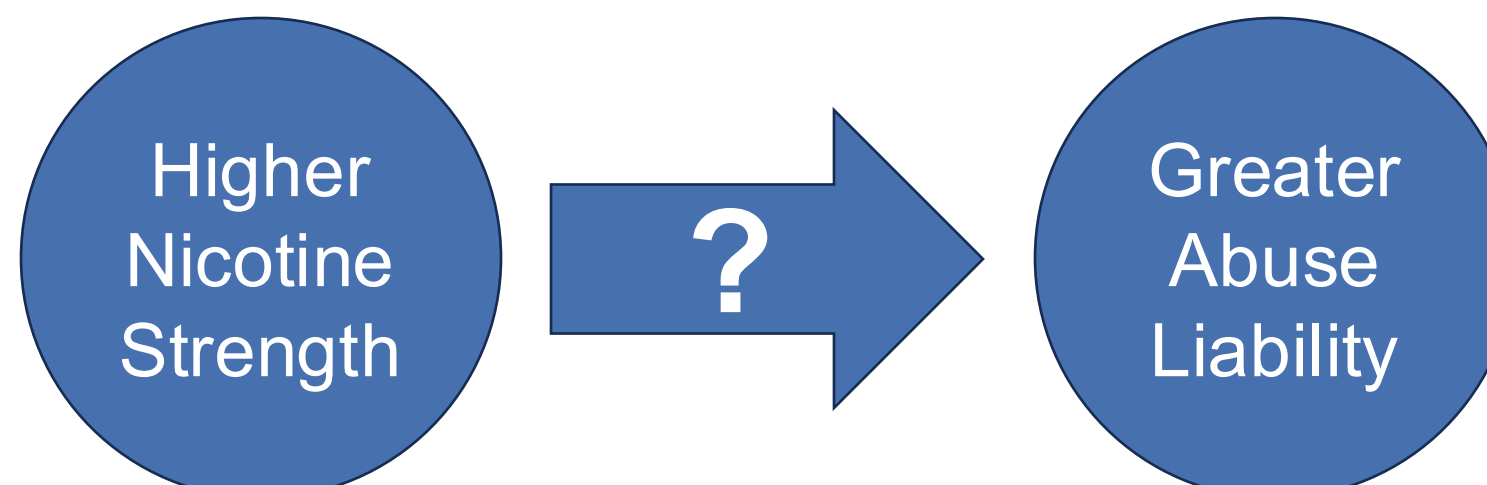


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CHEMULAR

Background

- Abuse liability is an important determinant of whether a nicotine pouch product is Appropriate for the Protection of the Public Health.
- Abuse liability studies assess nicotine pharmacokinetics, subjective effects, and use behaviors under both controlled and ad libitum conditions, with final determinations based on the totality of evidence.
- Labeled nicotine strength is often used as a simple proxy for abuse liability, but product chemistry, nicotine form, pH, release kinetics, matrix composition, and use behavior may substantially modify the relationship between labeled content and actual nicotine exposure.



- Purpose:** To determine whether nominal nicotine content is reliable predictor of abuse liability.

Methods

Overview: Cross-study analysis of 121 nicotine pouch products assessed across 25 published and unpublished abuse liability studies.

Product Database and Data Filtering:

- All studies had at least one abuse liability outcome measured during controlled or ad libitum use.
- Included commercial nicotine pouch products (nominal nicotine range 1.5–30 mg), excluding high-dose (>35 mg).
- Numerical outcome variables (13) included pharmacokinetic, pharmacodynamic, and behavioral.

Comparative Bivariate Modeling:

- Simple ordinary least squares linear regressions.
- Logarithmic power models ($\ln(Y) = \alpha + \beta \ln(\text{dose})$).

Formal Dose-Proportionality Testing:

- Evaluated log-power exponents (β) for nicotine exposure outcomes (C_{max}, AUC) in Controlled and Ad Libitum use.
- Test whether $\beta = 1.0$ (within 90% CIs) to determine whether nicotine exposure scales linearly with nominal content (Gough et al, 1995; Smith et al, 2000).

Synthesis and Interpretation:

