

Abstract
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Quantitative Risk Assessment: Use of Cumulative Excess Lifetime Cancer Risk in an Electronic Nicotine Delivery System Premarket Review

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Introduction

The U.S. Food and Drug Administration (FDA) has recently incorporated cumulative excess lifetime cancer risk (ELCR_c) estimates to inform its scientific evaluations of Electronic Nicotine Delivery System (ENDS) Premarket Tobacco Product Applications (PMTAs).¹⁻²

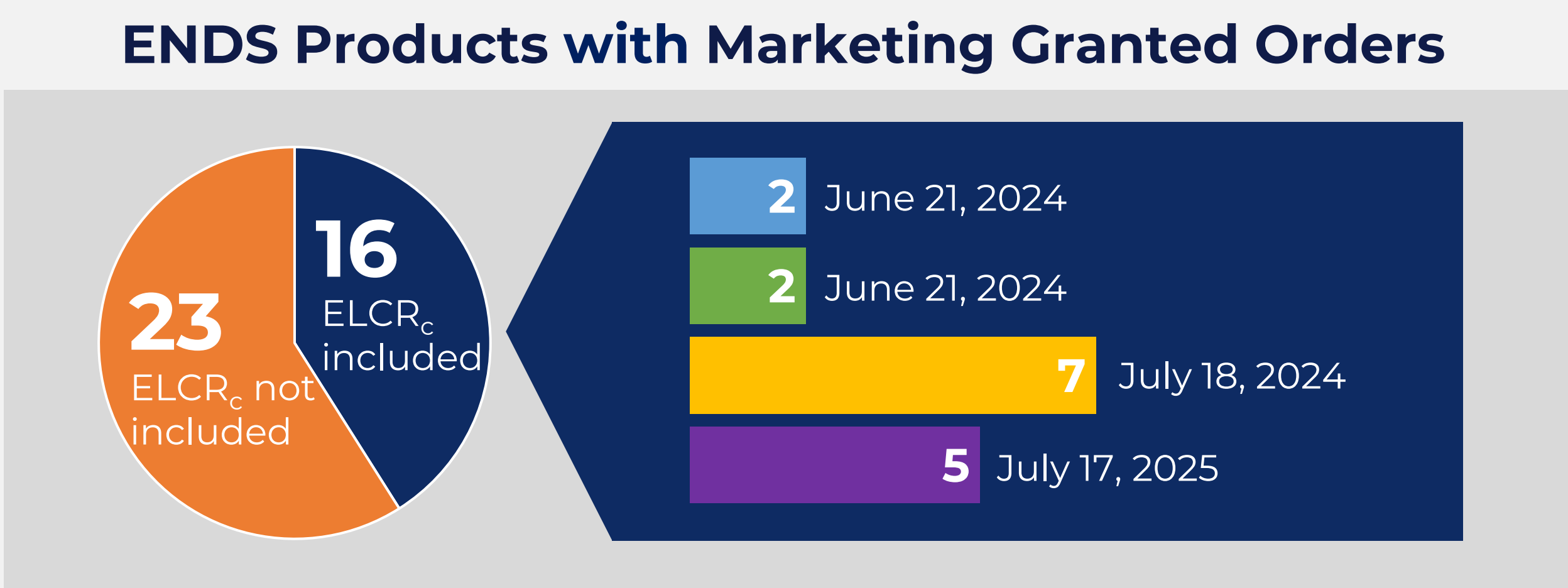


Figure 1. Of the 39 ENDS products with Marketing Granted Orders, ELCR_c is included in four Technical Project Lead (TPL) reviews totaling 16 products.³⁻⁶

Objectives

- Evaluate how ELCR_c was applied in FDA’s review of seven ENDS products that received Marketing Granted Orders on July 18, 2024
- Present results from the scientific studies critical for inclusion in the ELCR_c calculations
- Assess the implications of this methodology in FDA’s review

ELCR_c Overview

ELCR_c assessments align with a standard quantitative risk assessment framework: Hazard Identification, Exposure Assessment, Dose-Response Assessment, and Risk Characterization.

