## USEPA (2009) RAGS Part F equation for Exposure Concentration

$$EC_{(\mu g/m^3)} = \frac{Ca \times EF \times ED}{AT}$$

$$Ca = \frac{C \times Cpi}{IR}$$

Measured air concentration or estimated from soil/groundwater. Must estimate for evaluation of exposure from smoking.

HPHC yield (µg/cig)

Cigarettes smoked (cig/day)

Inhalation rate (m³/day)

Where: Ca – constituent concentration (µg/m³)
EF – exposure frequency (days/yr)
ED – exposure duration (yr)
AT – averaging time (days)

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# EXPOSURE EQUATIONS

## USEPA (2009) RAGS Part F equation for Exposure Concentration

$$EC\,(\mu g/m^3) = \frac{Ca \times EF \times ED}{AT}$$

$$Ca = \frac{C \times CpD}{IR}$$

Where: Ca – constituent concentration (µg/m$^3$)
EF – exposure frequency (days/yr)
ED – exposure duration (yr)
AT – averaging time (days)

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# EXPOSURE EQUATIONS

## Exposure Equation for Combustible Products

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

Where: C – HPHC yield (µg/cig)
CpD – cigarettes smoked (cig/day)
EF – exposure frequency (days/yr)
ED – exposure duration (yr)
IR – inhalation rate ($m^3$/day)
AT – averaging time (days)

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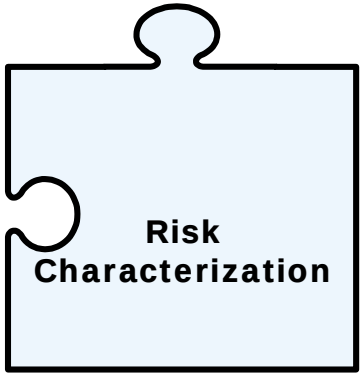
# QRA PROCESS

## Environmental

- 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




## Tobacco Products

- Adverse health impact due to exposure to HPHCs estimated based on combination of toxicity and exposure
- Comparison of risks and hazards between new vs. predicate compared incorporating potential variability and uncertainty
- Additivity preferred approach for summation of risk or hazard estimate

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# ADDITIVE MODEL FOR MIXTURES

- Conservative approach assuming independence of action by the constituents involved (e.g., no synergistic or antagonistic effects)
- Conservative assumptions:
  - Slope factor for each carcinogenic constituent based on upper 95$^{th}$ percentile
  - Noncancer toxicity may be based upon NOAEL (no observed adverse effect level) approach
  - Constituents with different evidence of toxicity are included in sum
  - Factors for animal and human data given equal weight

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# ADDITIVE APPROACHES RECOMMENDED BY OTHER REGULATORY AGENCIES

- The simple addition of “combining risk which accounts for the joint probability of the same individual developing cancer as a consequence of exposure of two or more carcinogens” is considered appropriate. [USEPA 1989]
- “When evaluating predicted cancer risks from multiple contaminants, risk assessors should estimate the cancer risk for each substance and then sum these risks.” [USEPA 2009, Section 8.1.1 Cancer Risks, page 29]
- “Use 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.” (ATSDR 2004, page 10)
- “The guidance recommends use of dose addition for determining the combined risk of the CAG [cumulative assessment group].” (USEPA 2002, page iv)

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# ENVIRONMENTAL EXAMPLE

| Constituent | Estimated Risk | | | | | |
|---|---|---|---|---|---|---|
| | Baseline | | 5-year Review | | Risk Change (5-Year/Baseline) | |
| | Mean | UB | Mean | UB | Mean | UB |
| 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 | 6.3E-08 | 6.3E-08 | 6.3E-08 | 6.3E-08 | 1.0 | 1.0 |
| Benzo(a)pyrene | 6.3E-07 | 6.3E-07 | 6.3E-07 | 6.3E-07 | 1.0 | 1.0 |
| Benzo(b)fluoranthene | 6.3E-08 | 6.3E-08 | 6.3E-08 | 6.3E-08 | 1.0 | 1.0 |
| Benzo(k)fluoranthene | 6.3E-09 | 6.3E-09 | 6.3E-09 | 6.3E-09 | 1.0 | 1.0 |
| Dibenz(a,h)anthracene | 6.3E-07 | 6.3E-07 | 6.3E-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 | 9.0E-06 | 1.9E-05 | 4.9E-06 | 9.1E-06 | 0.5 | 0.5 |

Comparison of risk of 5-year review to Baseline.

