Quantitative Risk Assessment to Compare Health Risks of Chemicals in Consumer Products

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What is Quantitative Risk Assessment (QRA)?

- A scientific, evidence-based process that utilizes known data to estimate risk.
- A method to identify relevant factors that influence risk.
- Used by government, industry, and research bodies to inform decisions about risk (e.g., financial, human health).

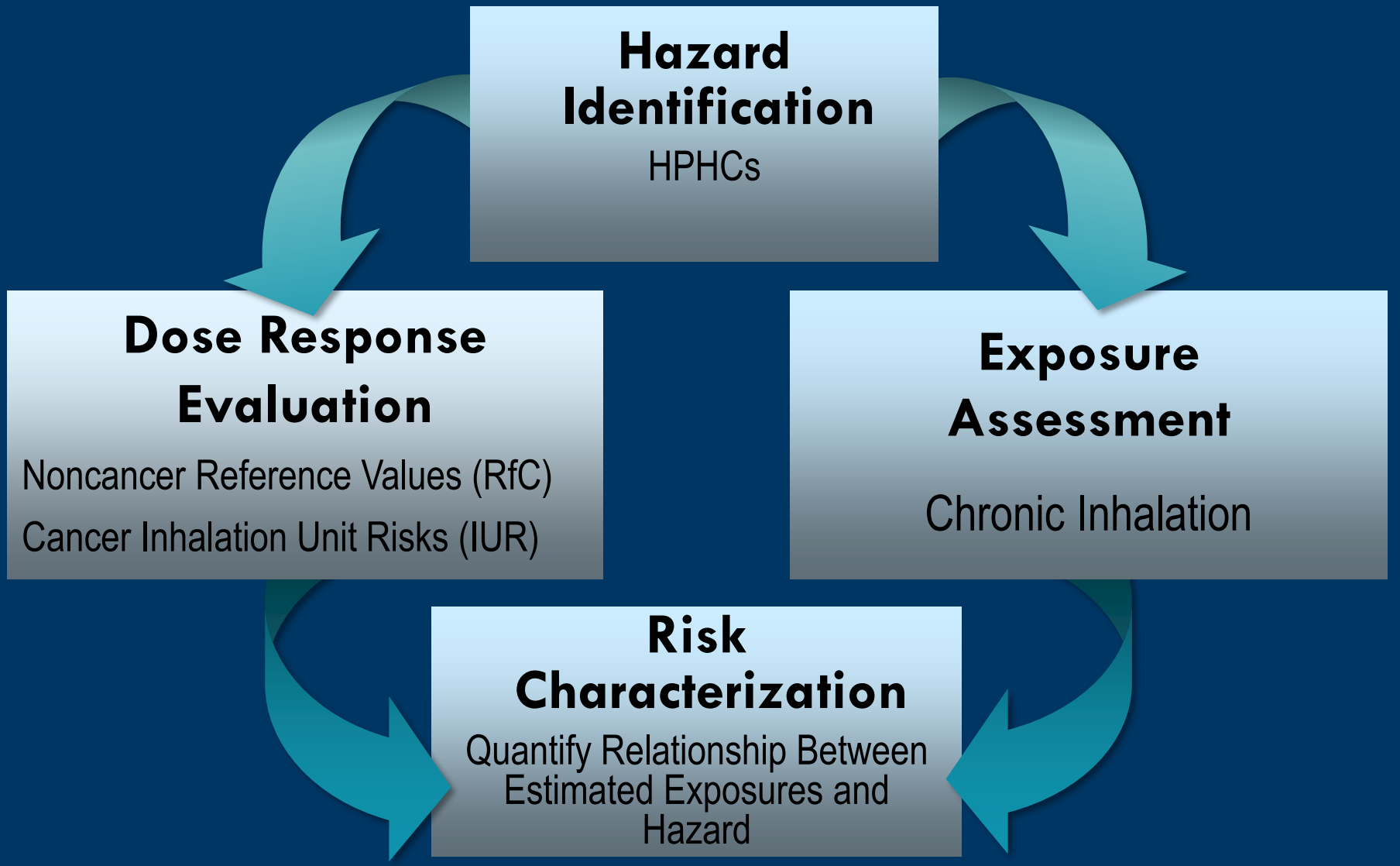
Health Risk Assessment Framework

- Hazard Identification
  - Identification of the adverse effects that a substance has an inherent capacity to cause.
- Dose-Response Evaluation
  - Estimation of the relationship between dose, or level of exposure to a substance and the incidence and severity of an effect.

