SILESIAN UNIVERSITY OF TECHNOLOGY PUBLISHING HOUSE

SCIENTIFIC PAPERS OF SILESIAN UNIVERSITY OF TECHNOLOGY 2025
ORGANIZATION AND MANAGEMENT SERIES NO. 235

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING OF NICOTINE

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Purpose: The purpose of this study is to develop an in silico PBPK model predicting nicotine pharmacokinetics in users of e-cigarettes and traditional cigarettes across health conditions.
Design/methodology/approach: The model was implemented in MATLAB ODE45 solver, incorporating ADME processes and disease-specific parameters for liver disease, obesity, cardiovascular, lung, and neurological disorders**.**
Findings: Nicotine pharmacokinetics varied significantly across health conditions. E-cigarettes produced sustained nicotine exposure, while traditional cigarettes led to sharp peaks. Liver disease and obesity caused major changes in nicotine clearance and storage.
Research limitations/implications: The model depends on literature-derived parameters and does not incorporate individual puffing behavior or pharmacogenomics. Future studies should integrate real-world vaping data.
Practical implications: Findings support the design of personalized smoking cessation strategies and improved risk assessment for vulnerable populations.
Social implications: Results suggest e-cigarettes may not be universally safer and highlight public health risks in patients with comorbidities.
Originality/value: This study is among the first to apply PBPK modeling across multiple health conditions for nicotine exposure in e-cigarette vs traditional cigarette users.
Keywords: Physiologically-Based Pharmacokinetic Model (PBPK), Nicotine Pharmacokinetics, E-Cigarettes, Traditional Cigarettes, Health Conditions.
Category of the paper: Research paper.

1. Introduction

Nicotine is a highly addictive substance with significant physiological effects, influencing cardiovascular, neurological, and metabolic functions (Besaratinia, 2019). The world has witnessed a shift in smoking behavior toward e-cigarettes which have gained popularity as an alternative to traditional tobacco products. The World Health Organization (WHO) reports that 1.3 billion people across the globe use nicotine products while e-cigarette usage has surged notably among younger generations (Birdsey, 2023). The number of worldwide e-cigarette users reached 82 million in 2023 while the user base expanded from just a few million in the previous decade (Center for Tobaco; 2025). Traditional cigarettes continue to be the main source of smoking-related illnesses but e-cigarettes present themselves as safer alternatives even though scientists continue to study their permanent health implications (Dorotheo, 2024).

E-cigarette usage has shown a significant increase in youth demographics. The U.S. Food and Drug Administration (FDA) together with the Centers for Disease Control and Prevention (CDC) documented that 2.1 million middle and high school students in the United States used e-cigarettes during 2023 thus creating worries about teenage nicotine addiction (Eaton, 2018); (Farsalinos, 2014). Studies demonstrate that e-cigarette brands contain different levels of nicotine which results in unstable nicotine exposure and elevates the risk of addiction (Guo, 2022).

The main difficulty in nicotine research involves studying how nicotine pharmacokinetics changes between combustible tobacco products and aerosolized nicotine delivery systems. The rate of nicotine absorption, its peak concentration, and systemic retention all vary depending on the mode of intake, which can influence addiction potential, toxicity, and cessation strategies (Helen, n.d.). The delivery of nicotine through traditional cigarettes results in fast nicotine delivery and high peak concentrations but e-cigarettes produce sustained nicotine exposure because of variations in aerosol deposition and bioavailability (Kramarow, 2021; Perry, 2020).

The method of administration plays a role but individual health conditions strongly affect how the body metabolizes and clears nicotine. The enzymatic activity and blood flow and organ-specific nicotine retention in the body change due to chronic diseases such as liver dysfunction, cardiovascular disease, obesity, pulmonary disorders and neurological impairments which produce substantial variations in nicotine disposition among individuals (Peters, 2021; Peters, 2019). Liver disease leads to longer nicotine retention because the liver cannot properly metabolize the substance yet obesity leads to increased nicotine storage in body fat which slows down its elimination from the body (Prasad, 2024). The traditional cigarette users with pulmonary diseases like COPD experience altered nicotine absorption rates and neurological disorders create challenges for nicotine to cross the blood-brain barrier (Prasad, 2024; Robinson, 1992).

The analysis of these effects requires systematic studies which use Physiologically-Based Pharmacokinetic (PBPK) models to simulate how nicotine enters the body and moves through it while being metabolized and eliminated across various physiological states (Prasad, 2024; Rostami, 2022). The models analyze how e-cigarette and traditional cigarette users experience pharmacokinetic profiles throughout a 24-hour period by measuring steady-state concentrations (Css), half-life (t1/2) and compartmental distribution (Rostami, 2022; Schneider, 1996). The research reveals major pharmacokinetic variations between nicotine delivery systems and shows that individualized smoking cessation strategies are essential for people with existing health issues (Rostami, 2022).

The integration of computational modeling into nicotine research enables scientists to quantify the risks between e-cigarettes and traditional cigarettes through mathematical evaluation. The obtained insights hold essential value for public health policy-making and clinical guidance as well as intervention development for smokers and vapers with different health profiles.

In this study, we developed a Physiologically-Based Pharmacokinetic (PBPK) model alongside an absorption, distribution, metabolism, and elimination (ADME) analysis, incorporating mathematical simulations of nicotine transport—supplied by traditional cigarettes and e-cigarettes—across various tissues and organs.

2. Methods

The Physiologically-Based Pharmacokinetic (PBPK) model replicated how nicotine moves through the body by absorption, distribution metabolism and elimination (ADME) across various physiological states (Fig. 1). The model divides into six compartments which include the lungs blood liver brain and fat tissue along with metabolites that exchange nicotine between compartments through first-order rate equations. The system of differential equations tracked compartmental nicotine concentrations while parameters needed adjustment for each health condition.