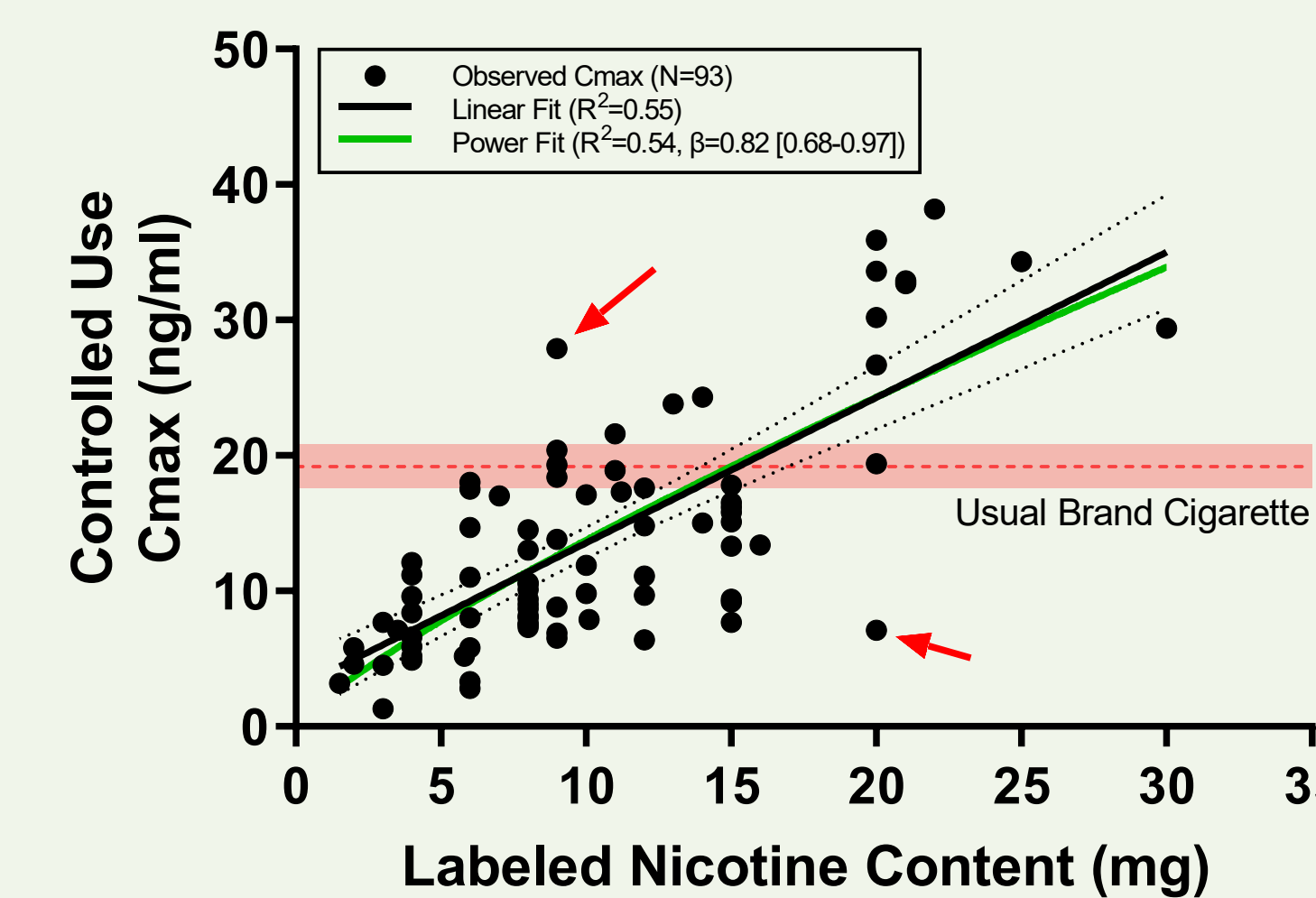
- Test predictive validity of nominal nicotine strength (R^2) for each outcome.
- Compare to aggregated data from Usual Brand Cigarette.

Published studies included: Lunell et al, 2020; Rensch et al, 2021; McEwan et al, 2022; Liu et al, 2022; Chapman et al, 2022; Azzopardi et al, 2022; Mallock-Ohnesorg et al, 2024; Renard et al, 2025; Kanobe et al, 2025; Azzopardi et al, 2026; Chapman et al, 2025; and Prizulj et al, 2025.