Health Risk Assessment Framework

- Exposure Assessment
  - Estimation of the concentrations to which human populations (i.e. workers, consumers, or individuals indirectly via the environment) may be exposed.
- Risk Characterization
  - The estimation of the incidence and severity of the adverse effects likely to occur in a human population due to predicted exposure to a substance.

Risk Assessment Framework for Comparing Health Risks (e.g., Cigarettes)



Hazard Identification

- WHO, USEPA, OSHA, CPSC
  - Chemicals expected to be present in the environment, workplace, or in consumer products
- Tobacco products – US FDA
  - Abbreviated list of 18 HPHCs for which testing and analytic methods are well established and widely available, and that represent different chemical classes representative of the list of 93 HPHCs

Dose-Response Evaluation

- Noncancer
  - US EPA provides estimates 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
- 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 $\mu g/m^3$
  - Oral – Cancer Slope Factor (CSF) in per mg/kg/day

Exposure Assessment

- Measurement or estimation of the intensity, frequency, and duration of human exposures to the chemical(s).
- To estimate human exposure to HPHCs in tobacco products:
  - **HPHC Yield (µg/cigarette)**
  - **Cigarettes per Day**
  - **Exposure Duration**
  - **Exposure Frequency (days/year)**
  - **Inhalation Rate (m^3/day)**
  - **Averaging Time (days of exposure)**

Comparative Risk Assessment

Comparison of estimated noncancer and cancer health risks between two products.

Deterministic Quantitative Risk Assessment

- DQRA is a commonly used technique to evaluate estimated health risks associated with exposure to consumer products, workplace exposures, and environmental contaminants.
- Uses relatively simple mathematical models to produce point estimates of risk.

Probabilistic Risk Assessment

- PRA utilizes computerized software to perform mathematical analyses designed to identify, characterize, and quantify key factors affecting calculated risk probabilities.
- Model factors are represented by known data distributions (normal, exponential, etc.) rather than discrete points (e.g., 50^{th} or 95^{th} percentile).
- Includes a sensitivity analysis of model factor variance and overall rank order.

Probabilistic Risk Assessment

- Estimates the probability of risk based on the full-range of model inputs.
- Uncertainty and/or variability associated with exposure and/or hazard can be more thoroughly evaluated.
- Risk management options may be much more explicit and transparent.
- Provides for better-informed risk management decisions.

Hypothetical example of a DQRA/PRA comparative analysis of two cigarette products

Hazard Identification

Rank Order and Percent Difference in HPHC yields			
HCI HPHCs	**Mean Yield (µg/cig)**		**Yield Difference**
	Product A	**Product B**	
Acrolein	210	180	15%
Carbon monoxide	32,500	28,026	15%
Acetaldehyde	1,801	1,598	12%
Formaldehyde	78	72	8%
Benzo[a]pyrene	0.0021	0.002	5%
Crotonaldehyde	27	26	4%
Ammonia	26	27	-4%
4-Aminobiphenyl	0.003	0.0032	-6%
NNK	0.12	0.13	-9%
1,3-Butadiene	79	90	-13%
Benzene	89	102	-14%
Toluene	115	136	-17%
NNN	0.1	0.13	-26%
Isoprene	386	517	-29%
1-Aminonaphthalene	0.017	0.023	-30%
2-Aminonaphthalene	0.02	0.028	-33%
Acrylonitrile	18	26	-36%

Exposure Model (DQRA & PRA)

$$\boldsymbol{EC} = \frac{C\ x\ Cpd\ x\ ED\ x\ EF}{IR\ x\ AT}$$

Where,

EC = Exposure Concentration (µg/m^3)
C = HPHC Yield (µg/cigarette)
CpD = Cigarettes per Day
ED = Exposure Duration (years)
EF = Exposure Frequency (days/year)
IR = Inhalation Rate (m^3/day)
AT = Averaging Time (days of exposure)

Exposure Factors for QRA

Factor	Definition	Value	Reference
C	Mean HPHC yield (µg/cigarette)	Average Yield	Company Data
CpD	Cigarettes/day	20	USFDA 2013
ED	Exposure Duration (years)	57.5	USFDA 2013
EF	Exposure Frequency (days/year)	365	Conservative assumption of daily exposure
IR	Inhalation Rate (m^3/day)	20	USEPA 2009
AT	Averaging Time 57.5 years x 365 days	20,987	---

Risk Characterization
Noncancer Risk

$$HQ = EC \div RfC$$

Where,

HQ = Hazard Quotient (unit less)

EC = Exposure Concentration ($\mu g/m^3$)

