A Revised Approach Urgently Needed for the Cancer Risk Assessment Supporting E-vapor Products PMTA

Panel Discussion – Sherwin Yan

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Background

CENTER FOR TOBACCO PRODUCTS

In 2024, FDA issued two scientific memoranda that:

- **Recommended both individual and cumulative excess lifetime cancer risk (ELCR) assessments for e-vapor PMTAs**
- **Established a conservative genotoxicity hazard assessment paradigm, which reflected a shift from mixture-based to component-based evaluation to consider in the ELCR**

This brief presentation shares our significant concerns about the deficiencies in FDA's approach.

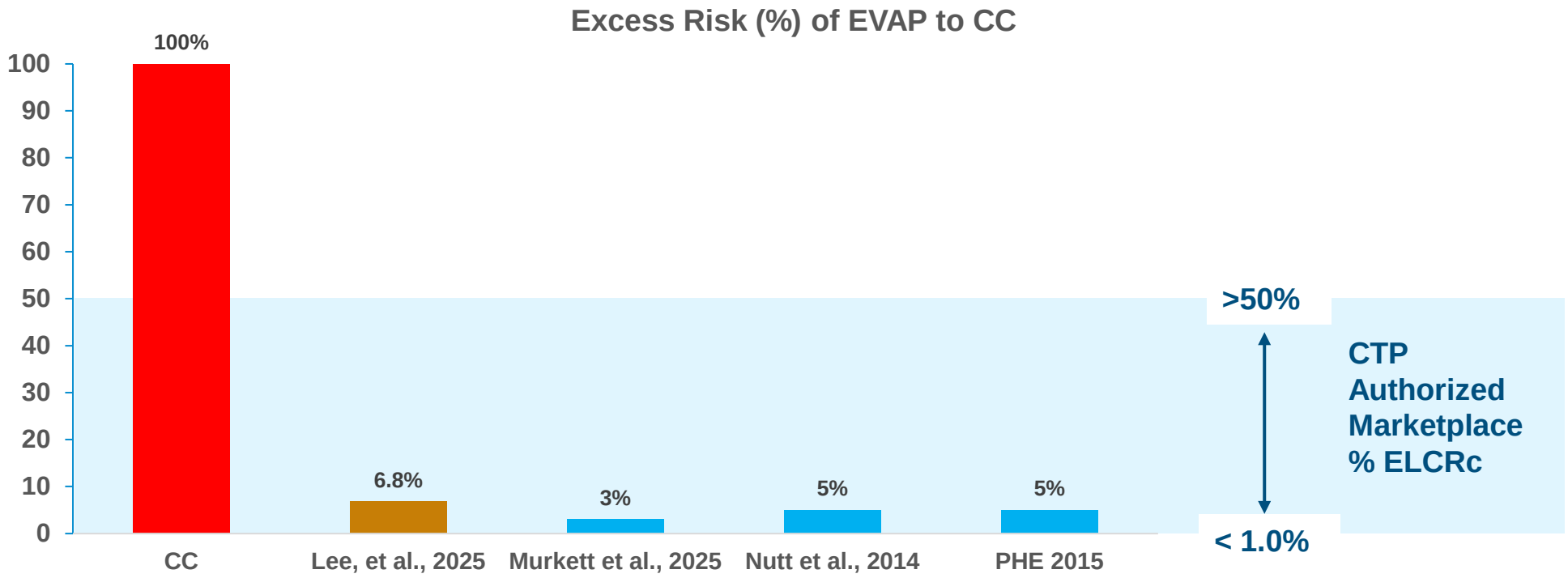
1. CTP's ELCR approach does not yield risk estimates aligned with other published analyses
2. The approach overestimates the cancer risk of ENDS
3. The CTP approach on hazard tiering precautionarily considers deficient studies instead of WOE
4. There is a fundamental lack of transparency

CTP=Center for Tobacco Products; ENDS=electronic nicotine delivery system; FDA=Food and Drug Administration; GLP=Good Laboratory Practice; OECD=Organization for Economic Co-operation and Development; PMTA=premarket tobacco application; WOE=weight of evidence.

