

Quantitative Risk Assessment in Action: FDA's Use of Cumulative Excess Cancer Risk in ENDS Premarket Reviews



Jenna Guynn, PhD, DABT | Senior Director – Scientific & Regulatory Affairs

Contents Disclaimer



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FDA's Use of Cumulative Excess Lifetime Cancer Risk (ELCR_c) in ENDS Premarket Reviews



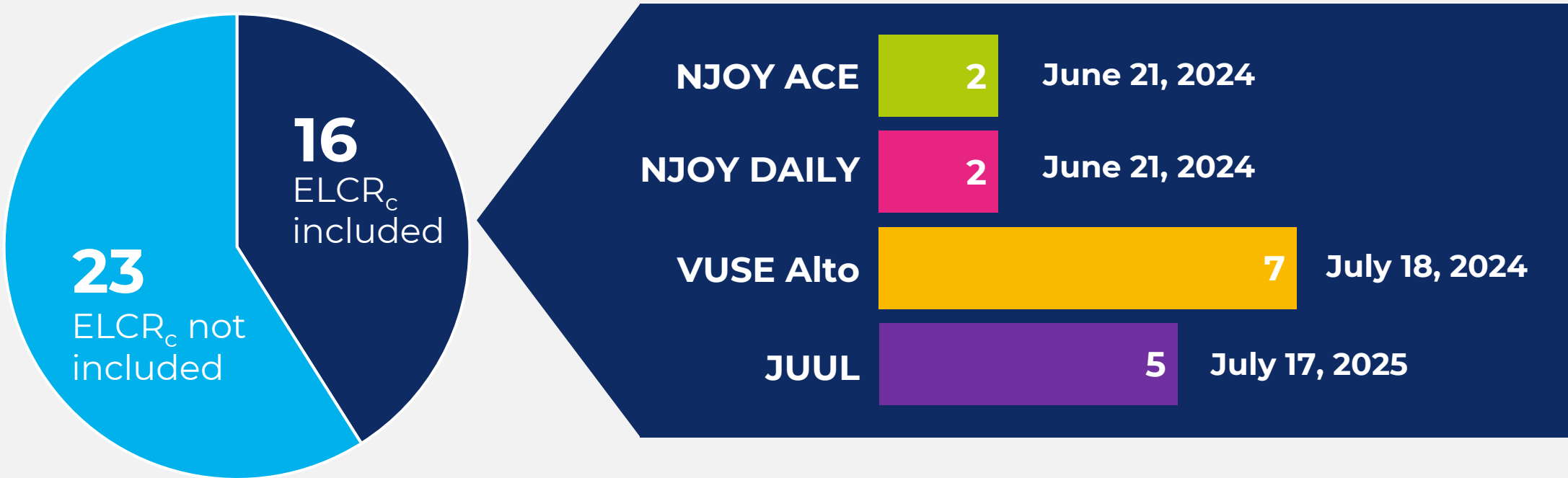
How does the FDA use ELCR_c in ENDS premarket reviews?

Which applications has the FDA incorporated ELCR_c in ENDS premarket reviews?