RfC = Noncancer Toxicity Value ($\mu g/m^3$)

Risk Characterization
Cancer Risk

$$CR = EC \; x \; IUR$$

Where,

CR = Cancer Risk (unit less)

EC = Exposure Concentration ($\mu g/m^3$)

IUR = Inhalation Unit Risk ($\mu g/m^3$)

HPHC Noncancer and Cancer Inhalation Reference Values

HPHC	RfC, REL, ReV (mg/m^3)	Source	IUR $(\mu g/m^3)^{-1}$	Source
Acetaldehyde	1.4E-01	CalEPA 2008	2.7E-06	CalEPA 2011
Acrolein	2.7E-03	TCEQ 2016	NA	NA
Acrylonitrile	7.1E-03	TCEQ 2015	6.8E-05	USEPA 1991
4-Aminobiphenyl	NA	NA	6.00E-03	CalEPA 1992
1-Aminonaphthalene	NA	NA	5.14E-04	CalEPA 1992
2-Aminonaphthalene	NA	NA	5.14E-04	CalEPA 1992
Ammonia	5.0E-01	USEPA 2016	NA	NA
Benzene	3.0E-02	USEPA 2003	7.8E-06	USEPA 2000
Benzo(a)pyrene	NA	NA	6.0E-04	USEPA 2017
1,3-Butadiene	3.3E-02	TCEQ 2015	5.0E-07	TCEQ 2015
Carbon monoxide	7.0E+00	WHO 2010	NA	NA
Crotonaldehyde	NA	NA	4.8E-04[a]	DTSC 2018
Formaldehyde	1.1E-02	TCEQ 2015	6.0E-06	CalEPA 2011
Isoprene	NA	NA	2.2E-08	TCEQ 2018
NNK	NA	NA	5.2E-03[b]	Naufal et al. 2009
NNN	NA	NA	2.4E-04[c]	CalEPA 1992
Toluene	5.0E+00	USEPA 2005	NA	NA

NA = not available or not relevant

[a]The IUR was extrapolated from an oral cancer slope factor for trans-crotonaldehyde by The Human and Ecological Risk Office (HERO) of the California Department of Toxic Substances (DTSC) (2018).

[b]IUR was extrapolated from an oral cancer slope factor from Naufal et al. (2009).

[c]IUR was extrapolated from an oral cancer slope factor from CalEPA (1992).