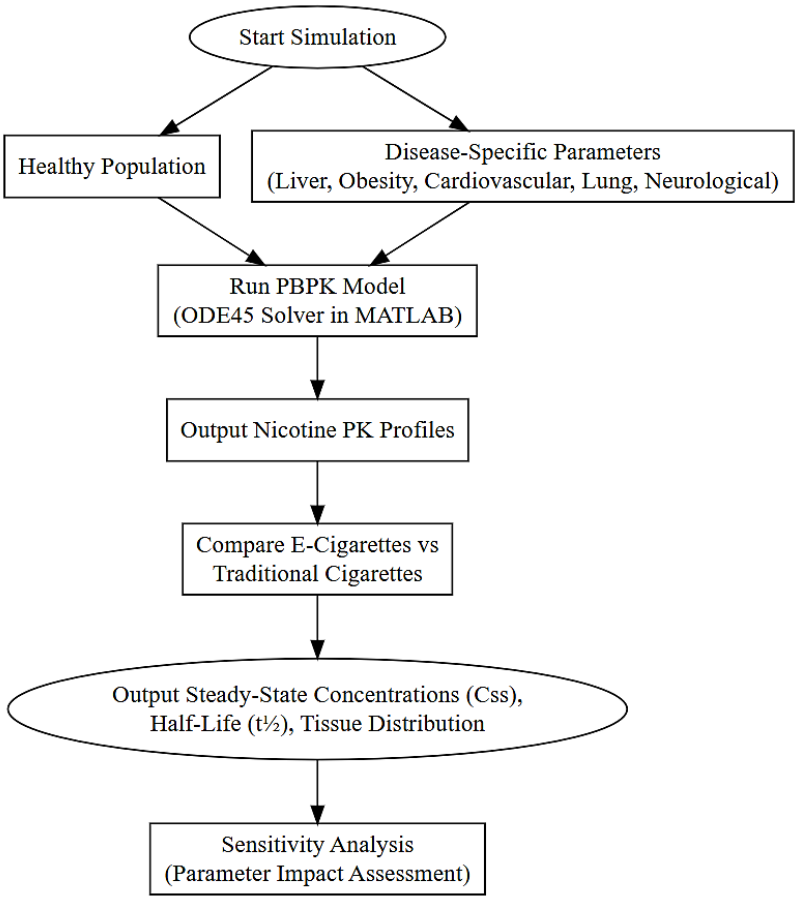

Figure 1. Workflow of the Physiologically-Based Pharmacokinetic (PBPK) Model Simulations and Analysis Steps.

Source: Authors' own.

2.1. Mathematical Modeling of Nicotine Transport and Tissue Distribution

Nicotine enters the lungs following inhalation and is transported into the systemic circulation, where it is further distributed to liver, brain, fat, and other tissues (Fig. 2).

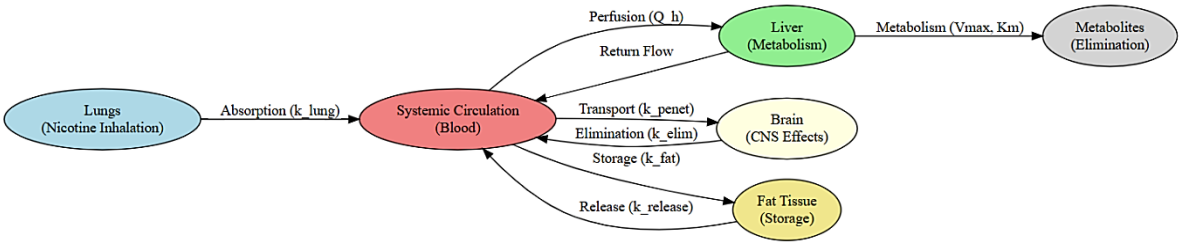

Figure 2. Physiologically-Based Pharmacokinetic Model (PBPK) of Nicotine Distribution and Metabolism Across Compartments.

Source: Authors' own.

The transport between compartments is governed by perfusion-limited kinetics (equations (1) and (2):

$$\frac{dC_{lung}}{dt} = \frac{Dose(t)}{V_p} - \frac{Q_p}{V_p}(C_{lung} - C_{blood}) \tag{1}$$

$$\frac{dC_{blood}}{dt} = \frac{Q_p}{V_b}(C_{lung} - C_{blood}) - \frac{Q_h}{V_b}(C_{blood} - C_{liver}) - k_{distrib}C_{blood} - k_{penetr}C_{blood} + k_{elim}C_{brain} - k_{fat}C_{blood} + k_{release}C_{fat} - k_{eliminb}C_{blood} \tag{2}$$

where:

- Q_p and Q_h represent blood flow to the lungs and liver (L/h), respectively.
- $k_{distrib}$ represents nicotine distribution to peripheral tissues (1/h).
- k_{penetr} and k_{elim} denote brain penetration and elimination rates (1/h).
- k_{fat} and $k_{release}$ account for nicotine storage and release from adipose tissue.
- $k_{eliminb}$ models nicotine elimination directly from the blood.

Nicotine metabolism occurs predominantly in the liver, where it undergoes enzymatic degradation following Michaelis-Menten kinetics (equations (3) and (4):

$$\frac{dC_{liver}}{dt} = \frac{Q_h}{V_l}(C_{blood} - C_{liver}) - \frac{k_{metabmax}C_{liver}}{K_m + C_{liver}} + k_{distrib}C_{blood} \tag{3}$$

$$\frac{dC_{metabolities}}{dt} = \frac{k_{metabmax}C_{liver}}{K_m + C_{liver}} \tag{4}$$

where:

- $k_{metabmax}$ is the maximum hepatic metabolism rate (ng/h).
- K_m is the Michaelis-Menten constant (ng/mL).