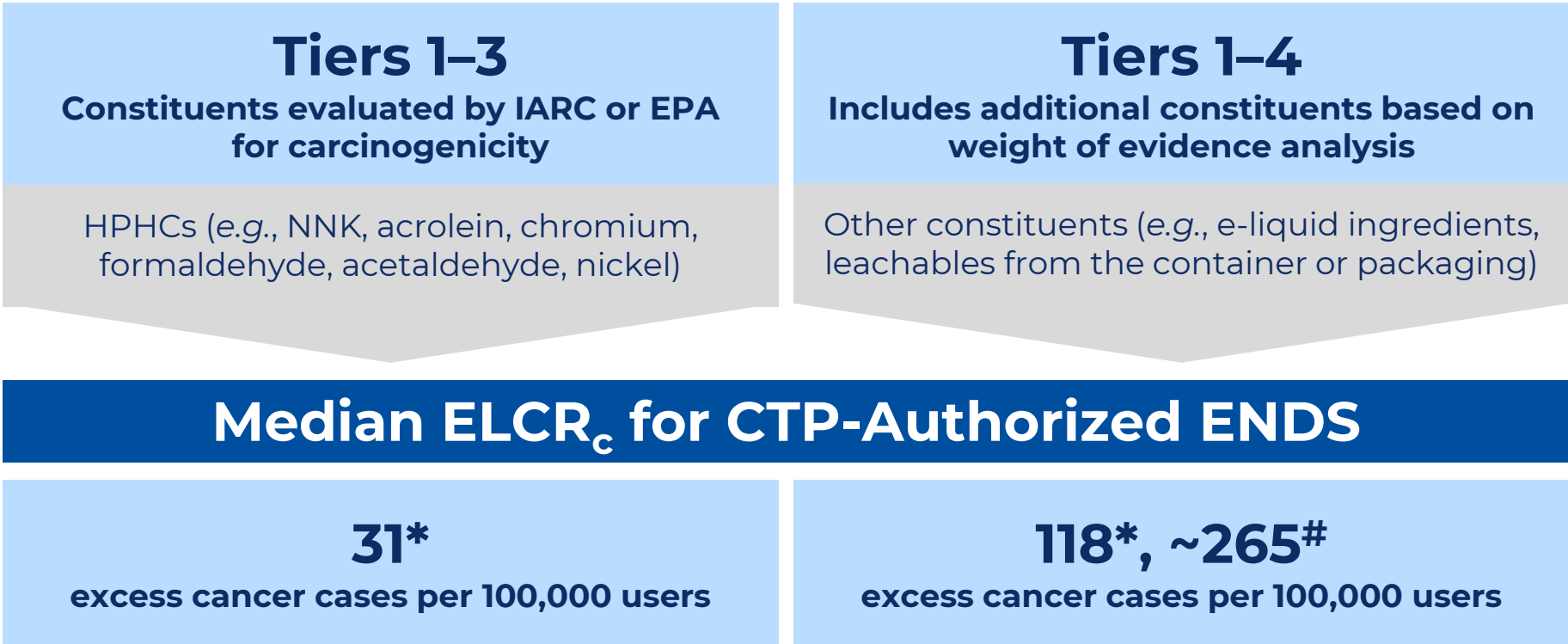
What are the outcomes of the FDA's ELCR_c assessments?

ELCR_c is Included in Four Technical Project Lead (TPL) Reviews Totaling 16 Products