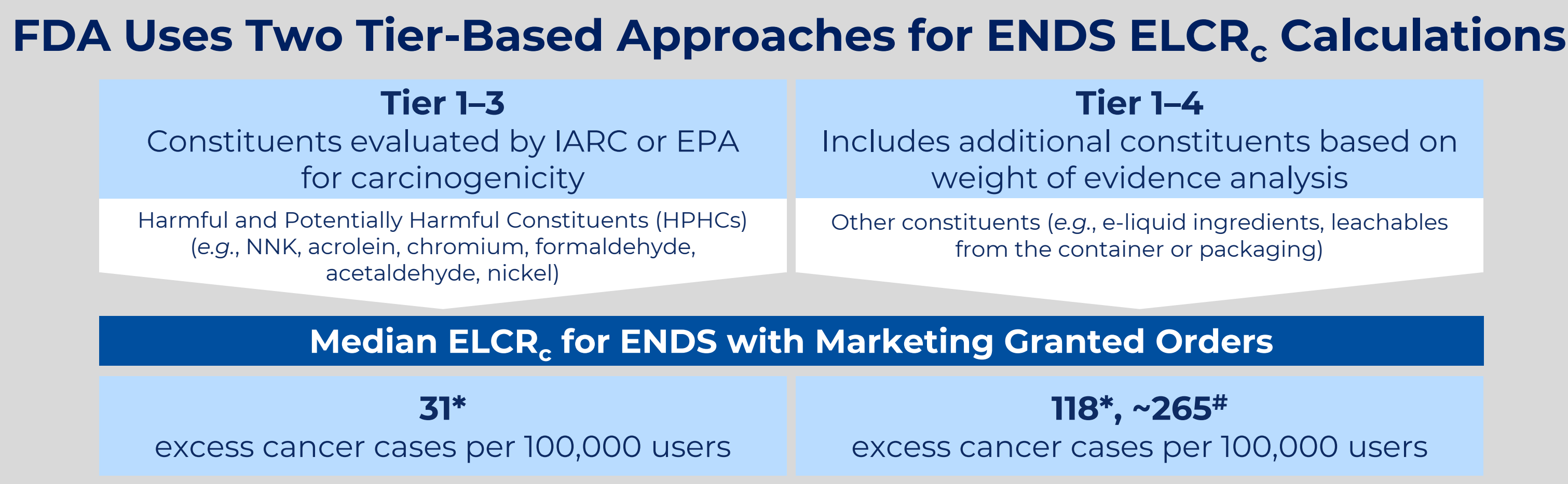


Figure 2. FDA’s two tier-based hazard identification approaches for ENDS ELCR_c calculations and the median ELCR_c for ENDS with Marketing Granted Orders. (*) As of February 2024 (#) Calculated from FDA (2025)⁶

