Uncertainty in the Quantitative Risk Assessment of ENDS

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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"**

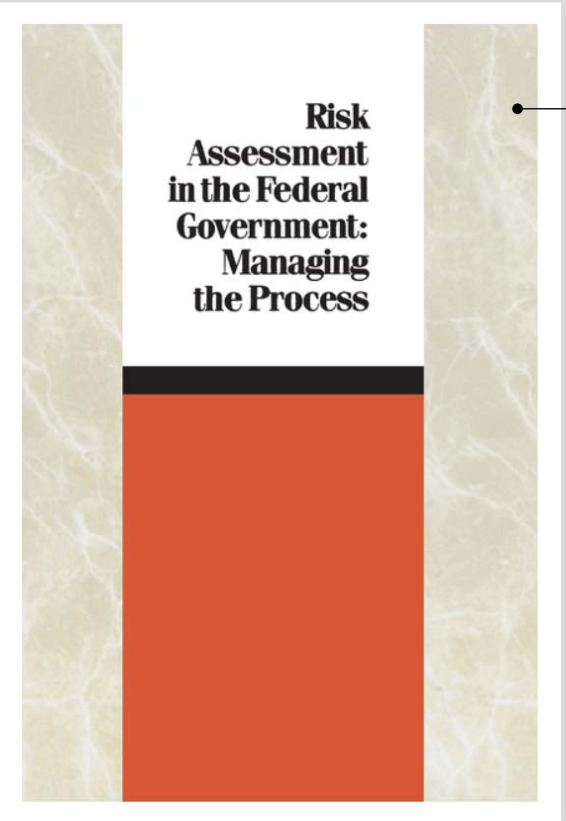
In some ways, the move to a more quantitative approach is a MAJOR, POSITIVE STEP:

- **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

Quantitative Risk Assessment Frameworks



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

Quantitative Risk Assessment Frameworks

2018 (Marano, et al.)

First industry publication on Quantitative Risk Assessment (QRA) for tobacco products

Built upon the US Environmental Protection Agency (EPA) Risk Assessment Guidance for Superfund (RAGS)

2019

CTP expressed a desire to create their own approach

Unclear what shortcoming CTP sees in other federal risk assessment approaches that makes them unsuitable for tobacco product risk assessment

The approach proposed in these memos does not clarify CTP's position. Instead, this approach introduces uncertainty and deficiencies into the risk assessment process

> **"While this process will take into account previous approaches to risk assessment of complex mixtures, the majority of the work required in the continued development of a comprehensive approach for tobacco products will require framing the risk assessment thinking specific to the comparison of tobacco products."**
>
> "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" CTP, 2019

CTP=Center for Tobacco Products

Uncertainty in the FDA Approach

CTP's current approach to QRA, as outlined in these two memos, presents a challenge in navigating uncertainty in tobacco product risk assessment

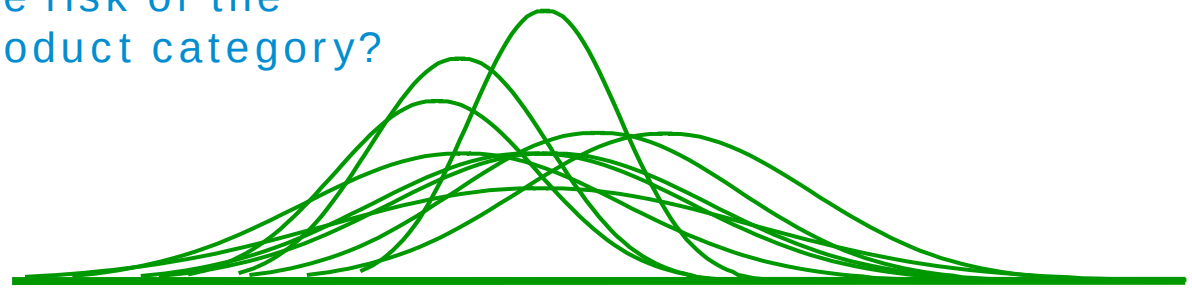
We must consider:

- **Uncertainty and variability** inherent to the assessment
- **Added uncertainty due to lack of transparency** regarding CTPs methods

Sources of uncertainty in the CTP approach:

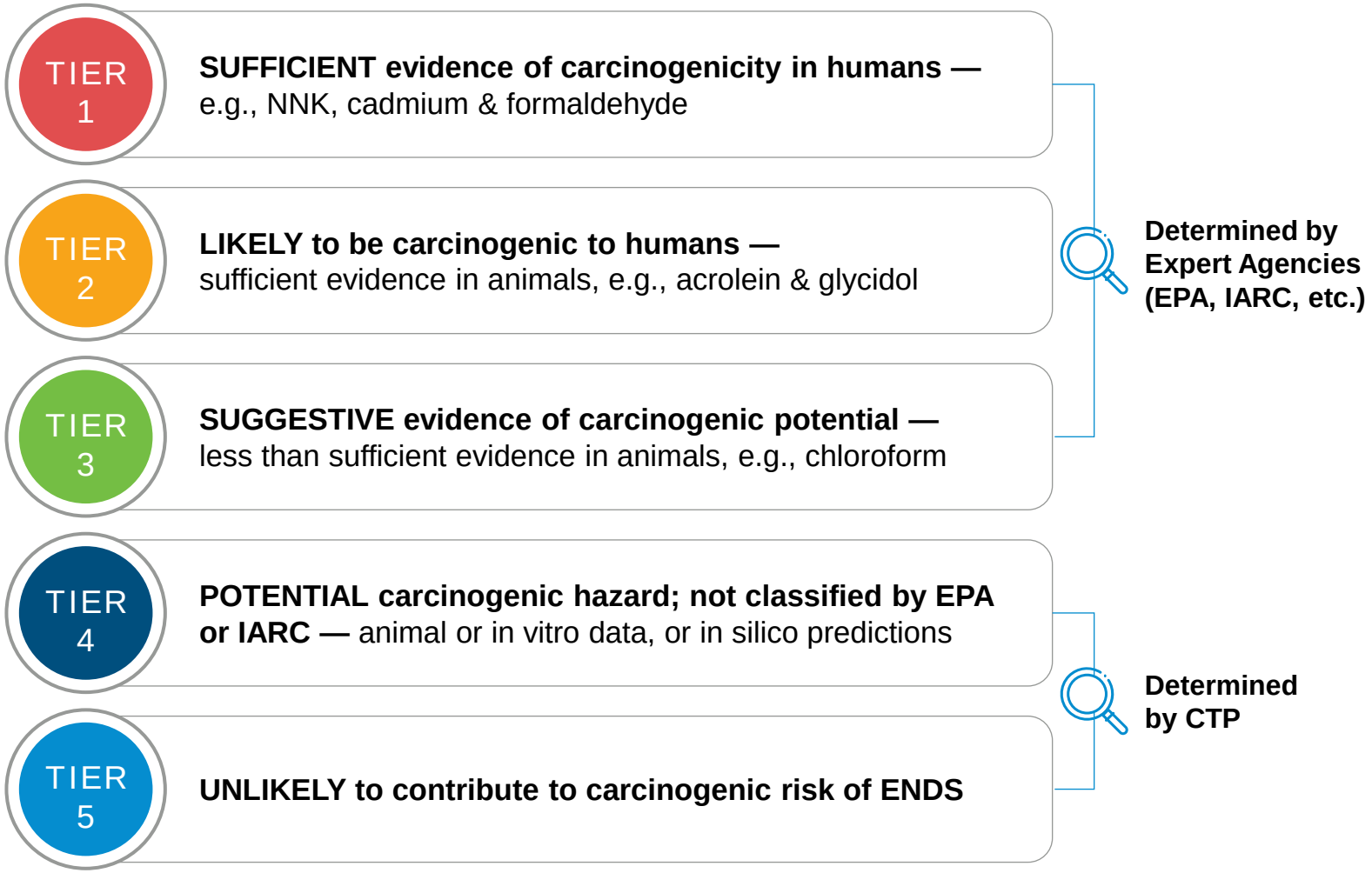
- Hazard Identification
- Dose-Response Assessment
- Risk Characterization
- Decision Making

Which distribution accurately reflects the risk of the product category?