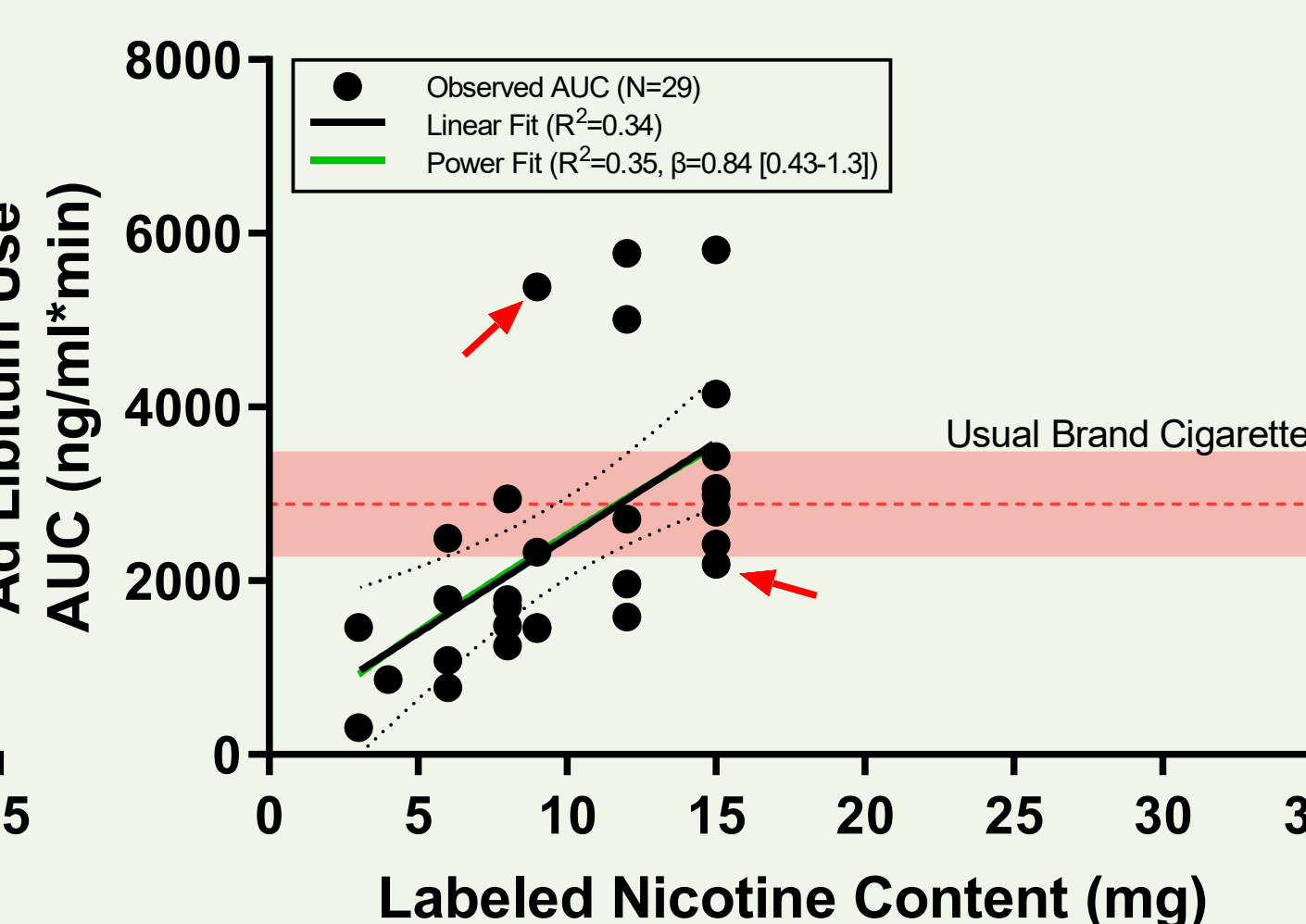
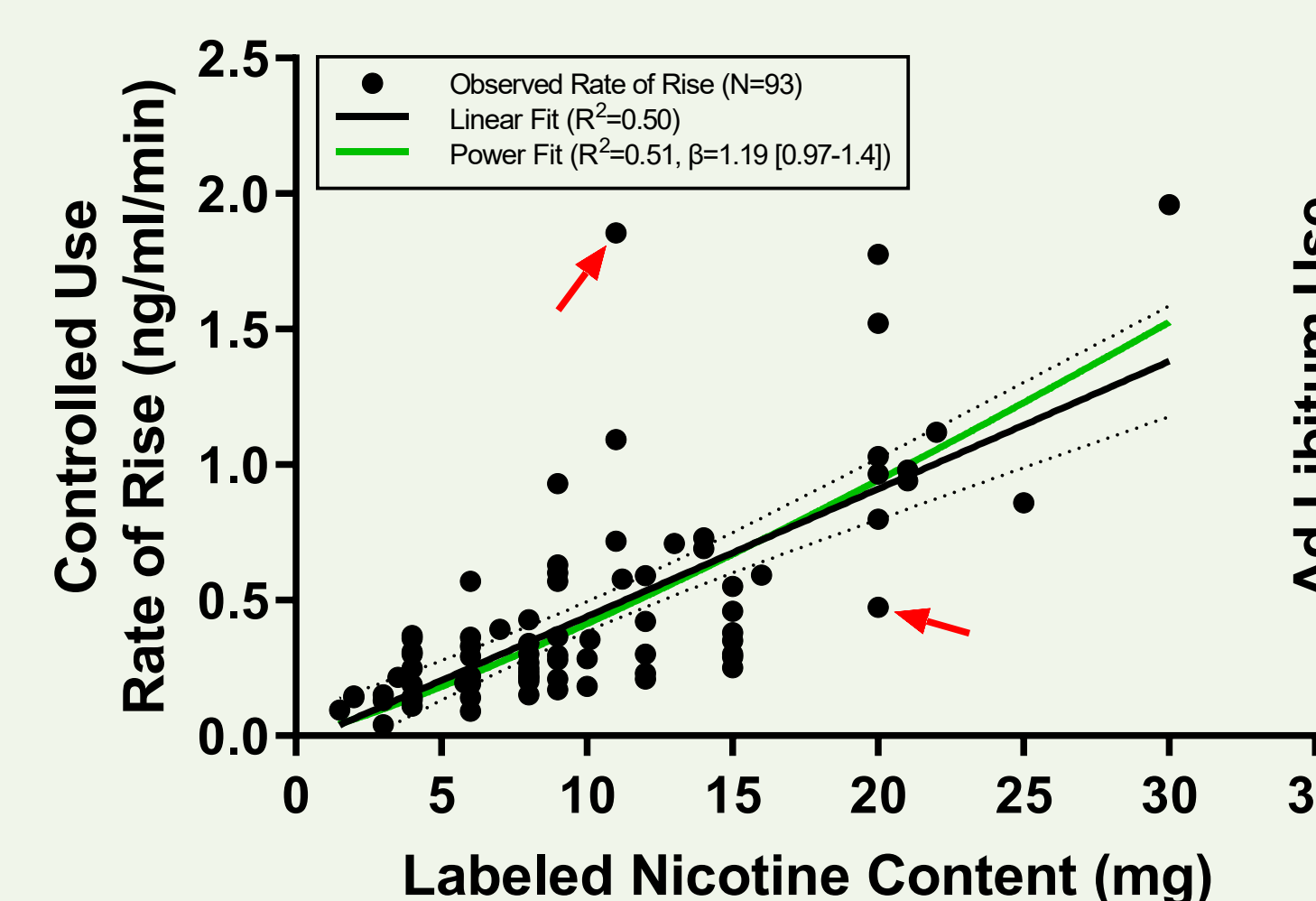
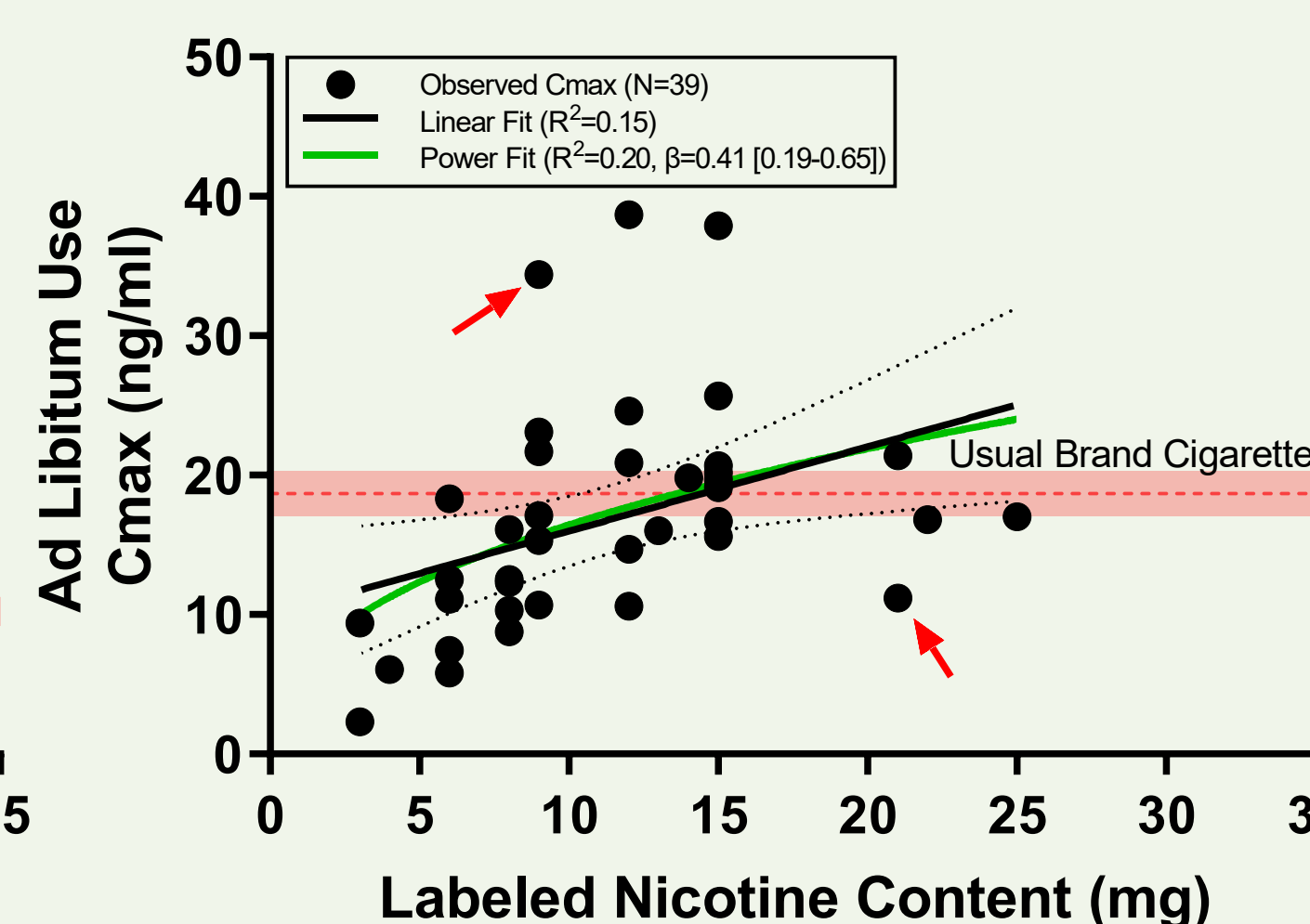
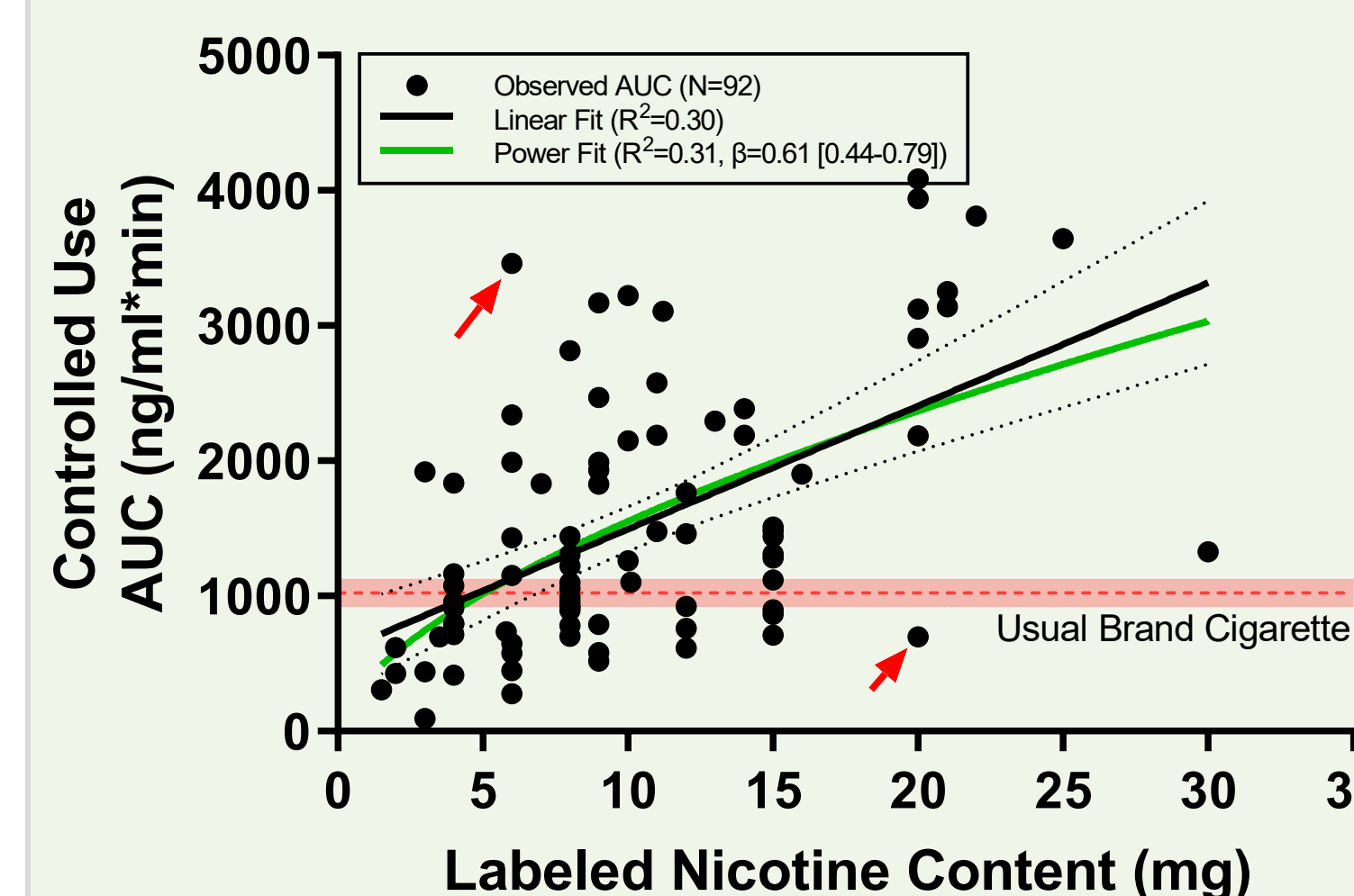
Outcomes Appropriate for the Protection of Public Health		
Outcome	Comparison to Cigarette	Reason
Controlled Use C _{max}	Lower	Lower nicotine exposure
Controlled Use Rate of Rise	Slower	Less reinforcing
Ad Libitum C _{max} and AUC	Lower	Lower nicotine exposure
Product Liking	Similar	Promotes switching
Intent to Use Again	Similar	Promotes switching
Suppression of Urge to Smoke	More Persistent	Promotes switching
Product Use	Fewer	Less reinforcing

