Quantitative Risk Assessment (QRA) Covering the Recommended Way to Perform ELCR and Hazard Index Calculations

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2025.11.13

Introduction

In 2024, the USFDA CTP released two memos:

- "Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications"
- "Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications"

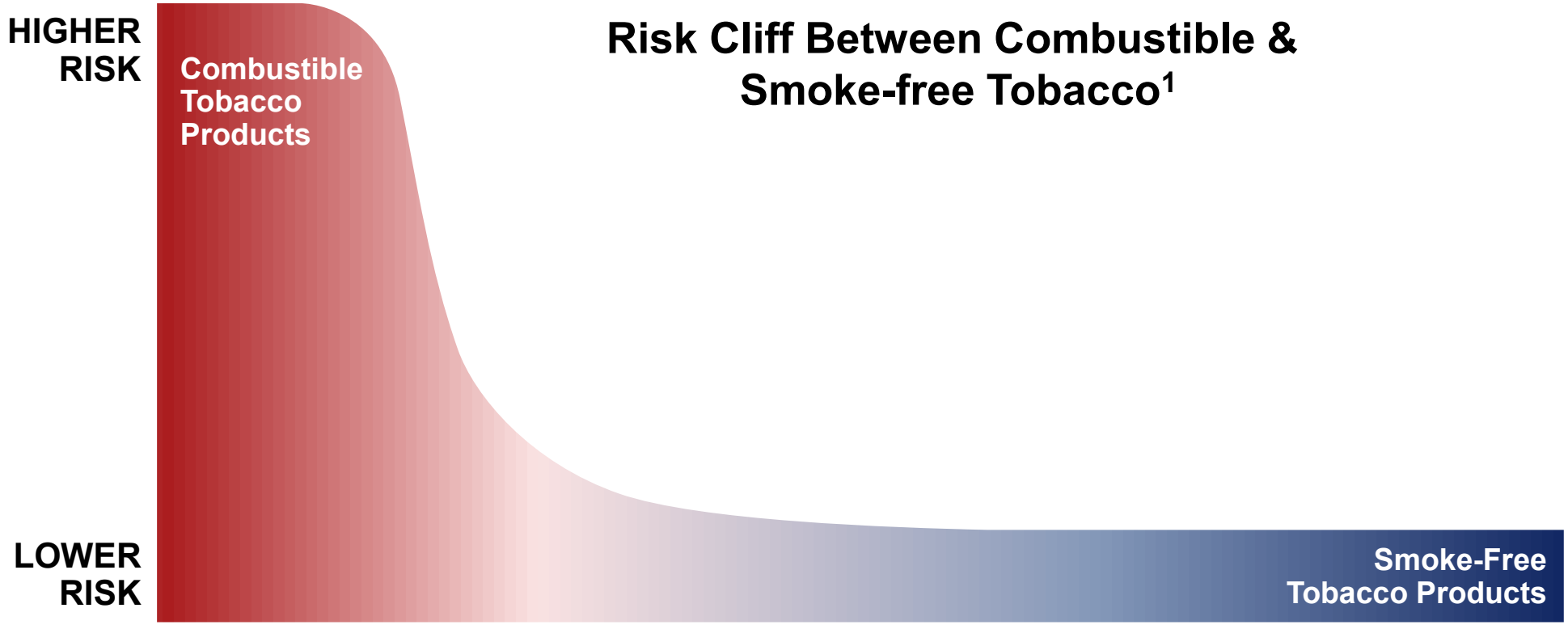
In some ways, the move to a more quantitative approach is a **MAJOR, POSITIVE STEP:**

- **Delivers on the stated intent of prior FDA memos from 2019–2023**
- **Brings FDA's approach more in line with other government agencies**
- **Potentially reduces subjectivity in market order determinations**

However, the methodology, underlying assumptions, and potential implications of the process as described in these two memos may overestimate product risks and undermine tobacco harm reduction

CTP=Center for Tobacco Products; ENDS=Electronic Nicotine Device System; FDA=Food and Drug Administration; USFDA=United States Food and Drug Administration.