Aerosol Chemistry

ENDS Aerosols Contain Fewer HPHCs Than Combusted Cigarettes

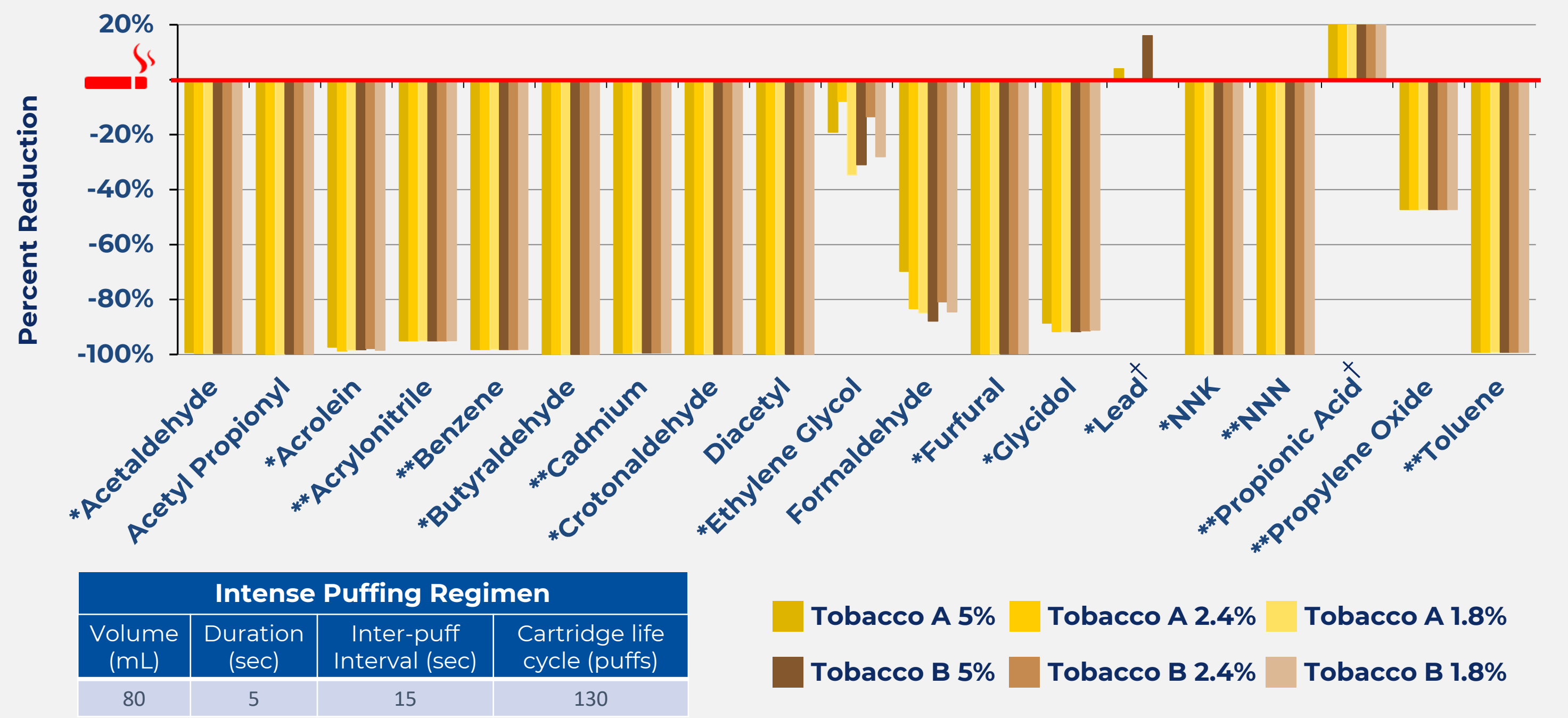
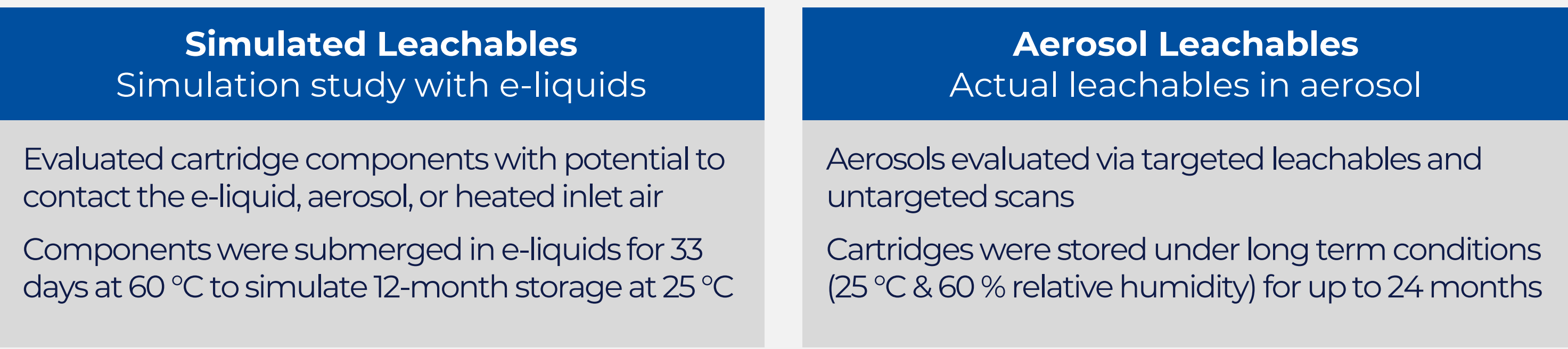