Nicotine crosses the blood-brain barrier, where it accumulates and undergoes elimination. Similarly, nicotine is stored in adipose tissue, affecting long-term retention (equations (5) and (6):

$$\frac{dC_{brain}}{dt} = k_{penetr}C_{blood} - k_{elim}C_{brain} \tag{5}$$

$$\frac{dC_{fat}}{dt} = k_{fat}C_{blood} - k_{release}C_{fat} \tag{6}$$

where:

- the brain penetration rate (k_{penetr}) and elimination rate (k_{elim}) are modified under neurological disorders,
- fat storage and release constants (k_{fat} and $k_{release}$) vary in obese individuals.

2.2. Nicotine Dosing Regimen

The nicotine dose intake function is modeled as a series of discrete inhalation events at a fixed time interval (equation (7)):

$$Dose\,(t) = \sum_{t_d} dose \cdot \delta(t - t_d) \tag{7}$$

where:

- E-cigarette users receive a dose of $3000 \times F_{e\text{-}cig}$ ng every hour.
- Traditional cigarette smokers receive $1500 \times F_{cig}$ ng every hour.
- $F_{e\text{-}cig}$ and $F_{cigrepresent}$ nicotine bioavailability.
- The Kronecker delta function δ(t) ensures nicotine is introduced at each dosing time.

2.3. Physiological and Disease-Specific Parameter Adjustments

To model the effect of different disease states, specific PBPK parameters were adjusted based on physiological alterations reported in the literature (Table 1).

Table 1.
Adjusted PBPK Model Parameters for Different Physiological Conditions, where:

Condition	Qh (L/h)	kmetabmax (ng/h)	kpenet	kelimin	kfat	krelease	keliminb
Healthy	1.5	1.2	2.0	0.7	0.1	0.05	0.2
Liver Disease	1.2 ⬇	0.6 ⬇	2.0	0.7	0.1	0.05	0.1 ⬇
Cardiovascular	1.0 ⬇	1.0	2.2 ⬆	0.75 ⬆	0.12 ⬆	0.045	0.18
Obesity	1.5	1.2	2.0	0.7	0.15 ⬆	0.035 ⬇	0.16 ⬇
Lung Disease	0.8 ⬇	1.1	2.0	0.7	0.1	0.05	0.2
Neurological	1.4	1.0 ⬇	2.5 ⬆	0.5 ⬇	0.11 ⬆	0.045	0.16 ⬇

⬆ = Increased ⬇ = Decreased.

Source: Authors' own.

2.4. Computational Simulations

The PBPK model was implemented in MATLAB v. R2024b (MathWorks Inc., Natick, MA, USA), using implemented ODE45 solver, which numerically integrates the system of differential equations governing nicotine absorption, distribution, metabolism, and elimination. The simulation was run over a 24-hour time period, with a temporal resolution of 500 time points, ensuring sufficient granularity to capture dynamic concentration changes across compartments.

The steady-state concentration (Css) for each compartment was determined by averaging nicotine levels over the final 6 hours of the simulation, ensuring that transient fluctuations did not impact the estimation of equilibrium values (equation (8)):

$$C_{ss} = \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} C(t)dt \quad (8)$$

where t_1 = 18 hours and t_2 = 24 hours mark the final portion of the simulation, allowing for nicotine distribution equilibrium to be captured effectively.

At the beginning of each simulation, the initial nicotine concentration in all compartments was set to zero, representing a baseline condition before nicotine exposure. The elimination of nicotine from the system was evaluated by computing its half-life ($t_{1/2}$), which depends on both the first-order elimination rate (k_{elim}) and the Michaelis-Menten metabolism rate ($k_{metabmax}$), using the following equation (9):

$$t_{1/2} = \frac{ln2}{k_{elim} - \frac{k_{metabmax}}{K_m + C_{ss}}} \quad (9)$$

2.5. Sensitivity analysis

The sensitivity analysis was used to determine how changes in key physiological and pharmacokinetic parameters affected model outcomes such as steady-state concentrations (C_{ss}) of nicotine, half-life ($t_{1/2}$) and tissue distribution across different health conditions. This analysis was undertaken to determine which parameters the PBPK model was most sensitive to, and thus which physiological factors were most important in determining nicotine pharmacokinetics.

The sensitivity analysis was performed separately for e-cigarettes and traditional cigarettes across key populations: healthy individuals, those with liver disease, obesity, and neurological disorders. For each scenario, all parameters were individually varied by ±30%. Changes in C_{ss} (brain and blood) and $t_{1/2}$ were recorded, and the relative sensitivity coefficient (RSC) was calculated as:

$$RSC = \frac{\Delta Output/Output}{\Delta Parameter/Parameter} \quad (10)$$

The analysis focused on comparing the relative influence of each parameter across the two nicotine delivery methods (e-cigarettes and traditional cigarettes) to capture method-specific pharmacokinetic differences. The results were visualized using a heatmap to highlight variations across conditions and delivery methods.

3. Results

The pharmacokinetic analysis of nicotine in various physiological conditions revealed significant differences in steady-state concentrations (C_{ss}) and half-life ($t_{1/2}$) (Table 2).