CTP's ELCR Approach May Vastly Overestimate Actual Human Health Risk

1

CTP's ELCR approach does not yield risk estimates aligned with other published analyses



CTP=Center for Tobacco Products; ELCR=excess lifetime cancer risk; ELCRc=calculated excess lifetime cancer risk; E-vapor Products=electronic nicotine delivery system.
Lee et al., 2025. Estimating lung cancer risk from e-cigarettes and heated tobacco products; Nutt et al., 2014. Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach; Public Health England 2015. Murkett et al., 2025. Nicotine products relative risk assessment: an updated systematic review and meta-analysis

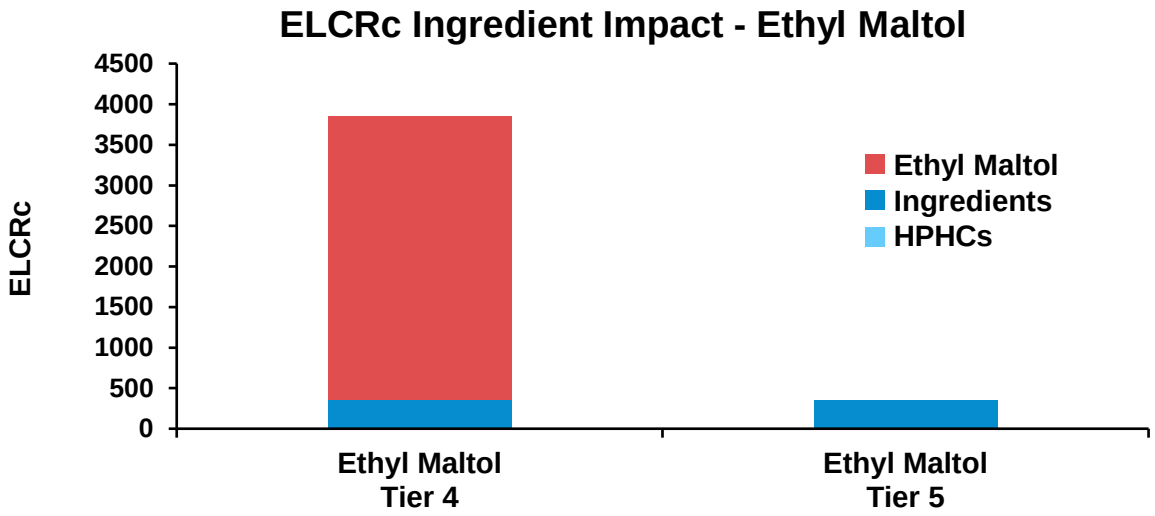
CTP's ELCR Approach May Vastly Overestimate Actual Human Health Risk (Cont'd)

2

CTP's ELCR approach overestimates the cancer risk of e-vapor products

CTP's ELCR approach conservatively includes chemicals that may have sufficient (oral) *in vivo* data demonstrating their lack of carcinogenicity

Defaulting to the TTC 1.5 µg/day (at 1 in 100,000 risk level) as the adjusted IUR for Tier 4A-E constituents potentially inflates the final ELCRc (e.g., ethyl maltol) and dwarfs the contribution of known carcinogenic HPHCs



Ethyl maltol classified as a Tier 4B artificially drives an ELCRc calculation from ~3.5% of 1R6F to ~38.6% of 1R6F

If classified as a Tier 5 based on an available 2-year carcinogenicity study, it would be removed from the ELCRc

Several well characterized carcinogens (HPHCs) have higher (less potent) IURs than the default TTC

HPHCs contribute relatively little to the ELCR of E-vapor Products: **~5.1 per 100,000**

1R6F=16RF reference cigarette; CTP=Center for Tobacco Products; ELCR=excess lifetime cancer risk; ELCRc=calculated excess lifetime cancer risk; E-vapor Products=electronic nicotine delivery system; HPHC=harmful and potentially harmful constituents; IUR=inhalation unit risk; TTC=threshold of toxicological concern.

CTP's ELCR Approach Has Other Limitations

3

The CTP approach **on hazard tiering** precautionarily considers deficient studies (e.g., non-OECD and/or non-GLP) for an identified hazard endpoint in lieu of new robust evidence**,** which depreciates the value of the weight of evidence (WOE) approach

4

There is fundamental lack of transparency:

- CTP has not made constituent/ingredient tiering publicly available
- The toxicology discipline review can only be obtained through FOIA

CTP=Center for Tobacco Products; ELCR=excess lifetime cancer risk; FOIA=Freedom of Information Act; GLP=Good Laboratory Practice; OECD=Organisation for Economic Co-operation and Development; WOE=weight of evidence.

Potential Considerations for Path Forward

All stakeholders, including scientists at FDA, should engage to develop a robust tool for a reasonable assessment of the cancer risk for e-vapor products

MAKE

the toxicological profiles and IURs public, provide industry opportunities to review and comment and/or provide additional tox data

DEVELOP

a system to engage stakeholders in a transparent process of compiling and reviewing data to establish the proper IURs

HAVE

clear criteria on the study qualities that can be included or excluded in the tox profile evidence

CTP=Center for Tobacco Products; ELCR=excess lifetime cancer risk; E-vapor Products=electronic nicotine delivery system; IUR=inhalation unit risk; QRA=quantitative risk assessment; (Q)SAR=(quantitative) structure–activity relationship.

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