ENDS Products with Marketing Granted Orders



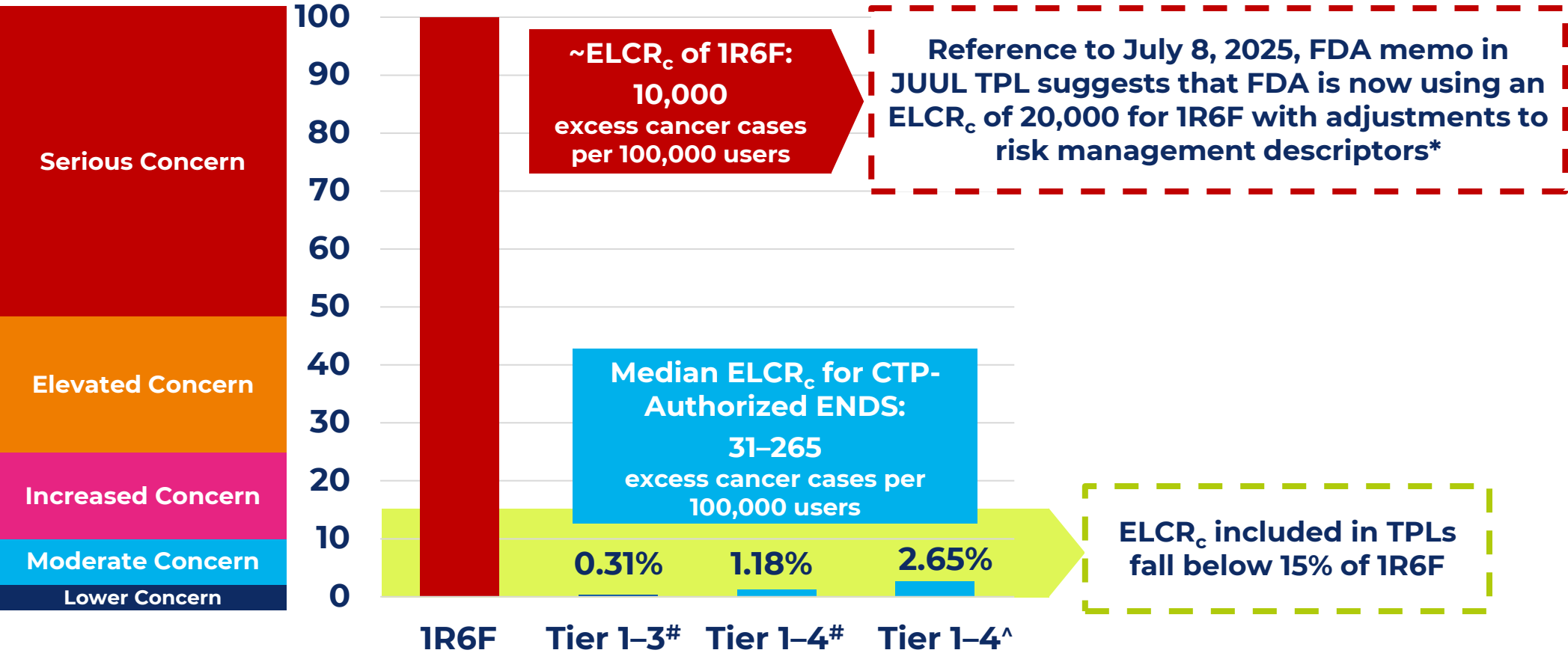
FDA Incorporates Two Tier-Based Approaches for ENDS ELCR_c Calculations