Risk Modelling



Risk Cliff Between Combustible & Smoke-free Tobacco[1]

1. Adapted from Nutt, et. al Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach. *Eur. Addict Res.* 2014; 20:218-225.

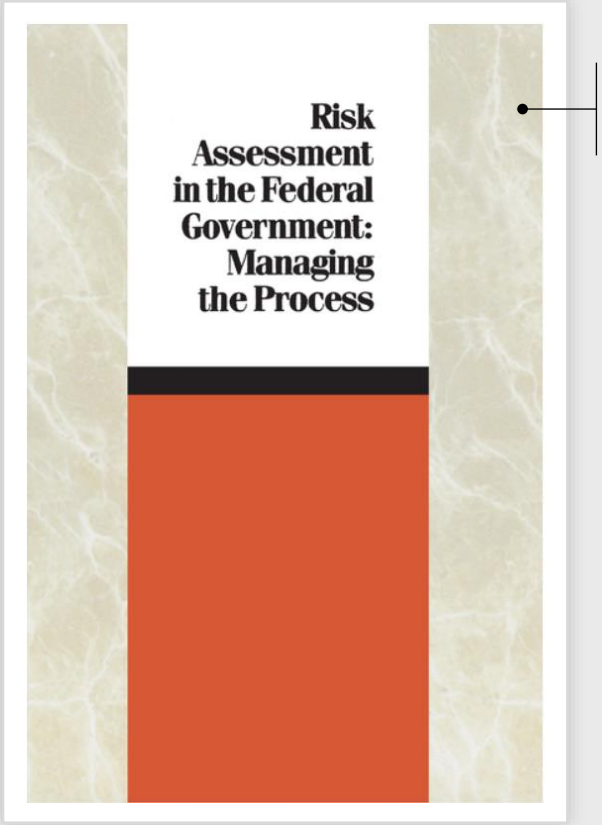
What is Risk?

Hazard:
Any potential source of harm or adverse effects

Risk:
The likelihood of a harm or adverse effect being realized

RISK = HAZARD x EXPOSURE

How Do We Assess Risk?



1983 | THE NATIONAL RESEARCH COUNCIL PUBLISHED:
"Risk Assessment in the Federal Government. Managing the Process."

The NRC paradigm, tailored for the U.S. federal government,
laid the groundwork for over 40 years of risk assessment

HAZARD IDENTIFICATION → **DOSE-RESPONSE ASSESSMENT** → **RISK CHARACTERIZATION**

↑

EXPOSURE ASSESSMENT

NRC=National Research Council.

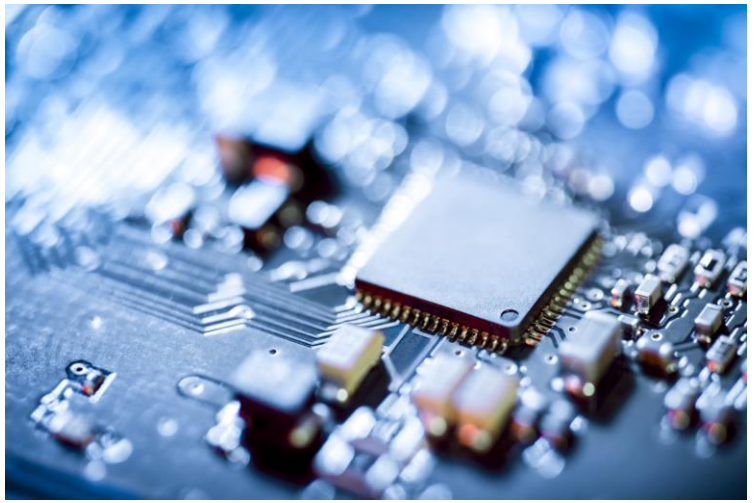
Hazard Identification

The first step is determining the presence of a hazard

For tobacco products:

- **Characterizing** the ingredients, materials, packaging, and extractables and leachables of a product
- **Evaluating** whether they are associated with any toxicological endpoint

Historically, this has been done through literature research; however, novel computational methods offer new ways to efficiently evaluate potential hazards. **Both methods can be combined into a weight-of-evidence assessment**