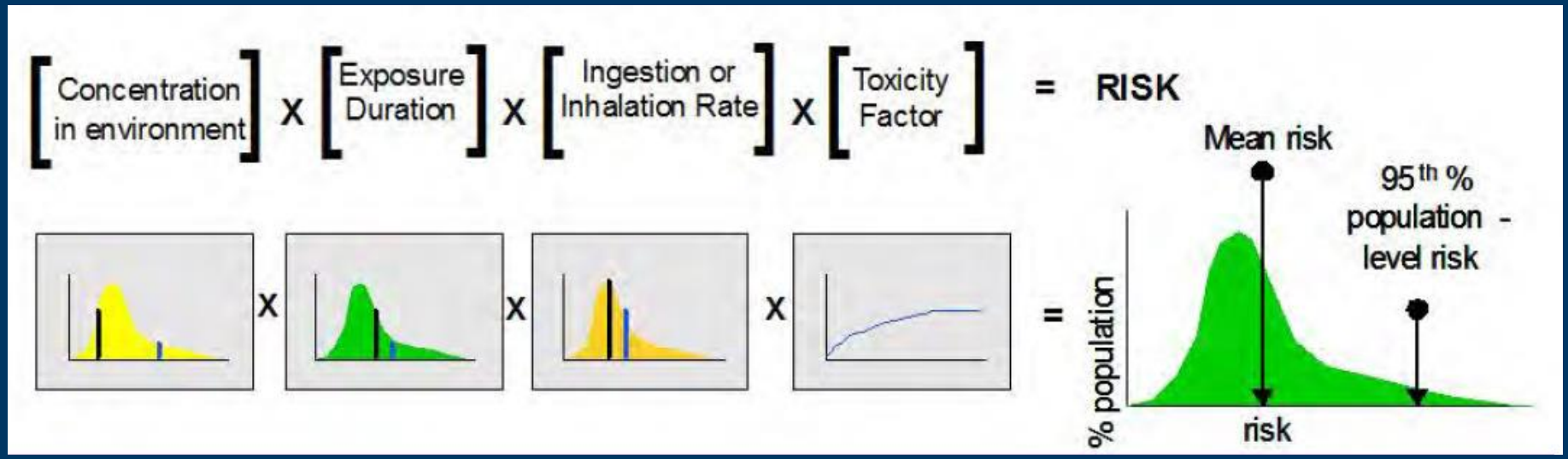
DQRA Results

HCI HPHCs	Mean Yield (µg/cig)		Exposure Concentration (µg/m^3)		Hazard Quotient (HQ)		Cancer Risk (CR)	
	Product A	Product B	Product A	Product B	Product A	Product B	Product A	Product B
Acetaldehyde	1801	1598	1801	1598	13	11	4.9E-03	4.3E-03
Acrolein	210	180	210	180	78	67	--	--
Acrylonitrile	18	26	18	26	2.5	3.7	1.2E-03	1.8E-03
4-aminobiphenyl	0.0030	0.0032	0.0030	0.0032	--	--	1.8E-05	1.9E-05
1-aminonaphthalene	0.017	0.023	0.017	0.023	--	--	8.7E-06	1.2E-05
2-aminonaphthalene	0.020	0.028	0.020	0.028	--	--	1.0E-05	1.4E-05
Ammonia	26	27	26	27	0.052	0.054	--	--
Benzene	89	102	89	102	2.97	3.40	6.9E-04	8.0E-04
Benzo(a)pyrene	0.0021	0.0020	0.0021	0.0020	--	--	1.3E-06	1.2E-06
1,3-Butadiene	79	90	79	90	2.4	2.7	4.0E-05	4.5E-05
Carbon Monoxide	32,500	28,026	32,501	28,027	4.64	4.00		
Crotonaldehyde	27	26	27	26	--	--	1.3E-02	1.2E-02
Formaldehyde	78	72	78	72	7.09	6.55	4.7E-04	4.3E-04
Isoprene	386	517	386	517	--	--	8.5E-06	1.1E-05
NNK	0.12	0.13	0.12	0.13	--	--	6.3E-04	6.9E-04
NNN	0.10	0.13	0.10	0.13	--	--	2.4E-05	3.1E-05
Toluene	115	136	115	136	0.0230	0.0272	--	--
				Composite	**HI**		**CR**	
					110	**99**	**2.1E-02**	**2.1E-02**
				Difference	**12%**		**2%**	

Rank Order of Differences in HPHC Contributions to the Hazard Index

HCl HPHCs	Hazard Quotient		Product A Contribution to HI	Product B Contribution to HI	Difference
	Product A	Product B			
Acrolein	78	67	70%	68%	4%
Carbon Monoxide	4.6	4.0	4.2%	4.1%	3%
Acetaldehyde	13	11	12%	12%	1%
Formaldehyde	7.1	6.5	6.4%	6.6%	-3%
Ammonia	0.052	0.054	0.047%	0.055%	-15%
1,3-Butadiene	2.4	2.7	2.2%	2.8%	-24%
Benzene	3.0	3.4	2.7%	3.5%	-25%
Toluene	0.023	0.027	0.021%	0.028%	-28%
Acrylonitrile	2.5	3.7	2.3%	3.7%	-47%
	Hazard Index (HI)				
Sum	110	99			
Difference	**12%**				