Table 2.
Summary of Nicotine Pharmacokinetics Across Conditions

Condition	Css in Brain (ng/mL) (E-Cig)	Css in Brain (ng/mL) (Cig)	Css in Blood (ng/mL) (E-Cig)	Css in Blood (ng/mL) (Cig)	t1/2 (h) (E-Cig)	t1/2 (h) (Cig)
Healthy	11.00	18.64	04.08	07.01	0.96	0.96
Liver Disease	24.74	3.40	9.18	1.41	0.98	0.98
Cardiovascular	16.32	6.89	6.1	2.74	1.12	1.12
Obesity	21.41	15.38	7.64	5.79	1.12	1.12
Lung Disease	13.06	2.91	05.05	01.02	01.03	01.03
Neurological	4.69	9.52	0.98	02.02	1.33	1.34

Source: Authors' own.

In a healthy population, nicotine exhibited rapid metabolism and clearance, resulting in a short half-life of approximately 0.96 hours for both e-cigarette and traditional cigarette users. However, the source of nicotine significantly influenced its distribution. Traditional cigarette smokers had higher nicotine concentrations in the brain (C_{ss} = 18.64 ng/mL) and blood (C_{ss} = 7.01 ng/mL) compared to e-cigarette users, where these values were lower (11.00 ng/mL and 4.08 ng/mL, respectively). This discrepancy suggests that the rapid combustion of tobacco in traditional cigarettes facilitates a faster and more intense nicotine delivery, while the aerosolized nicotine from e-cigarettes provides a more gradual and sustained release. The plot of nicotine concentration over time (Figure 3) further illustrates this difference, showing sharper peaks in the lungs and blood for traditional cigarettes, whereas e-cigarette users exhibit a smoother, prolonged nicotine profile.

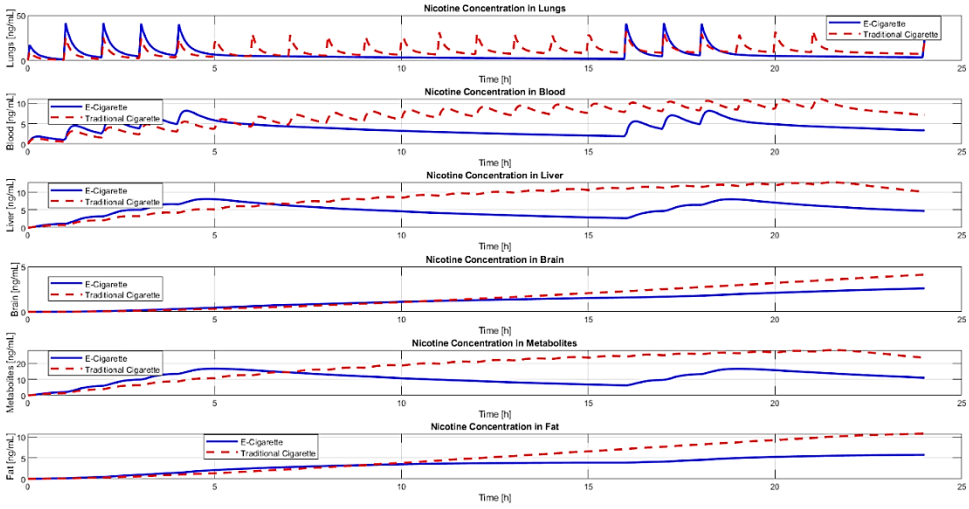

Figure 3. Nicotine concentration in a healthy individual.

Source: Authors' own.

The pharmacokinetics of nicotine underwent a significant transformation in patients with liver disease especially among e-cigarette users. The hepatic metabolic impairment led to excessive brain and blood nicotine accumulation at levels of 24.74 ng/mL and 9.18 ng/mL

respectively in e-cigarette users compared to healthy individuals. Traditional cigarette smokers demonstrated lower brain nicotine concentrations (C_{ss} = 3.40 ng/mL) and blood nicotine levels (C_{ss} = 1.41 ng/mL) compared to other participants. The results depicted in Figure 4 confirm that liver dysfunction affects e-cigarette-derived nicotine more significantly which could elevate toxicity risks because of extended exposure times.

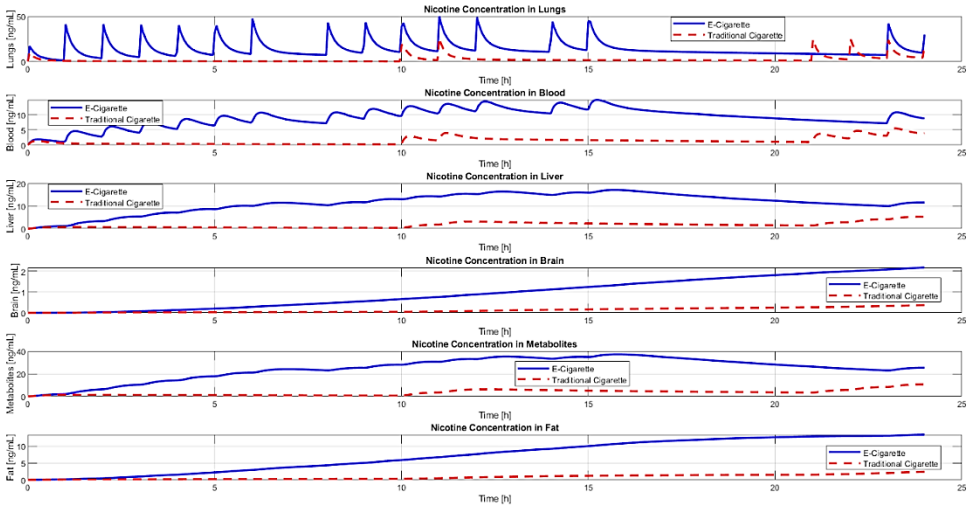

Figure 4. Nicotine concentration in liver disease.

Source: Authors' own.