Data presented in the table was randomly generated.

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# SUBSTANTIAL EQUIVALENCE COMPARISON EXAMPLE

| Constituent | Estimated Risk: Predicate Product Mean | Predicate Product UB | New Product Mean | New Product UB | Risk Change (New/Predicate) Mean | Risk Change (New/Predicate) UB |
|---|---|---|---|---|---|---|
| 1,3-Butadiene | 5.9E-06 | 1.6E-06 | 2.7E-06 | 3.2E-06 | 0.5 | 0.5 |
| 2-Aminonapthalene | 1.4E-06 | 9.7E-06 | 3.0E-06 | 3.6E-06 | 2.2 | 2.7 |
| Acetaldehyde | 2.3E-04 | 2.3E-04 | 2.2E-04 | 2.3E-04 | 0.9 | 1.0 |
| Acrylonitrile | 2.8E-04 | 1.0E-04 | 1.6E-04 | 1.7E-04 | 0.6 | 0.6 |
| Benzene | 1.6E-04 | 3.9E-05 | 6.5E-05 | 7.7E-05 | 0.4 | 0.5 |
| Benzo[a]pyrene | 5.2E-06 | 3.4E-06 | 4.1E-06 | 4.2E-06 | 0.8 | 0.8 |
| Formaldehyde | 4.2E-05 | 2.8E-05 | 3.3E-05 | 3.5E-05 | 0.8 | 0.8 |
| Isoprene | 3.4E-04 | 8.6E-04 | 5.1E-04 | 5.4E-04 | 1.5 | 1.6 |
| NNK | 1.3E-04 | 1.9E-04 | 1.4E-04 | 1.6E-04 | 1.0 | 1.2 |
| NNN | 1.8E-05 | 1.7E-05 | 1.7E-05 | 1.7E-05 | 0.9 | 1.0 |
| Total Estimated Risk | 1.2E-03 | 1.2E-03 | 1.1E-03 | 1.2E-03 | 0.9 | 1.0 |

Risk for New Product is the same or lower than Predicate Product

Data presented in the table was randomly generated.

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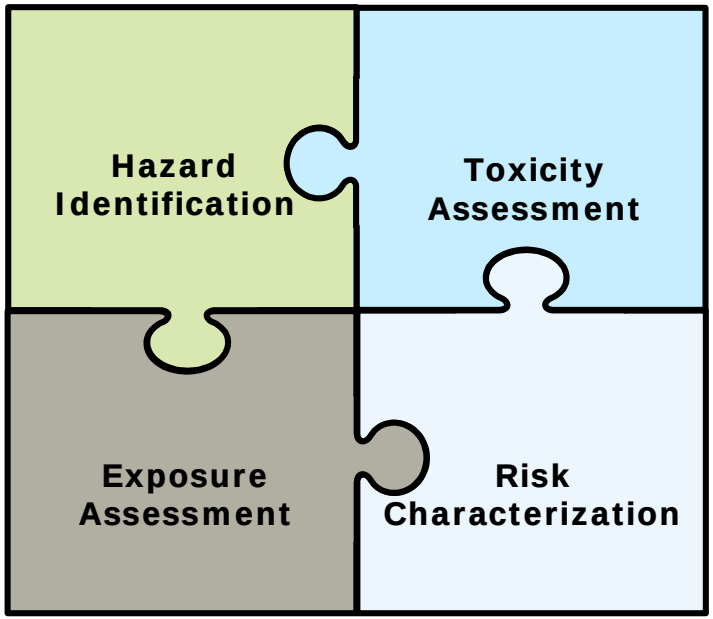
# REGULATORY DECISION-MAKING




- Integration of the steps to define the overall risk/hazard:
  - between products (tobacco)
  - impacted area versus regulatory measures (environmental)

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# CONCLUSIONS

- An approach that compares changes for the product as a whole, not just individual constituents, which is useful in addressing different questions of public health potentially associated with a new product.
- Consistent with approaches used by other regulatory agencies and authoritative bodies for decisions regarding public health.
- Provides a data-driven method for using the most appropriate available science, increasing the confidence and decreasing the uncertainty in the risk characterization for comparison across products.

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