General PRA Model

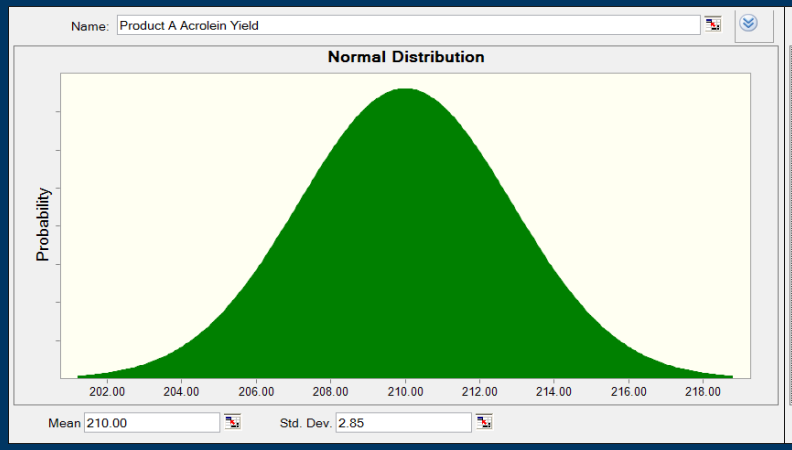


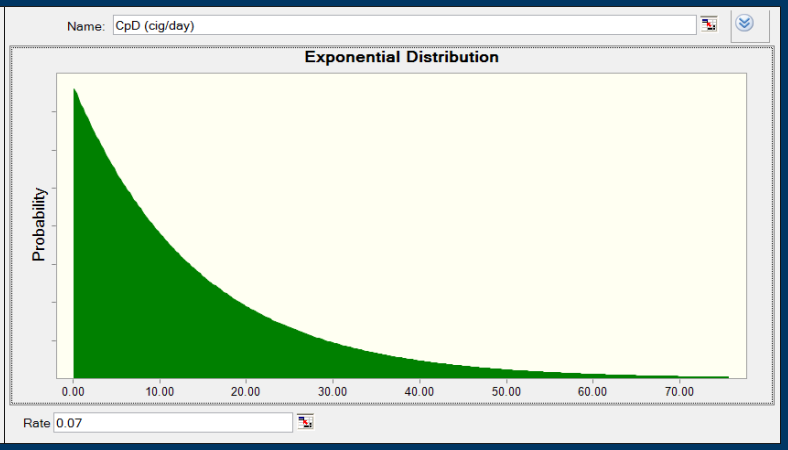
USEPA 2014

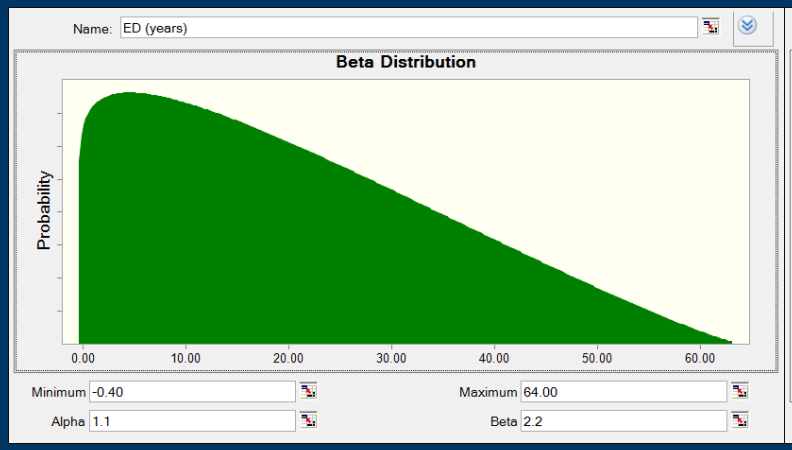
Exposure Factors for PRA

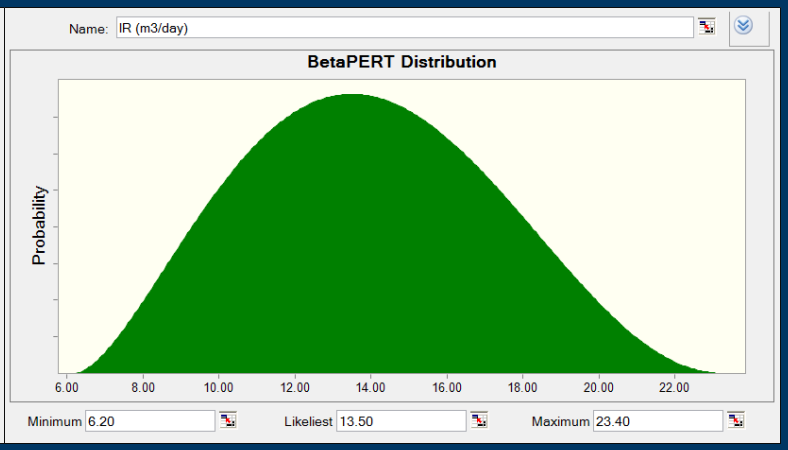
Factor	Definition	Distribution	Reference
C	HPHC yield (µg/cigarette)	Normal	HPHC yields
CpD	Cigarettes/day	Exponential	CDC 2015
ED	Exposure Duration (years)	Beta	CDC 2015
EF	Exposure Frequency (days/year)	365 days/year	Conservative assumption of daily exposure
IR	Inhalation Rate (m^3/day)	Beta PERT	USEPA 2011
AT	Averaging Time Years x 365 days	Beta	CDC 2015