Results

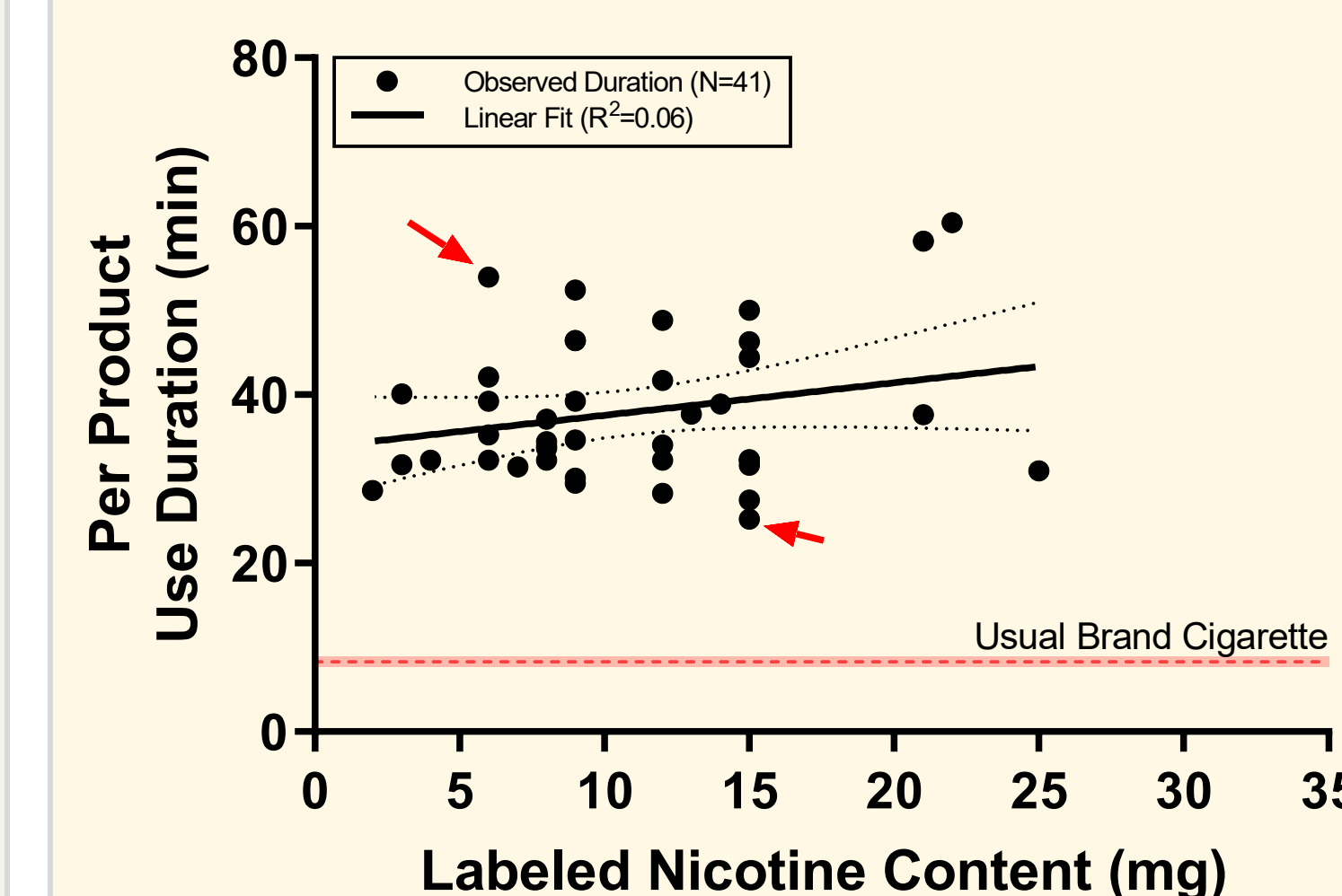
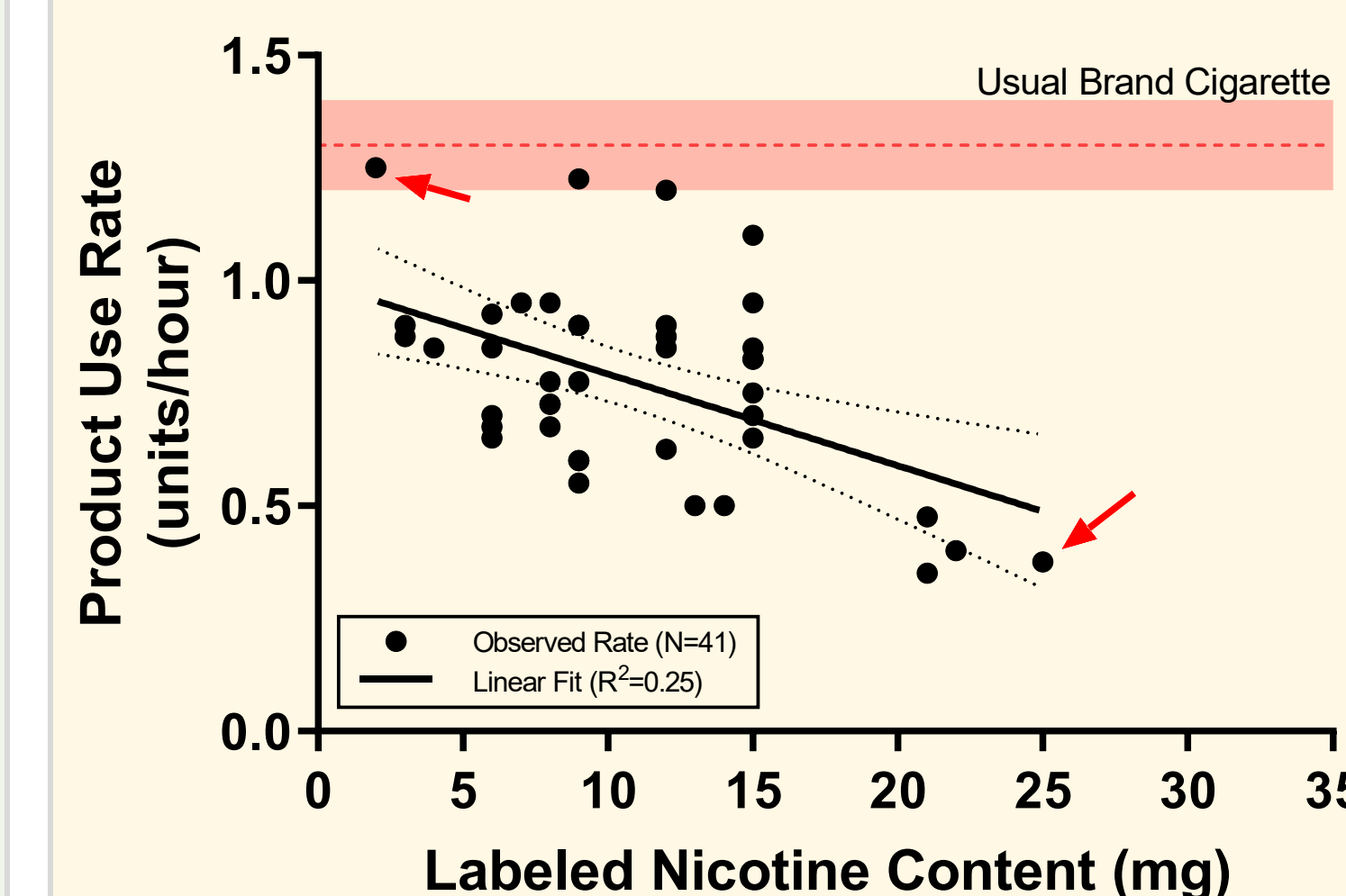
Pharmacokinetic