Figure 3. Percent reductions of HPHCs in aerosols compared to combusted cigarettes. (*)Some or (**) all replicates were <LOQ. (!) Note: The LOQs for lead and propionic acid are numerically equivalent to or higher than, respectively, the reported mean values in combusted cigarette smoke. Thus, the levels for lead and constituent increase noted for propionic acid (off scale) versus combusted cigarette smoke are likely overestimated.

Simulated & Aerosol Leachables



Seven Aerosol Leachables Present at Levels > 1.5 µg/day[#]

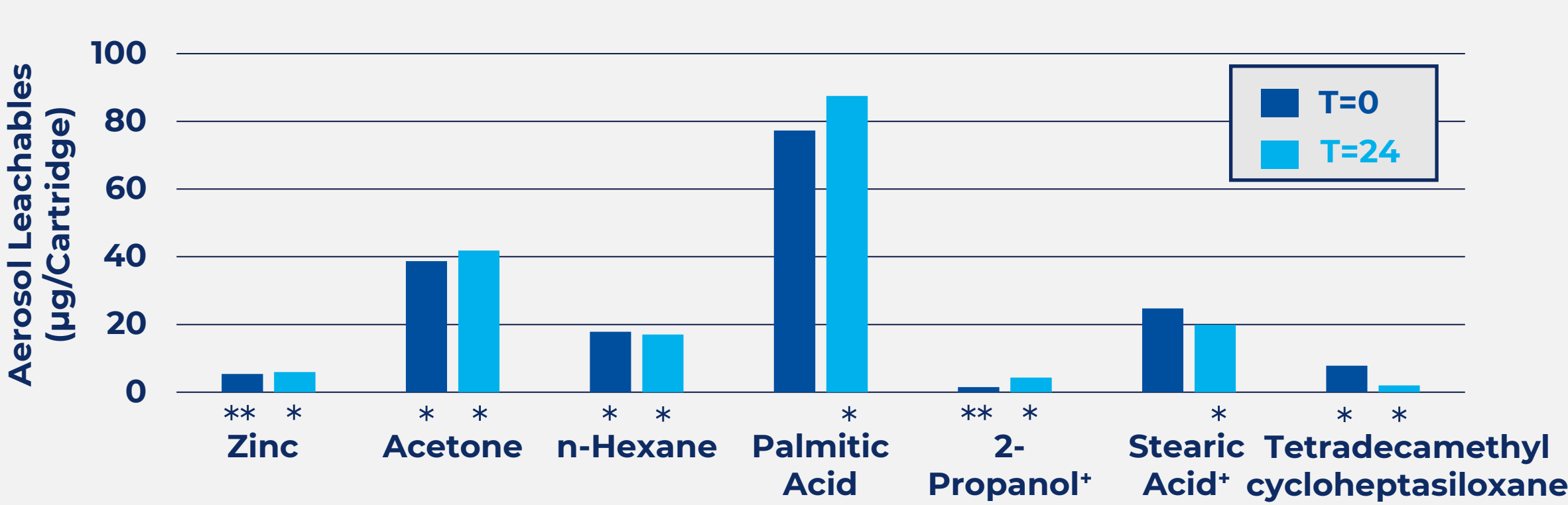


Figure 4. Aerosol leachables present at > 1.5 µg/day at set down (T=0) or after 24 months of storage (T=24) under long term conditions based on estimated daily product use of 1 cartridge/day. (#) The cancer-hazard TTC (1.5 µg/day) for individual ENDS constituents? (*)Some or (**) all replicates were <LOQ or <1.5 µg/cartridge. (!)Estimated value derived from untargeted scans.