Example Hazard Identification Endpoints	
Bacterial Mutagenicity	**Respiratory Toxicity**
Mammalian Genotoxicity	**Cardiovascular Toxicity**
Mammalian Carcinogenicity	**Other Organ System Toxicity**

FDA's Cancer Hazard Identification Rubric

TIER 1 — **SUFFICIENT evidence of carcinogenicity in humans —** e.g., NNK, cadmium & formaldehyde

TIER 2 — **LIKELY to be carcinogenic to humans —** sufficient evidence in animals, e.g., acrolein & glycidol

TIER 3 — **SUGGESTIVE evidence of carcinogenic potential —** less than sufficient evidence in animals, e.g., chloroform

Determined by Expert Agencies (EPA, IARC, etc.)

TIER 4 — **POTENTIAL carcinogenic hazard; not classified by EPA or IARC —** animal or in vitro data, or in silico predictions

TIER 5 — **UNLIKELY to contribute to carcinogenic risk of ENDS**

Determined by CTP

CTP's has recently announced an approach to carcinogenicity hazard identification, departing from the traditional list of tobacco HPHCs to an open-ended ingredient assessment using their own classification system

Tier 1–3 classifications are made based on publicly available work from expert agencies. Tier 4 & 5 classifications are made by CTP. Unfortunately, these classifications have not been made publicly available

Working transparently to ensure that there is a robust scientific framework behind these classifications would help clearly communicate risk

CTP=Center for Tobacco Products; EPA=Environmental Protection Agency; ENDS= Electronic Nicotine Delivery System ; IARC= International Agency for Research on Cancer.

Dose-Response Assessment

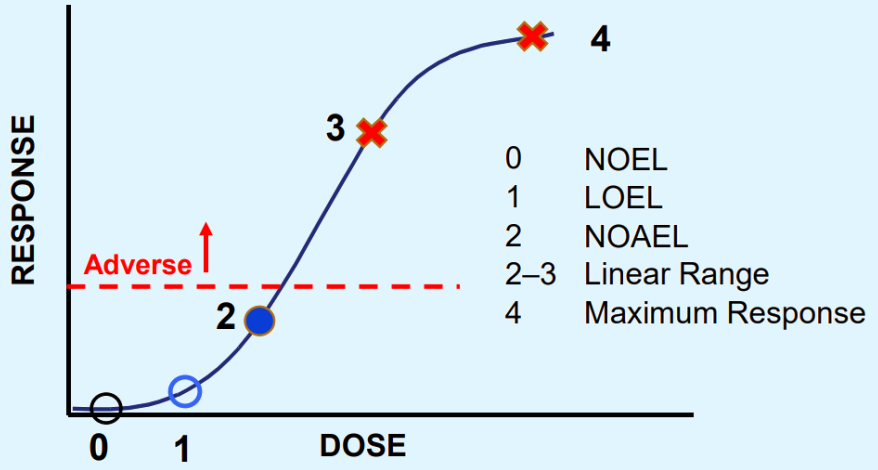
Once we establish that a hazard exists, we can determine the potency of that hazard through dose-response assessment

Two Types of Dose-Response Model:

	Approach	Use
1	**Threshold-based**	Non-cancer hazards like organ toxicity
2	**Non-threshold**	Genotoxic carcinogens

All things are poison, and nothing is without poison; only the dose makes it so that a thing is not a poison

— *Paracelsus 1538*



CSF, IUR, RfD, RfC

There are numerous ways to represent potency for both cancer and non-cancer hazards, dependent on the route of exposure

- Cancer Slope Factor (**CSF**)
- Inhalation Unit Risk (**IUR**)

CSF & IUR:
These represent the linear increase in risk with exposure

- Reference Dose (**RfD**)
- Reference Concentration (**RfC**)

RfD & RfC:
These represent the threshold under which no harm is expected to occur

FDA

FDA has:

- recently proposed using a value derived from an IUR, modified to represent excess cancer cases per 100,000 individuals
- also suggested using the **TTC** as the basis for a modified IUR, a practice likely to both over- and under-estimate product risk