The nicotine metabolism of people with cardiovascular disease showed moderate impairment which resulted in a 1.12-hour half-life for users of both e-cigarettes and traditional cigarettes. The brain concentration of nicotine reached C_{ss} = 16.32 ng/mL in e-cigarette users while traditional cigarette smokers only achieved 6.89 ng/mL. E-cigarette users maintained higher blood nicotine concentrations at 6.01 ng/mL compared to traditional cigarette users who had 2.74 ng/mL. The slower elimination of e-cigarette nicotine in cardiovascular-impaired individuals results in prolonged systemic exposure according to these findings. The brain concentration plots in Figure 5 show that e-cigarette users maintain nicotine levels for longer periods while traditional cigarette smokers experience rapid nicotine spikes.

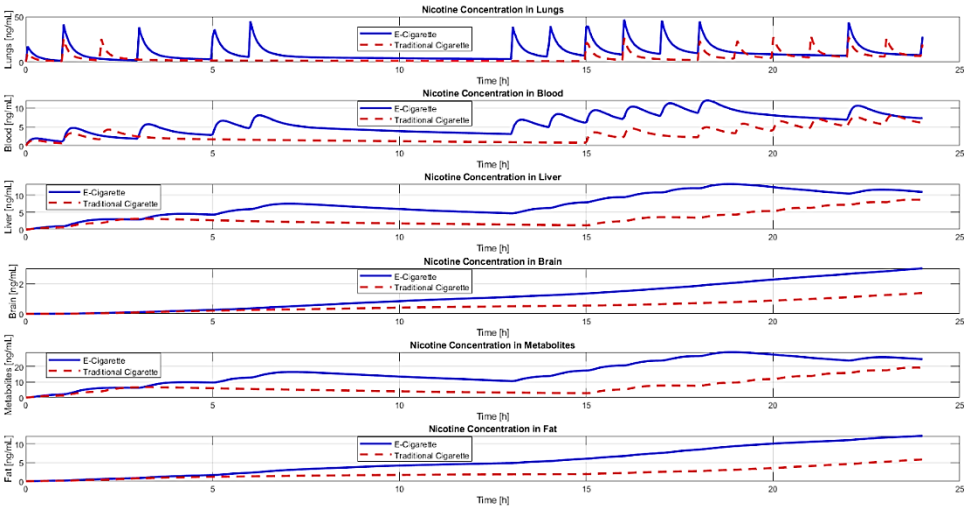

Figure 5. Nicotine concentration in cardiovascular disease.

Source: Authors' own.

The pharmacokinetics of nicotine underwent significant changes because obesity led to increased storage of nicotine in body fat which resulted in delayed elimination. The brain nicotine concentration reached 21.41 ng/mL in e-cigarette users who had higher levels than traditional cigarette users at 15.38 ng/mL because obesity slows down metabolic clearance thus extending nicotine retention especially for aerosolized nicotine products. The fat tissue storage of nicotine increased more than twofold between e-cigarette users who reached 9.82 ng/mL and traditional cigarette smokers who reached 6.28 ng/mL. The half-life measurements showed similar results between both groups at approximately 1.12 hours even though their nicotine exposure times differed. The effects are shown clearly in Figure 6 because nicotine levels in blood and fat tissues stay elevated throughout time especially in e-cigarette users.

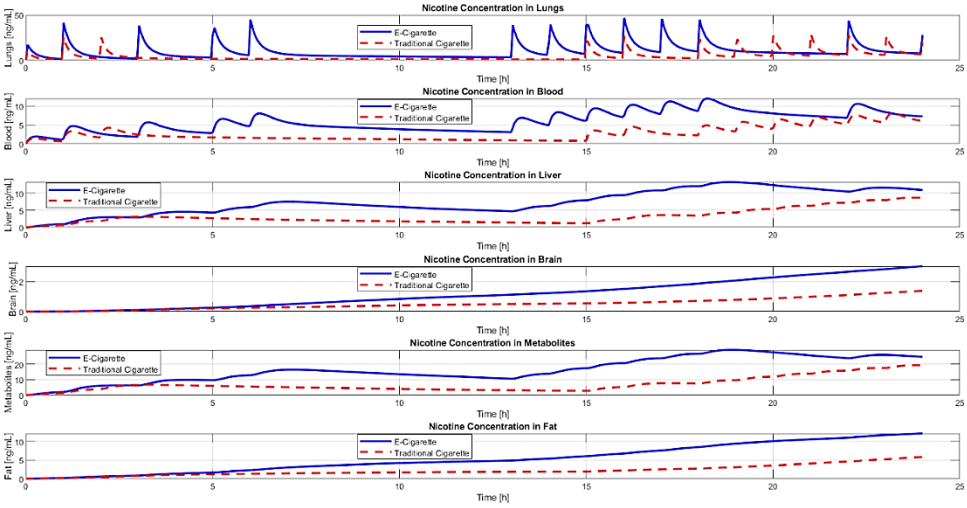

Figure 6. Nicotine concentration in obesity.

Source: Authors' own.

The absorption of nicotine became severely impaired in individuals with pulmonary disease and traditional cigarette smokers experienced an even greater impact. The brain nicotine concentration levels were significantly lower in users of traditional cigarettes at 2.91 ng/mL compared to e-cigarette users who had 13.06 ng/mL. The blood nicotine concentration in traditional cigarette users dropped to 1.02 ng/mL while e-cigarette users sustained levels at 5.05 ng/mL. The data presented in Figure 7 shows that traditional cigarette smokers receive lower systemic nicotine exposure because their lung impairment reduces alveolar absorption of combustion products. The aerosol delivery system of e-cigarettes functions differently from traditional cigarettes so it experiences reduced impact from lung diseases.