CTP=Center for Tobacco Products; QRA=Quantitative Risk Assessment

Hazard Identification



A major change in CTP's approach is the EXPANSION of their hazard identification 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. These classifications have not been made publicly available

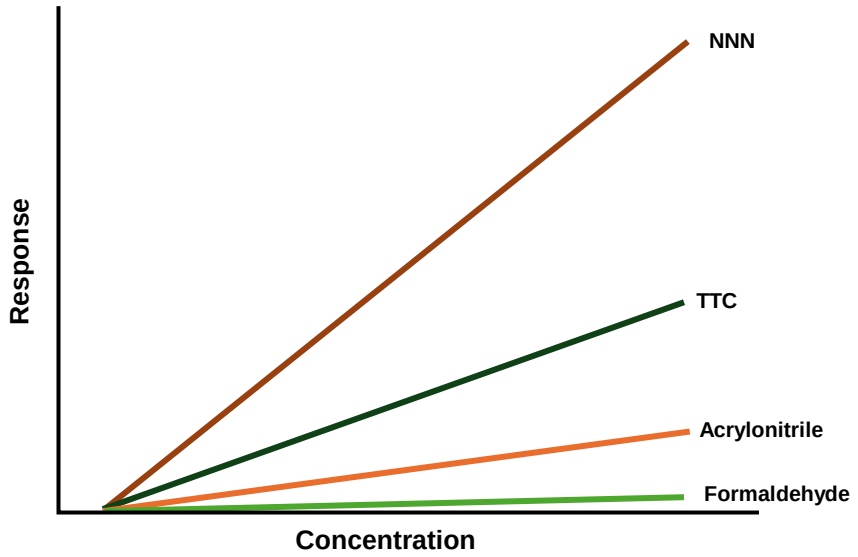
Working transparently to ensure that there is a robust scientific framework **behind these classifications would help clearly communicate risk**

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

Dose-Response Assessment

Risk assessment of ingredients classified into Tiers 1–3 is often relatively straightforward based on the amount of evidence of their carcinogenic potential

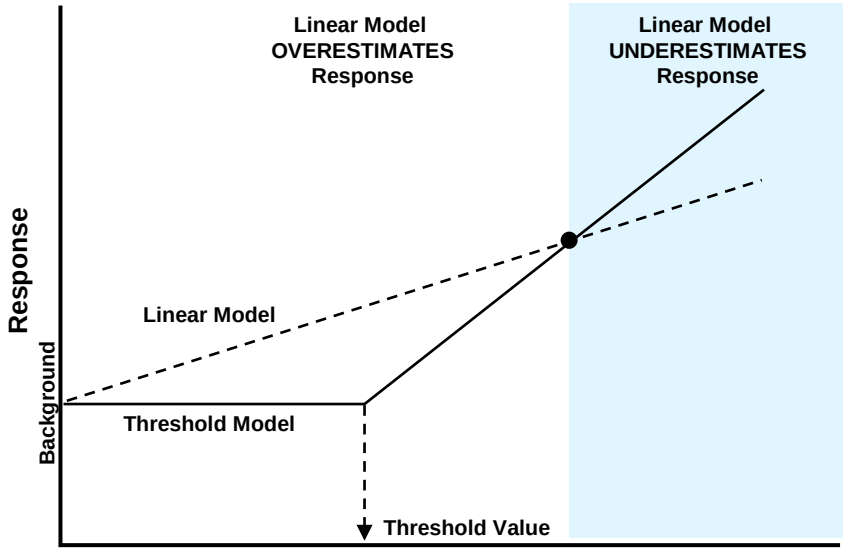
With the addition of Tier 4 ingredients to a QRA, CTP is attempting to quantify the excess lifetime cancer risk of extremely data-poor chemicals