TTC:
special threshold designed to control the risk of genotoxic impurities in drugs

Exposure Assessment

Exposure

is multi-faceted and product- as well as user-dependent

However, **exposure is often abstracted to a conservative average or worst-case scenario**

FDA currently defaults to an assumption of:

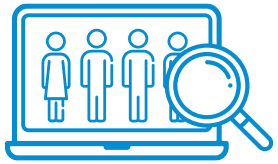
- 1 pack a day
- Intense use
- 100% transfer

A **core assumption** in comparison across products and product categories is **nicotine normalization**

i.e. calculating exposure based on consuming the amount of a product necessary to equal the nicotine in one pack of cigarettes

$$Exposure = C \times \frac{CR \times EFD}{BW} \times \frac{1}{AT}$$

BETTER exposure estimates can be obtained through:



- **Evaluating actual use data**
- **Analytical testing**
- **Modelling the transfer efficiency of individual components**

C=Concentration; CR=Contact Rate; EFD=Exposure Frequency and Duration; BW=Body Weight; AT=Averaging Time

Risk Characterization

The risk contribution of any single component can be calculated by evaluating the potency of the hazard in relation to exposure to calculate an Excess Lifetime Cancer Risk or a Hazard Quotient

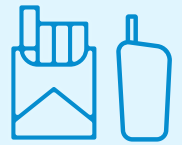
These can be aggregated into a cumulative ELCR or Hazard Index to represent the risk of the whole product

$$ELCR = CSF\ (or\ IUR) \times Exposure \qquad HQ = Exposure/RfD$$

$$cumulative\ ELCR = \sum_{i}^{n} ELCR_i \qquad HI = \sum_{i}^{n} HQ_i$$

Notably FDA departs from the traditional ELCR calculation above due to their adjusted IUR:

$$\mathrm{ELCR} = \mathrm{Exposure}/IUR_{adjusted}$$



CTP's method compares the risk of a new product to a risk estimate of the median risk of market order products and combustible cigarettes

Notably CTP's risk estimates lacks sufficient data for robust understanding

CSF=Cancer slope factor; ELCR=Excess lifetime cancer risk; HI=Hazard index; HQ=Hazard quotient; IUR=Inhalation unit risk; RfD=Reference dose

Risk Characterization

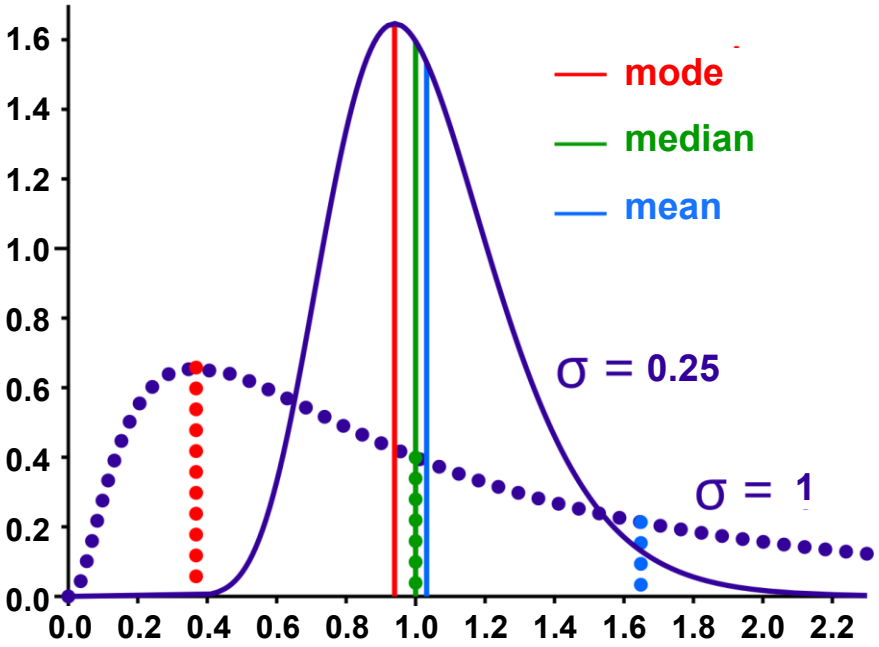
Summary statistics, such as mean, median, mode, standard deviation, variance, etc. **describe the probability distribution of specific outcomes**