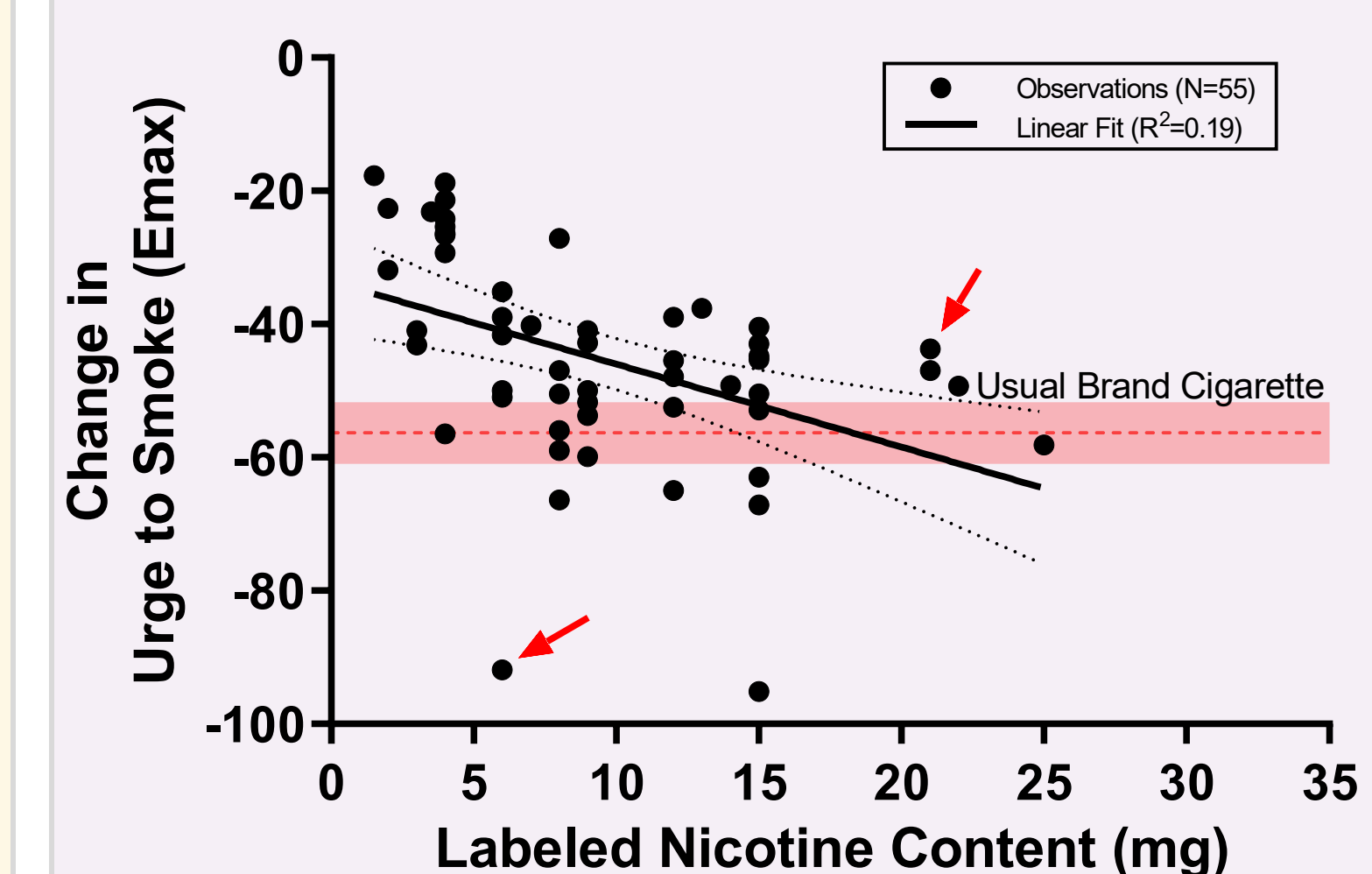
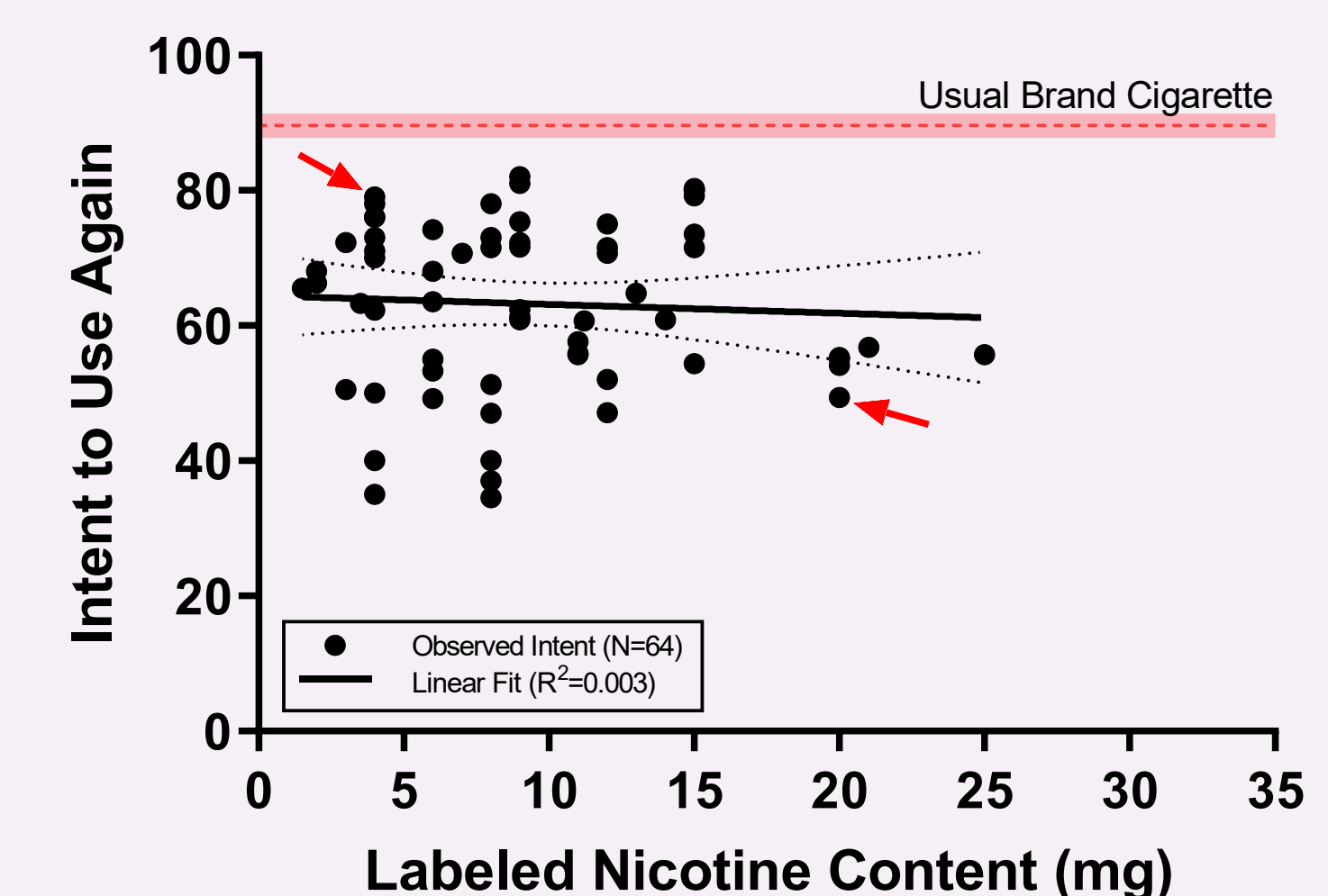
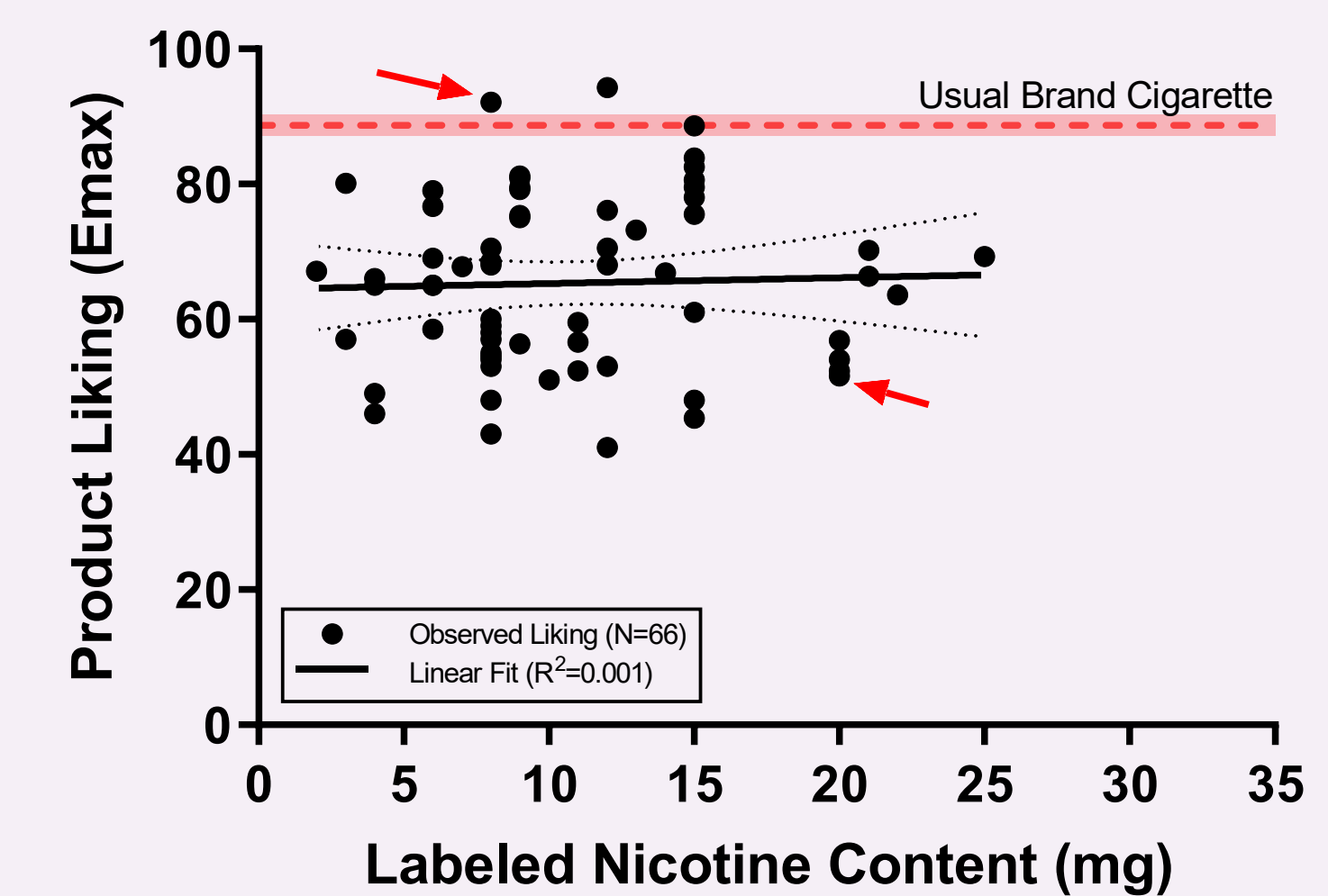
Note: Usual Brand Cigarette results generated from a meta-analysis of all database results