PRA Model Distributions





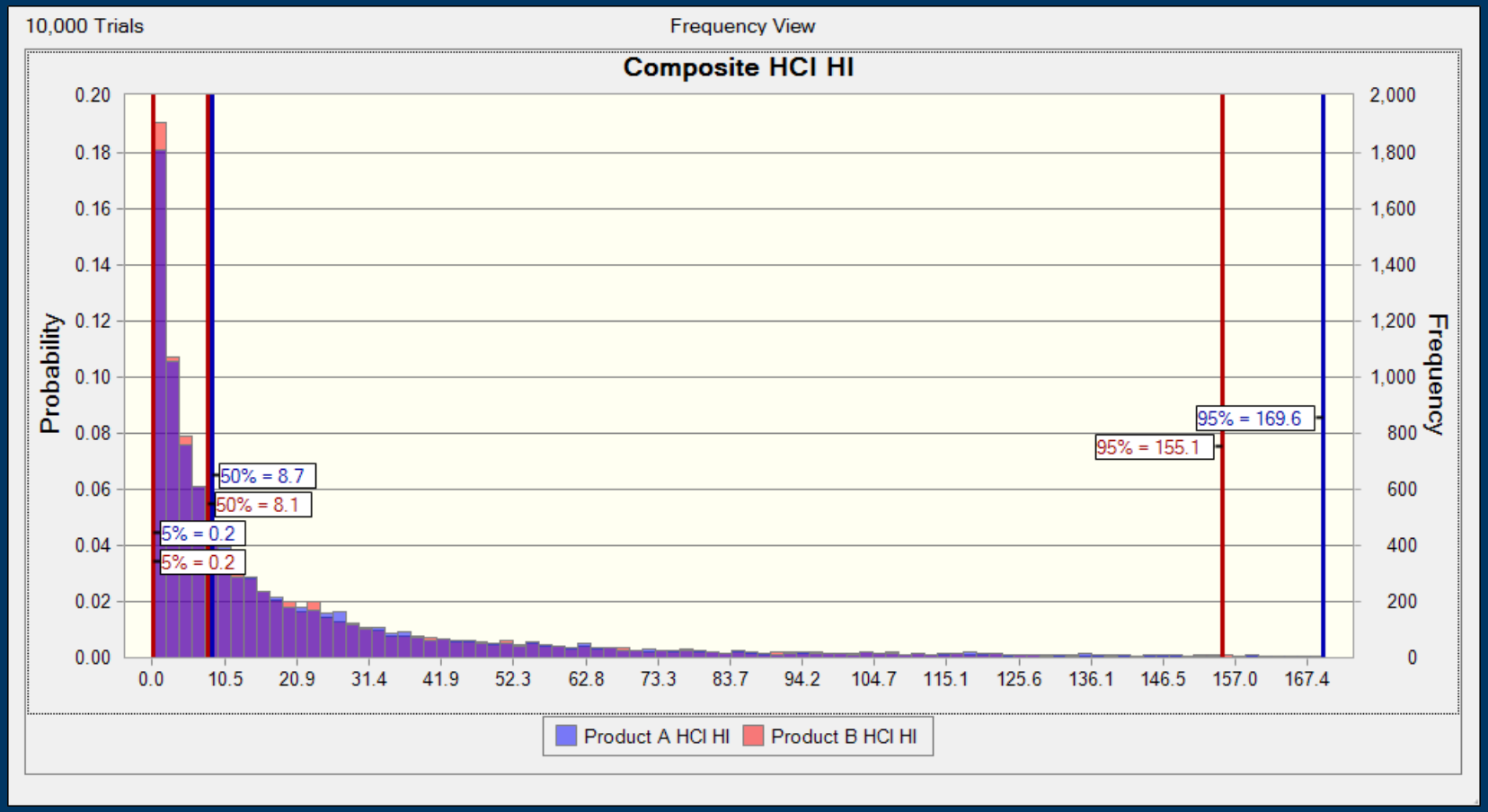




PRA Results

HCI HPHCs	Product A HQ	Product B HQ Range		Product A CR	Product B CR Range	
	50%	5%	95%	50%	5%	95%
Acetaldehyde	8.4	0.13	153	3.0E-03	4.8E-05	5.4E-02
Acrolein	57	0.8	939	--	--	--
Acrylonitrile	1.5	0.04	44	7.0E-04	1.7E-05	2.0E-02
4-aminobiphenyl	--	--	--	1.1E-05	2.0E-07	2.3E-04
1-aminonaphthalene	--	--	--	5.1E-06	1.3E-07	1.5E-04
2-aminonaphthalene	--	--	--	3.2E-06	7.8E-08	8.9E-05
Ammonia	0.03	0.0006	0.7	--	--	--
Benzene	1.5	0.03	34	3.3E-04	6.5E-06	7.5E-03
Benzo(a)pyrene	--	--	--	6.9E-06	1.2E-07	1.4E-04
1,3-Butadiene	1.6	0.03	37	2.5E-05	5.1E-07	5.8E-04
Carbon Monoxide	3.2	0.05	55	--	--	--
Crotonaldehyde	4.0	0.07	84	--	--	--
Formaldehyde	5.6	0.09	108	3.5E-04	5.8E-06	6.6E-03
Isoprene	0.01	0.02	18	5.1E-06	1.2E-07	1.4E-04
NNK	--	--	--	1.6E-04	3.1E-06	3.5E-03
NNN	--	--	--	1.4E-05	3.4E-07	3.9E-04
Toluene	0.02	0.0003	0.4	--	--	--
Composite	**HI**			**CR**		
	8.7	**0.17**	**155**	**6.62E+00**	**1.18E-01**	**1.16E+02**