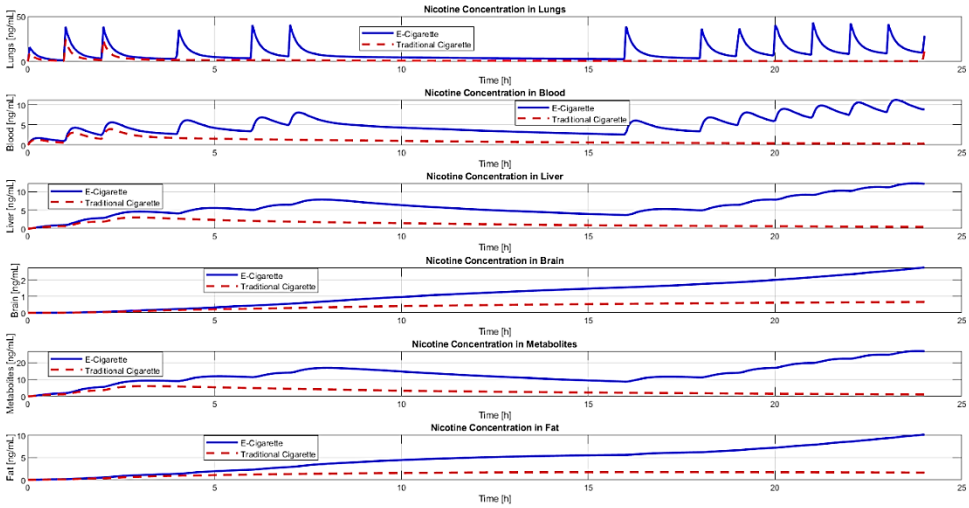

Figure 7. Nicotine concentration in lung disease.

Source: Authors' own.

The nicotine distribution in people with neurological diseases demonstrated substantial variations between using e-cigarettes and traditional cigarettes. The brain nicotine concentration of e-cigarette users dropped dramatically to 4.69 ng/mL because their blood-brain barrier transport was impaired or their neurovascular regulation was altered. Traditional cigarette users maintained brain nicotine concentrations at 9.52ng/mL while their blood nicotine levels remained lower than e-cigarette users at 2.02 ng/mL compared to 0.98 ng/mL. The prolonged half-life observed in e-cigarette users (~1.33 hours) suggests a delayed clearance pattern, despite their overall lower systemic exposure. The brain nicotine profile of traditional cigarette users remains steady throughout while e-cigarette users experience a gradual decrease in systemic nicotine concentrations as shown in Fig. 8.

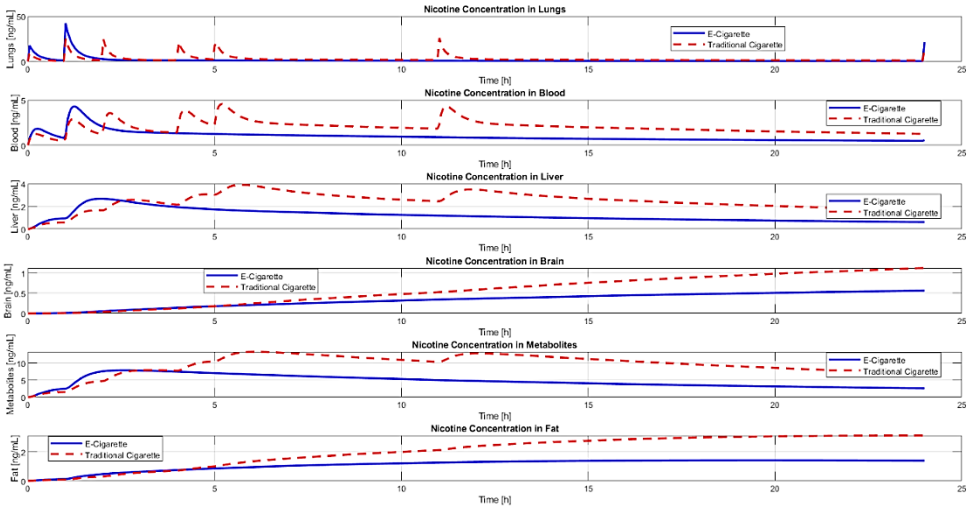

Figure 8. Nicotine concentration in neurological disease.

Source: Authors' own.

Fig. 9 presents simulated nicotine concentration profiles over a 24-hour period, comparing e-cigarette and traditional cigarette users across various health conditions. These profiles illustrate how both the route of nicotine delivery and individual health status shape the time-course of systemic nicotine concentrations, revealing important differences between combustion-derived nicotine and aerosolized nicotine.

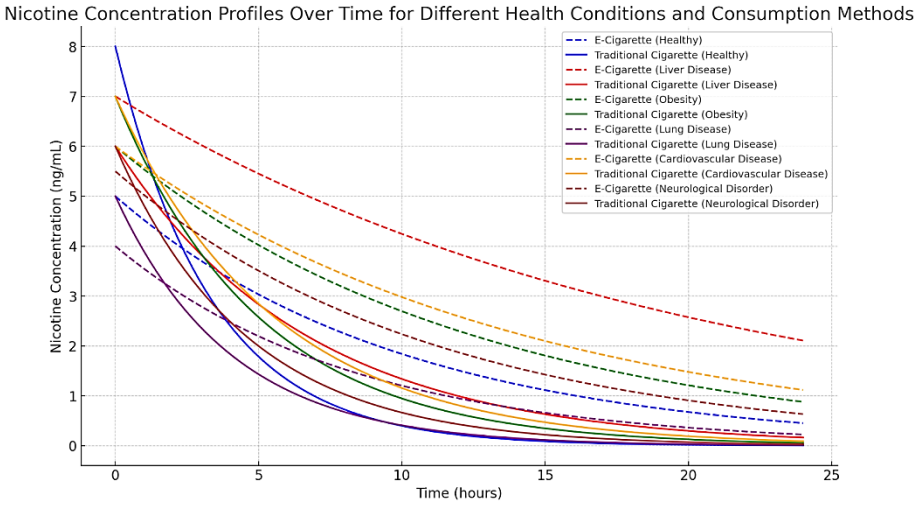

Figure 9. Nicotine Concentration Profiles Over Time Across Health Conditions and Consumption Methods.