ELCR_c Estimates

ELCR_c Estimates of the Seven ENDS Products Indicate Lower Cancer Risk Relative to Combusted Cigarettes

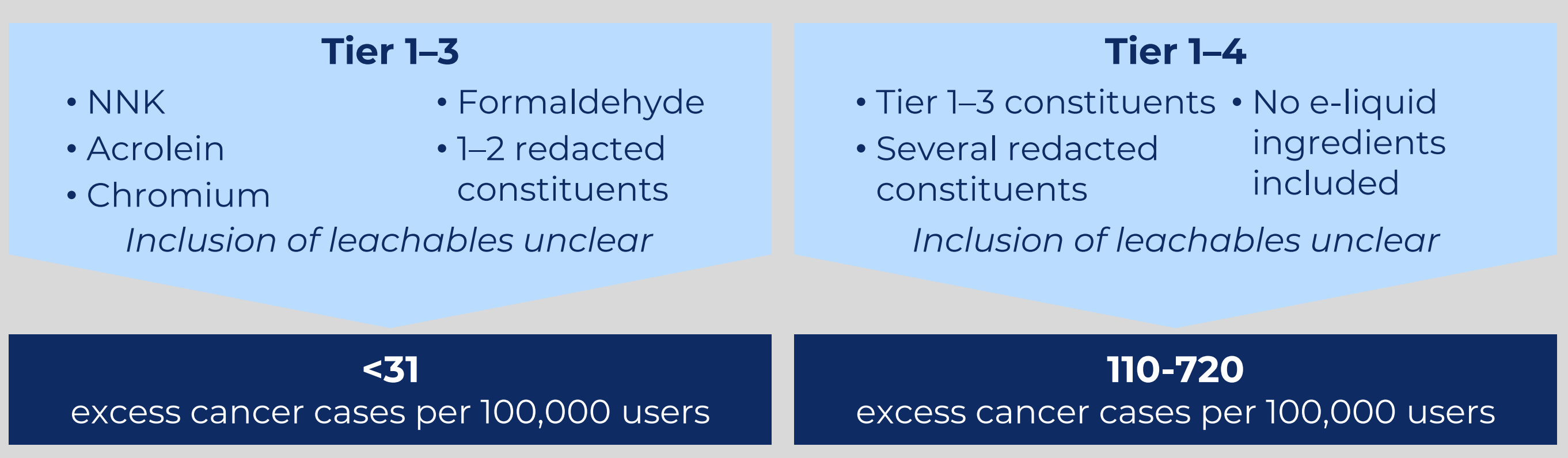


Figure 5. Tier 1-3 ELCR_c calculations included well-established carcinogens. Tier 1-4 ELCR_c calculations notably did not include e-liquid ingredients. Inclusion of leachables in ELCR_c calculations not clearly identified. Tier 1-3 and Tier 1-4 ELCR_c estimates ranged from less than 31 to 720 excess cancer cases per 100,000 users.



Figure 6. ELCR_c values of the seven ENDS products were substantially lower than those of combusted cigarettes. These estimates represent less than 0.31% to 7.2% of the cited² 1R6F reference cigarette benchmark of 10,000 excess cancer cases per 100,000 users corresponding to FDA’s risk management descriptors of lower to moderate concern.

Conclusions

- ELCR_c provides a standardized, quantitative approach for evaluating carcinogenic risk across ENDS products.
- Tier-based evaluations include carcinogenic constituents with varying levels of evidence, generating robust risk estimates
- Overall findings for the seven ENDS products consistently indicate substantially lower predicted excess cancer risks than those associated with combusted cigarettes.