Composite HI PRA Graph



Variability/Uncertainty

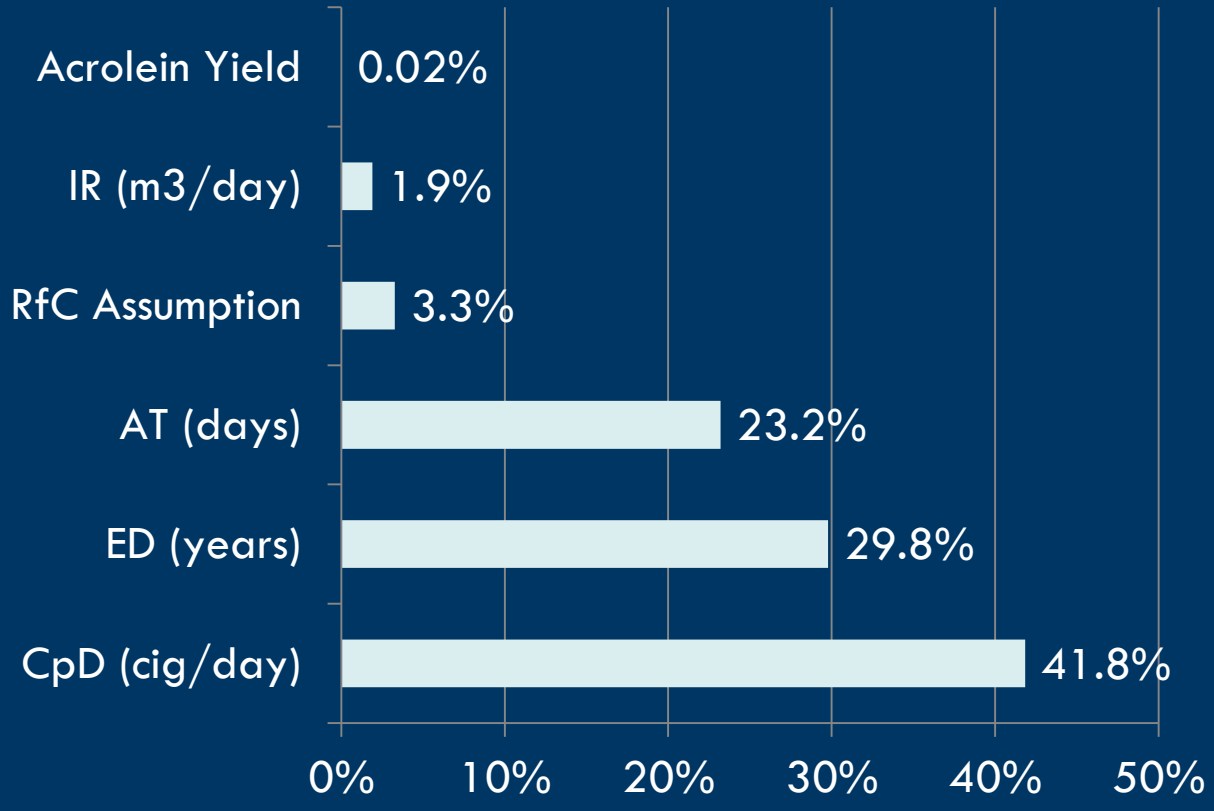
- Exposure factors (CpD, ED, IR)
- HPHC toxicity values (RfC, IUR)
- HPHC smoking machine yields (C)