Source: Authors' own.

Traditional cigarette smokers showed a rapid increase in nicotine concentration during the initial phase which reflects the quick delivery process of tobacco combustion. The nicotine levels in e-cigarette users showed a steady increase followed by an extended period of stable levels because aerosolized nicotine absorption occurs more slowly. The pharmacokinetic profiles demonstrate the core distinction between traditional cigarettes which deliver quick intense nicotine bursts and e-cigarettes which produce sustained smooth nicotine exposure.

The effects of health conditions further modulate these profiles. The liver disease patients experienced severely limited nicotine clearance which resulted in extended nicotine retention especially among e-cigarette users who received continuous low-dose exposure on top of their impaired hepatic metabolism. The nicotine levels in obese individuals decreased gradually with e-cigarette users showing the longest decline because their bodies stored nicotine in fat tissue that released the substance back into circulation at a slow rate. The delayed clearance pattern became most evident in the e-cigarette group because nicotine's fat-soluble nature reacts with changes in body composition.

Traditional cigarette users among individuals with pulmonary disease showed reduced peak concentrations and faster elimination times compared to healthy subjects because their impaired alveolar function restricts combustion product nicotine absorption. The nicotine levels of e-cigarette users remained elevated compared to traditional cigarette users because aerosol particles seem to adhere better to damaged lungs thus providing longer systemic exposure.

The cardiovascular disease group showed e-cigarette and traditional cigarette users retained nicotine for a slightly longer period yet e-cigarette users maintained higher nicotine levels throughout the study period because their nicotine clearance from the body was slower. The blood-brain barrier permeability differences between traditional cigarette users and e-cigarette users resulted in traditional cigarette users reaching higher peak concentrations because of faster nicotine absorption but e-cigarette users maintained lower systemic levels for longer periods.

The sensitivity analysis demonstrates the need of accounting for individual physiological variables when modeling nicotine pharmacokinetics. In healthy people (Fig. 10), the PBPK model was most sensitive to hepatic metabolism rate ($k_{metabmax}$) and liver blood flow (Qh). These parameter adjustments resulted in considerable variations in brain nicotine concentration, demonstrating that hepatic clearance is an important element in regulating systemic and central nicotine exposure. The brain penetration rate (k_{penet}) had a significant impact, particularly for e-cigarette users, as the slower aerosol delivery allowed for a longer duration of nicotine absorption into the brain.

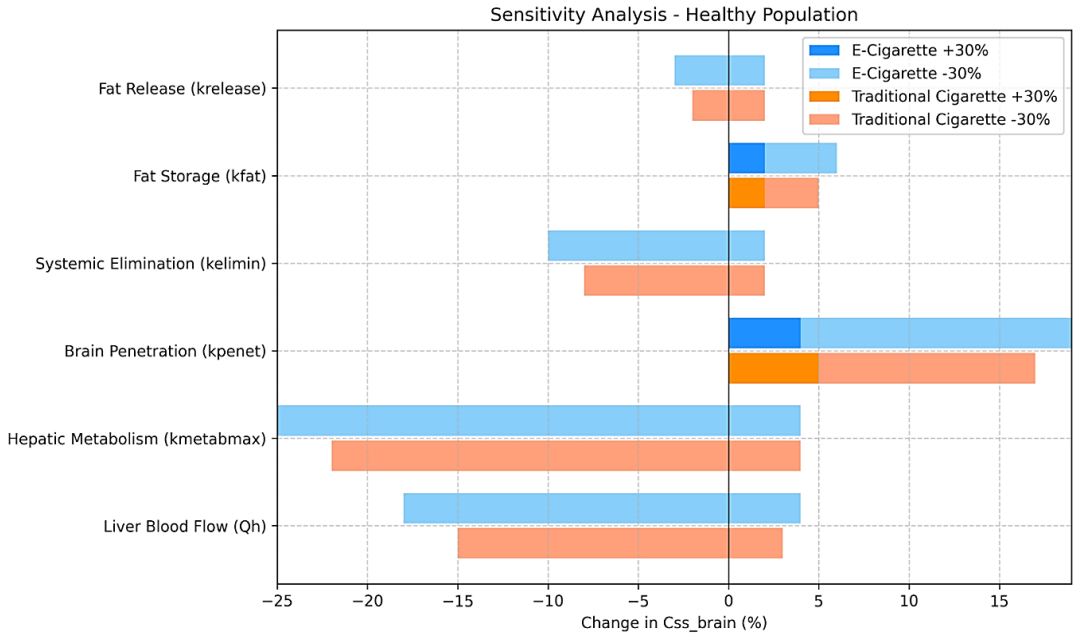

Figure 10. Sensitivity Analysis of Healthy Population (E-Cigarette vs Traditional Cigarette).
Source: Authors' own.

In individuals with liver disease, hepatic metabolism rate ($k_{metabmax}$) had the strongest influence on nicotine concentrations, reflecting the impaired metabolic capacity in this population (Fig. 11). Reduced hepatic clearance led to markedly increased C_{ss_brain} in both e-cigarette and traditional cigarette users, though the effect was more pronounced in e-cigarette users due to prolonged exposure patterns. Liver blood flow (Qh) also had a considerable effect, highlighting the importance of perfusion in hepatic clearance.