Product Use



Subjective Effects



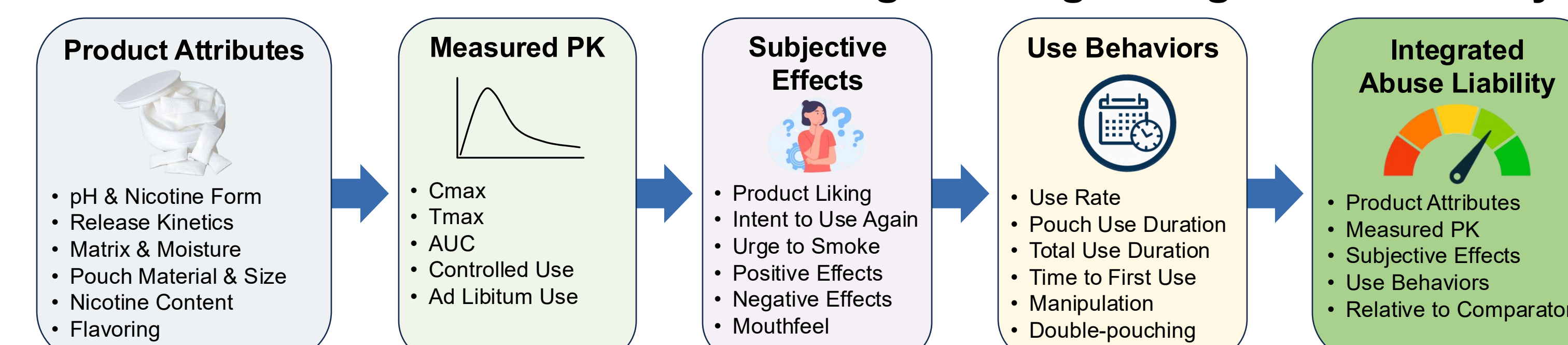
Conclusions

- Nominal nicotine strength alone explained little of the variability in abuse liability outcomes.**
- Higher labeled strength was not consistently associated with higher C_{max}, AUC, peak subjective effects, or use behaviors.
- Duration of Use, Product Liking, and Intent to Use Again showed very weak relationships with nicotine content, suggesting these outcomes may not adequately differentiate products of differing abuse liabilities.
- Approach is limited by sparse data on many outcomes and nicotine strengths, as well as extensive variability in study designs (e.g., duration of assessment period), sample size, and analytical approach.

- Collectively, these findings indicate that labeled nicotine strength, considered in isolation, is an unreliable basis for assessing abuse liability or establishing categorical nicotine content limits.

- Instead, abuse liability determinations should integrate product attributes with PK, subjective effects, and use behaviors.

A Better Framework for Understanding and Regulating Abuse Liability



Related Presentations:

- # 67 (Tuesday 11:30AM) - Machine learning identification of product attributes associated with nicotine pharmacokinetics under controlled use conditions
- # 79 (Tuesday Poster) - AI-based nicotine pharmacokinetic prediction to support product development and regulatory decision-making

Scan here for a copy of the poster or more information