Threshold of toxicological concern is a threshold below which no toxicological results are expected to occur

CTP suggests the TTC can be applied as a linear risk model

This approach inherently
INCORRECTLY ESTIMATES product risk
for Tier 4 ingredients



Bukowski, 2013

CTP=Center for Tobacco Products; QRA= Quantitative Risk Assessment; TTC=Threshold of toxicological concern

Risk Characterization

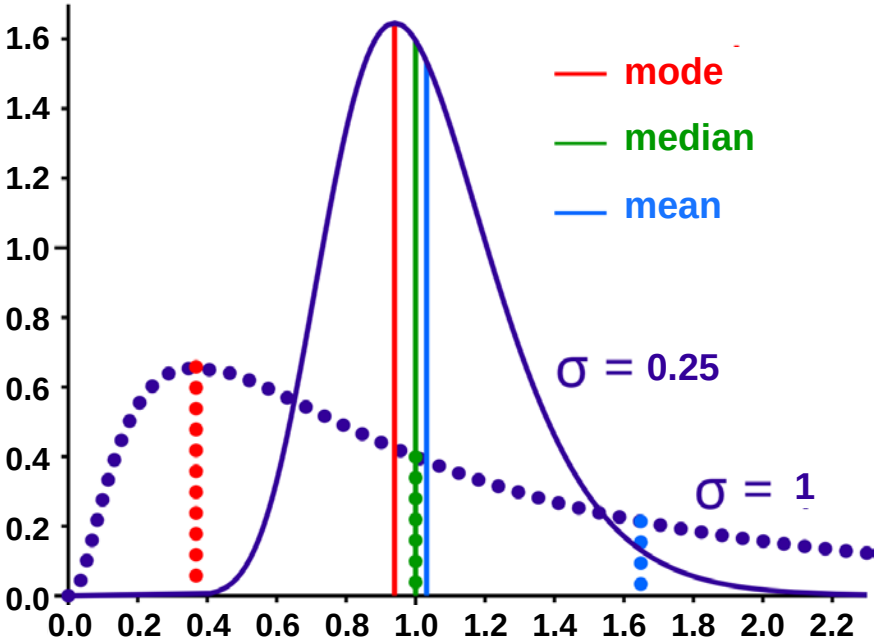
Summary statistics, **such as mean, median, mode, standard deviation, variance, etc.** describe the probability distribution of specific outcomes

★ **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:

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



If CTP could provide details of their market median calculation, we could have a much better understanding of the risk of the product category and where our products fit compared to other products

CTP=Center for Tobacco Products

Decision Making

IN ADDITION TO A COMPARISON TO A MARKET MEDIAN,
CTP also points to comparing the risk of a new product to a risk estimate of conventional tobacco cigarettes

Notably this risk estimate also lacks sufficient data for robust understanding

ELCR memo contains a table of concern levels based on the relationship to a risk estimate of conventional tobacco cigarettes, **but it is unclear how these semi-quantitative concern levels are integrated into decision making**

Percentage of 1R6F ELRC$_a$	Descriptor	Calculated Cancer Risk
< 1.0%	Lower Concern	≤ 1:1000
1–10%	Moderate Concern	1:999 – 1:100
10–25%	Increased Concern	1:99 – 1:44
25–50%	Elevated Concern	1:43 – 1:20
> 50%	Serious Concern	> 1:20

Call to Action

These are just some of the deficiencies in the approach as outlined in these two memos

These deficiencies have the potential to create unnecessary hurdles in the PMTA process and contribute to either under- or overestimation of the risk of new products and product categories

We believe there is a role for CORESTA to play

in working with CTP, other regulatory agencies, and the broader risk science community to develop a robust yet pragmatic approach for the risk assessment of tobacco and nicotine products

This will benefit both industry and CTP

CTP=Center for Tobacco Products; PTMA=Premarket Tobacco Product Application

Thank you!