*As of February 2024

#Calculated from FDA (2025). PMTA Technical Project Lead Review, PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1

FDA's Risk Management Descriptors are Based on Percentage of 1R6F ELCR_c

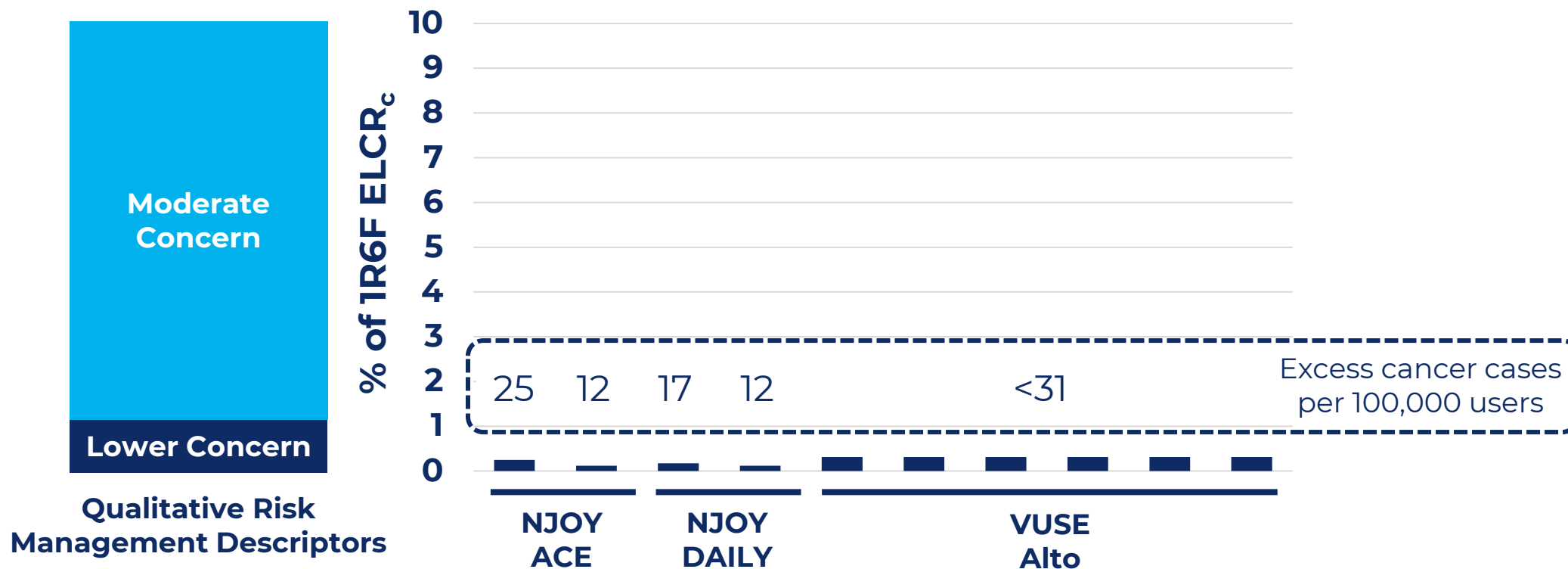


*Memorandum: "Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications;" signed