★ **This is important in risk assessment, as a risk model is based on the probability of a negative outcome**

All probability distributions are specified by multiple parameters

Without these parameters, we can't:

- **Say anything about the shape of the risk distribution**
- **Test whether any perceived difference** in product risk is significant



If CTP could provide details of their 1R6F and market median calculation ▶ **we could have a much better understanding of the risk** of the product category and where our products fall within it

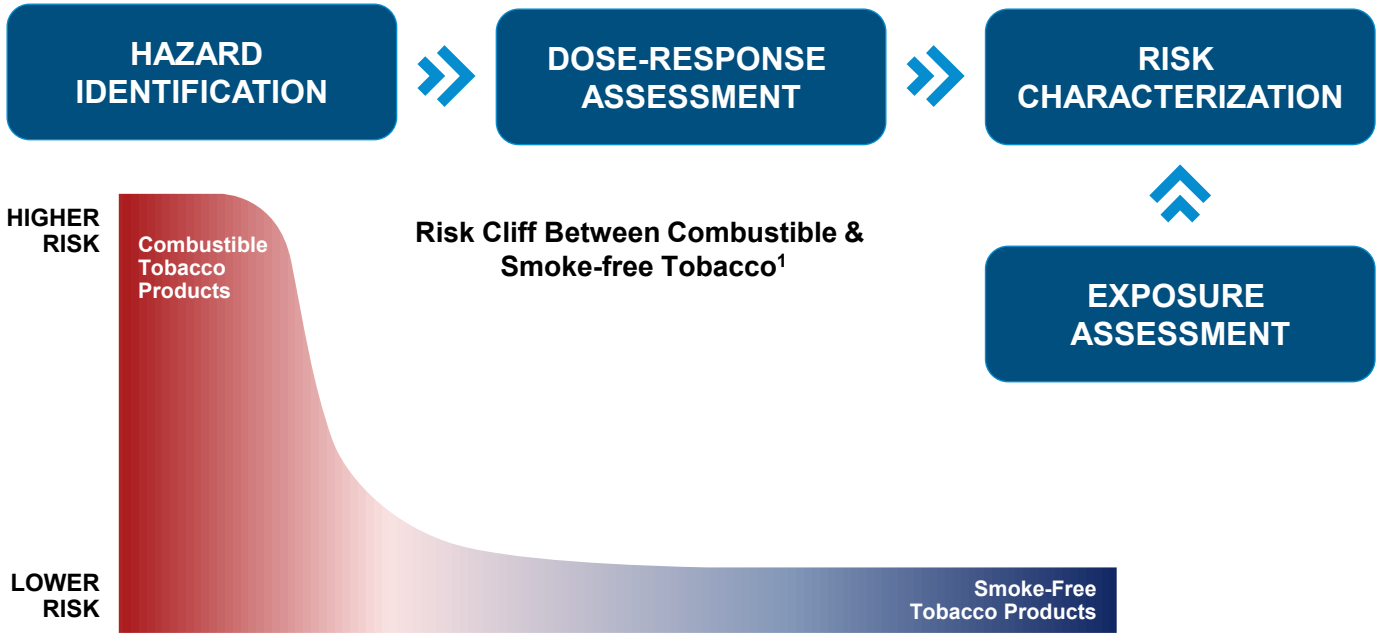
CTP=Center for Tobacco Products.

Conclusions

Risk Modelling Is a Powerful Tool

- Best way to determine whether a new tobacco product is appropriate for the protection of public health
- Can provide insights into both cancer and non-cancer risk of a product and can be applied within and across product categories

There are deficiencies in CTP's current approach to risk modelling that may under- or over-estimate the risk of new products



Scientific organizations have an opportunity to come together to lay the foundation for robust science-based risk modelling of tobacco product risk

CTP=Center for Tobacco Products.

Thank you!