PRA Sensitivity Analysis

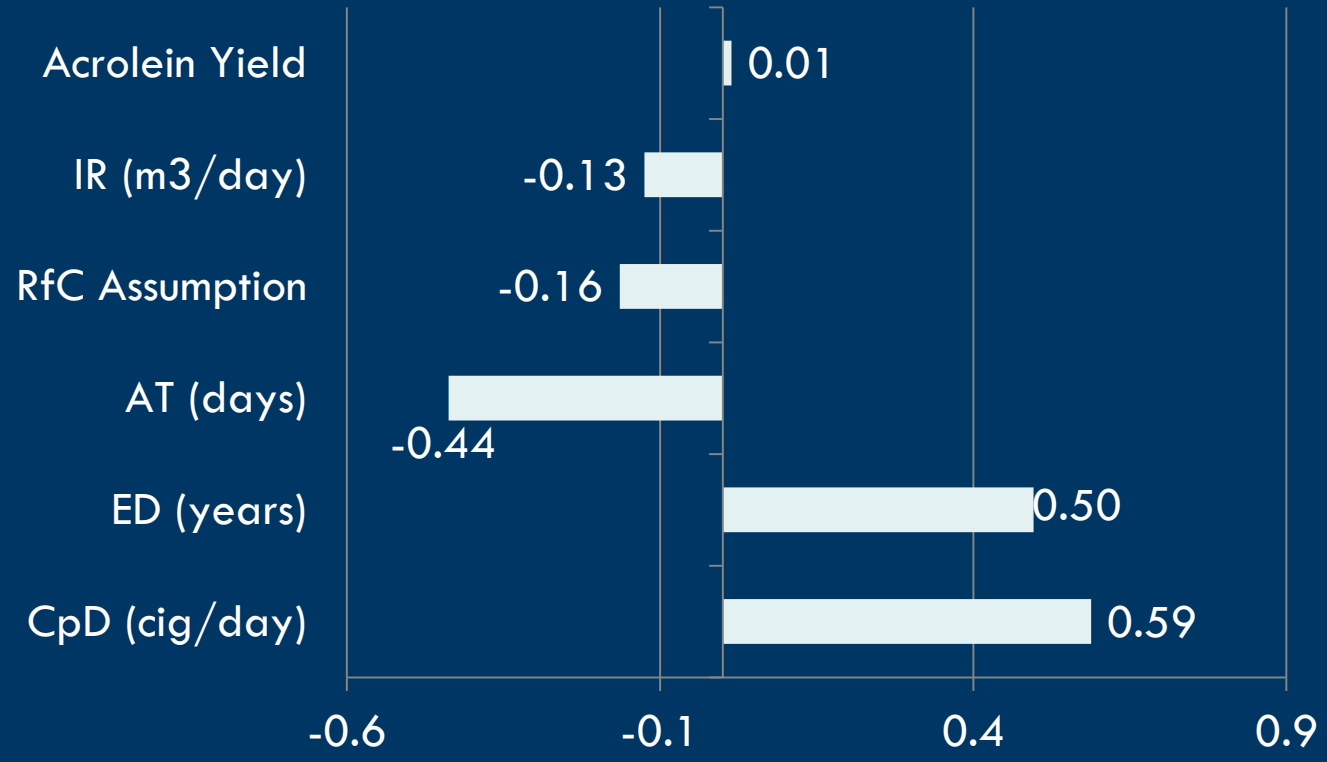
- Contribution to Variance:
  - Influence of variance among model factors.

- Rank Correlation:
  - Relationship between model factors and risk.

Acrolein HCI HQ Contribution to Variance



Acrolein HCl HQ Rank Correlation



Conclusions

- DQRA showed a 12% difference in composite noncancer HI, predominately attributable to acrolein (70%).
- Sensitivity analysis suggests that smoking behaviors and uncertainty associated with toxicity values represented >99% of model variability and they were more strongly correlated with noncancer risk than differences in acrolein yield.
- PRA showed that noncancer risk overlapped and is comparable between the two products.

Deterministic Risk Assessment

- DQRA and PRA are reasonable quantitative tools to compare health risks between consumer products such as tobacco products.
- DQRA estimates are directly proportional to HPHC-specific yields. All other model factors (e.g., exposure parameters, toxicity values) remain constant and mathematically cancel out during the analysis.
- DQRA Uses relatively simple mathematical models to produce point estimates of risk.

Probabilistic Risk Assessment

- PRA quantitatively evaluates the contribution of model parameter uncertainty, variability, and the correlation of the model parameters to the model outputs.
- PRA provides the risk assessor with the tools to identify, characterize, and quantify key factors affecting risk.
- PRA significantly enhances the risk management decision-making process by providing a clear picture of risk, the impact of individual model factors, and the range of expected variability/uncertainty.

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