July 8, 2025

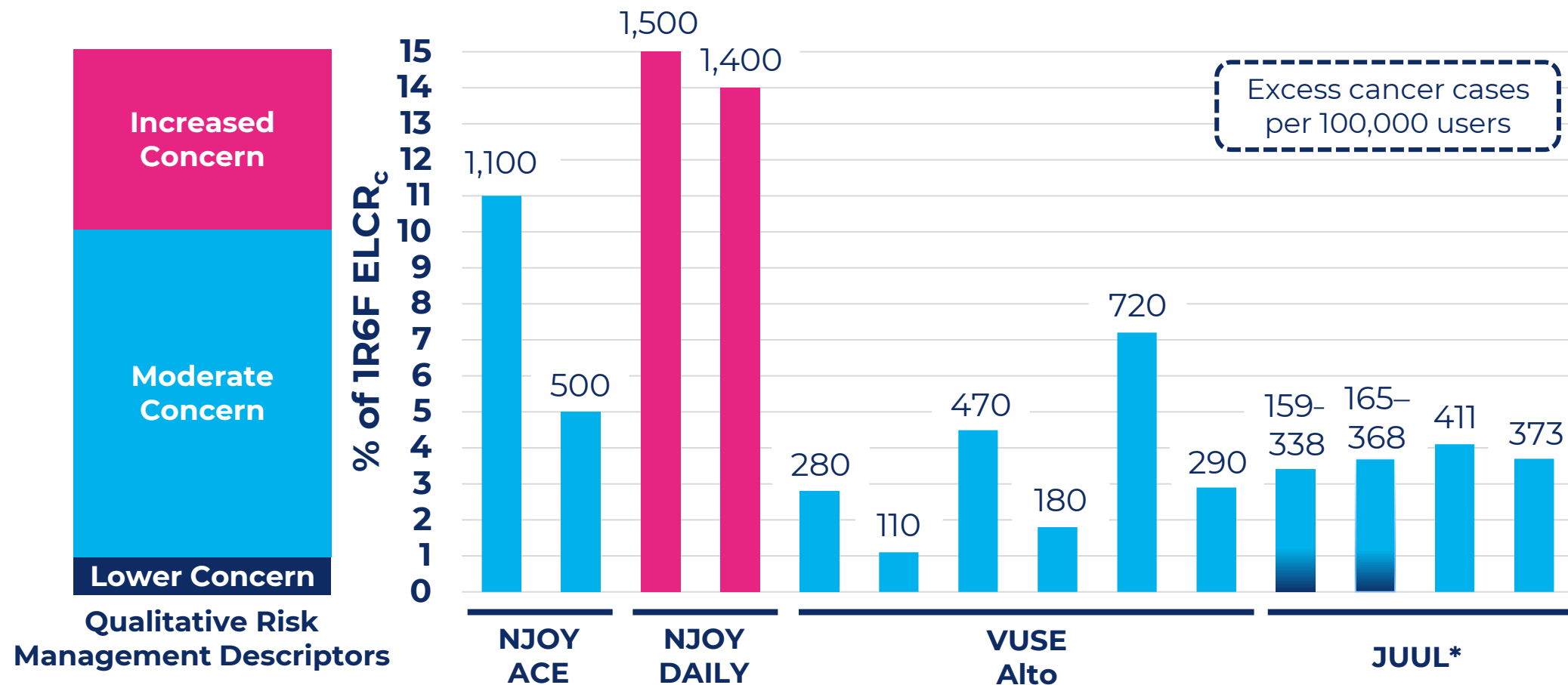
As of February 2024

^Calculated from JUUL TPL using 1R6F ELCR_c of 10,000 excess cancer cases per 100,000 users (FDA (2025). PMTA Technical Project Lead Review, PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1)

Tier 1-3 ELCR_c Calculations Characterized as “Lower Concern” or “Moderate Concern”



Tier 1-4 ELCR_c Calculations Characterized as “Lower Concern” to “Increased Concern”



*Percentage of 1R6F for JUUL products calculated using 1R6F ELCR_c of 10,000

Marketing Granted Orders of VUSE Alto Include ELCR_c in APPH Determination

“

...the new products' cumulative estimated lifetime cancer risk (ELCR_c) predicts that people who exclusively use the new products will have **lower cancer risks** than people who smoke CC [combusted cigarettes].

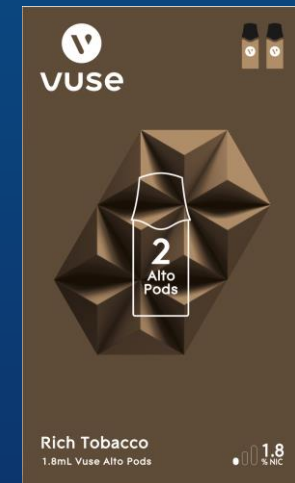
FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11; emphasis added.

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Marketing Granted Orders Received July 18, 2024



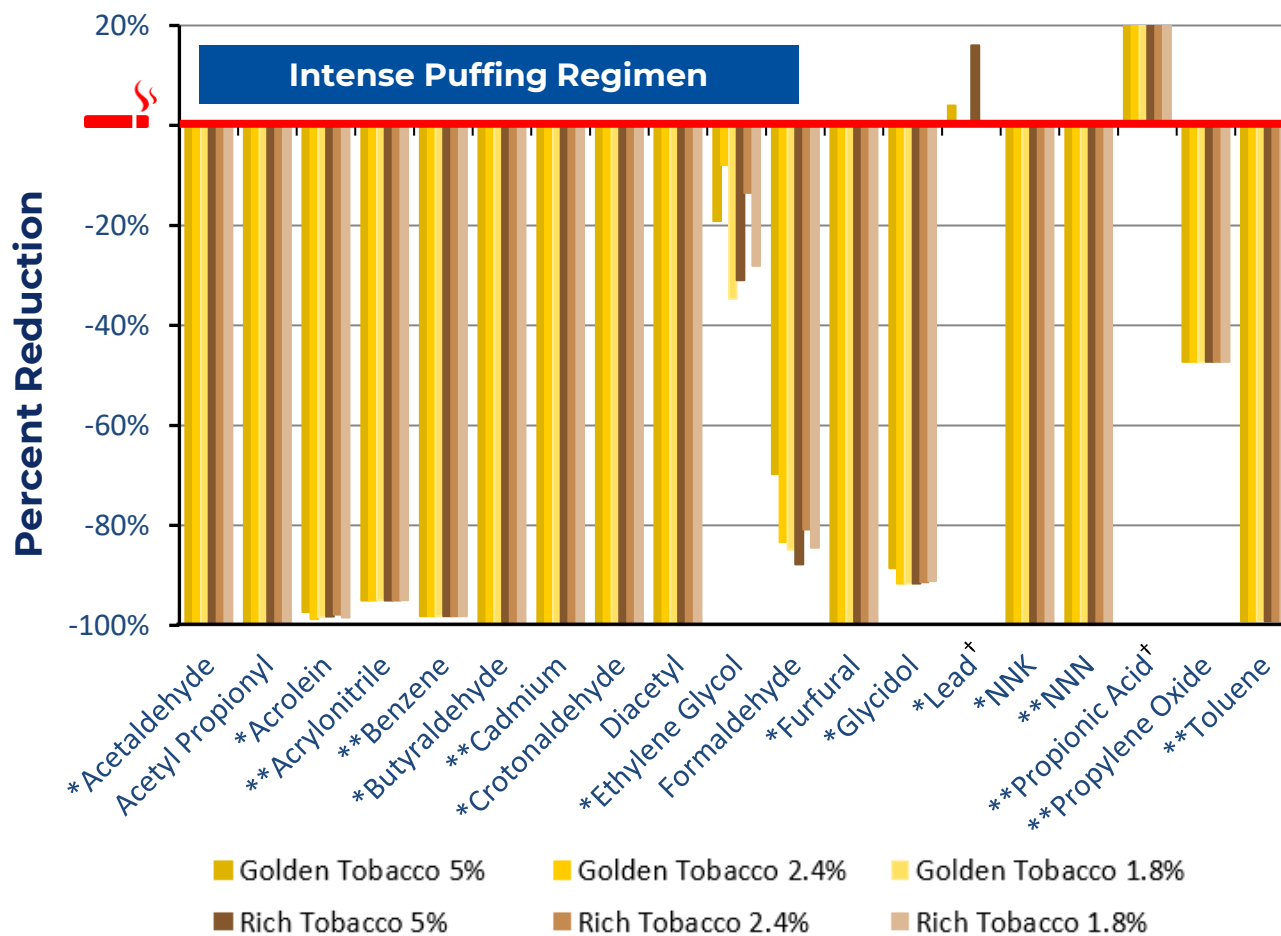
Power Unit



Golden Tobacco & Rich Tobacco Cartridges
1.8%, 2.4%, 5.0%

APPH: Appropriate for the protection of the public health

VUSE Alto Aerosols Contain Fewer HPHCs Than Combusted Cigarettes



“

...the new products' aerosols have **fewer HPHCs than CC smoke** and many of the HPHCs present in the aerosols have **comparatively lower potencies** (i.e., lower magnitude or severity of toxicological effect at a given dose or exposure level) than those present in CC smoke.

FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11; emphasis added.

”

Other constituents analyzed:

Benzyl acetate, Chromium, Diethylene glycol, Ethyl acetate, Ethyl acetoacetate, Glycerin, Isoamyl acetate, Isobutyl acetate, Menthol, Methyl acetate, N-butanol, Nickel, Propylene glycol

(<LOQ for all VUSE Alto replicates)

† Note: The LOQs for lead and propionic are numerically equivalent to or higher than, respectively, the reported mean values in combustible cigarette smoke. Therefore, the levels for lead and constituent increase noted for propionic acid (off scale) versus combustible cigarette smoke are likely overestimated.

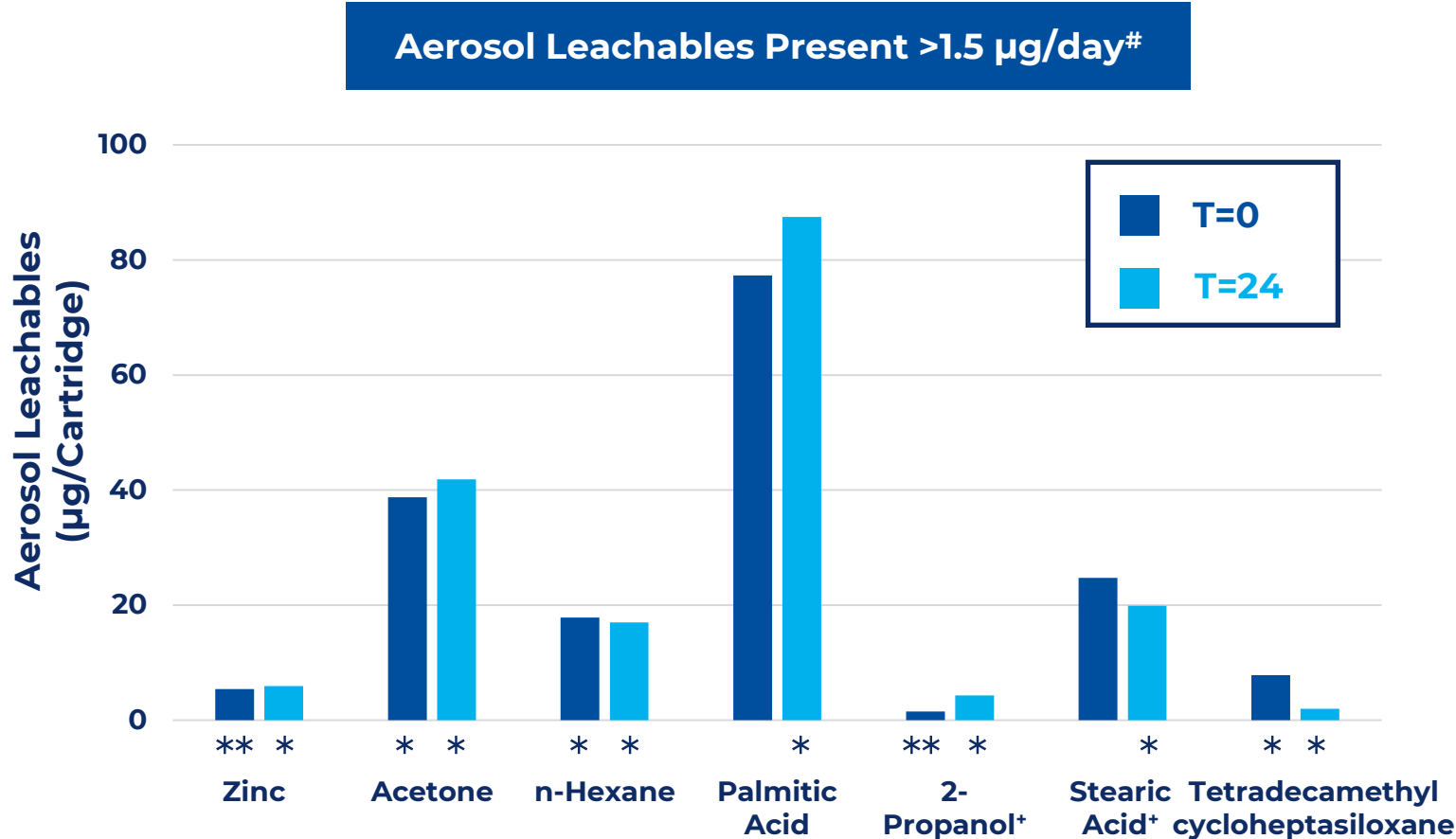
Inclusion of VUSE Alto Leachables in Tier 1–4 ELCR_c Calculations Not Clearly Identified

Simulated Leachables
Simulation study with e-liquids

Evaluated VUSE Alto cartridge components with potential to contact the e-liquid, aerosol, or heated inlet air

Aerosol Leachables
Actual Leachables in aerosol

VUSE Alto cartridges were stored at Long Term conditions (25°C & 60% relative humidity) for up to 24 months



[#]Based on estimated daily product use of 1 cartridge/day ^{**}All VUSE replicates were <LOQ or <1.5 µg/cartridge
^{*}Some VUSE replicates were <LOQ or <1.5 µg/cartridge ⁺Estimated value derived from untargeted scans

ELCR_c Calculations Indicate Lower Cancer Risk of VUSE Alto Relative to Combusted Cigarettes

Tier 1–3

- NNK
- Acrolein
- Chromium
- Formaldehyde
- 1–2 redacted constituents

<31

excess cancer cases per 100,000 users

Tier 1–4

- Tier 1–3 constituents
- Several redacted constituents
- No e-liquid ingredients included

110-720

excess cancer cases per 100,000 users

“

When the risk assessment includes Tier 1 – 4 constituents, the ELCR_c for the new [VUSE Alto] products fall between 1 – 10% of the 1R6F CC ELCR_c indicating **lower cancer risk** relative to CC [combusted cigarettes].

FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11; emphasis added.

”

FDA's Use of Cumulative Excess Lifetime Cancer Risk ($ELCR_c$) in ENDS Premarket Reviews



$ELCR_c$ calculations have been used to inform APPH determinations in four TPL reviews totaling 16 ENDS products



Tiered constituent analysis (Tier 1–3 vs Tier 1–4) provides lower and upper estimates of cancer risk



$ELCR_c$ estimates for these products are $\leq 15\%$ of 1R6F indicating lower cancer risk relative to combusted cigarettes

Tobacco Harm Reduction is *A Better Way to A Better Tomorrow™*

Our science & technology is bringing potentially reduced risk alternatives to the almost 30 million adult smokers. Knowledge and choice drive change.

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