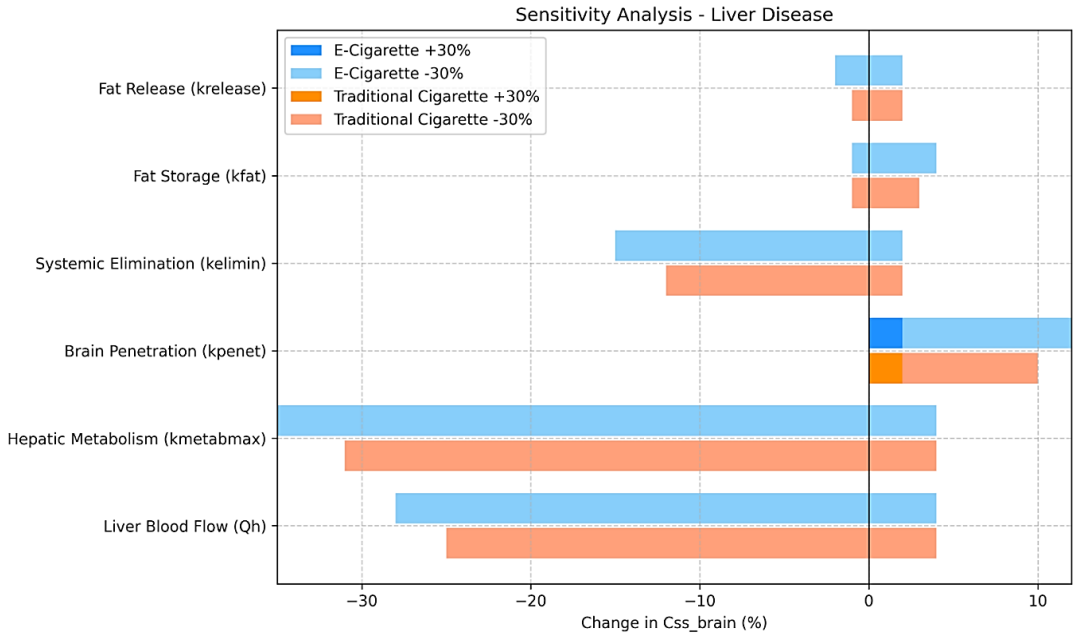

Figure 11. Sensitivity Analysis - Liver Disease (E-Cigarette vs Traditional Cigarette).
Source: Authors' own.

In obese individuals, fat storage (k_{fat}) and fat release ($k_{release}$) were the most influential parameters, particularly for e-cigarette users (Fig. 12). Nicotine's high lipophilicity causes extensive sequestration in adipose tissue, which significantly alters its systemic and brain concentrations over time. While liver blood flow and hepatic metabolism remained important, the prolonged nicotine release from fat stores introduced an additional regulatory mechanism, especially in the context of chronic e-cigarette use.

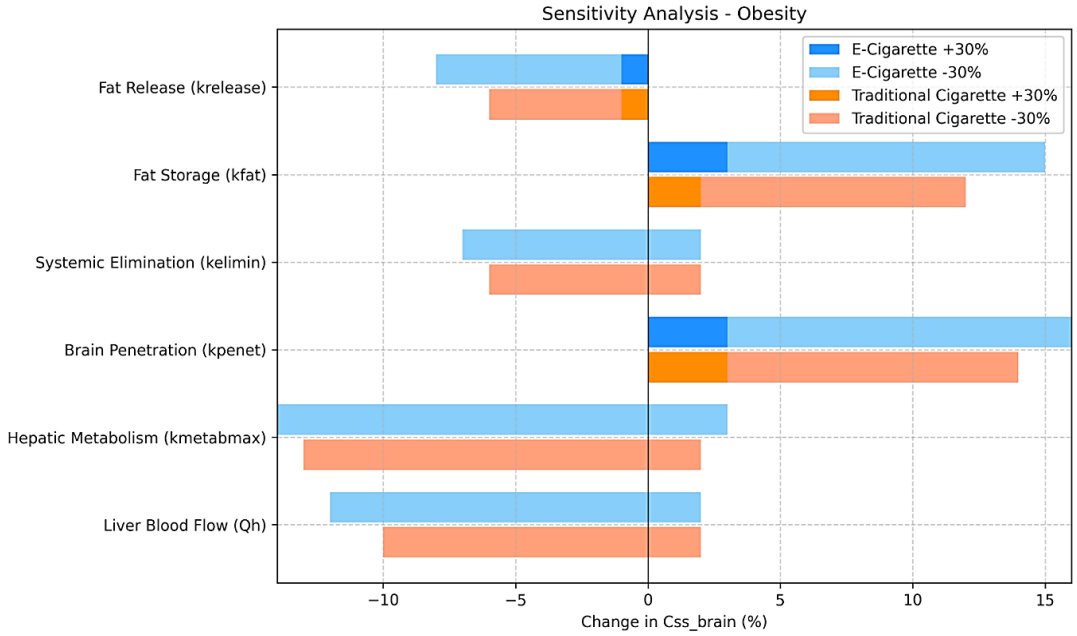

Figure 12. Sensitivity Analysis - Obesity (E-Cigarette vs Traditional Cigarette).

Source: Authors' own.

In individuals with neurological disorders, brain penetration rate (k_{penet}) emerged as the dominant driver of C_{ss_brain}, particularly for e-cigarette users (Fig. 13). Variability in blood-brain barrier permeability significantly altered brain nicotine concentrations, amplifying the role of disease-induced changes in central nervous system exposure. While hepatic parameters still played a role, the direct modulation of nicotine entry into the brain became a distinguishing factor in this population.

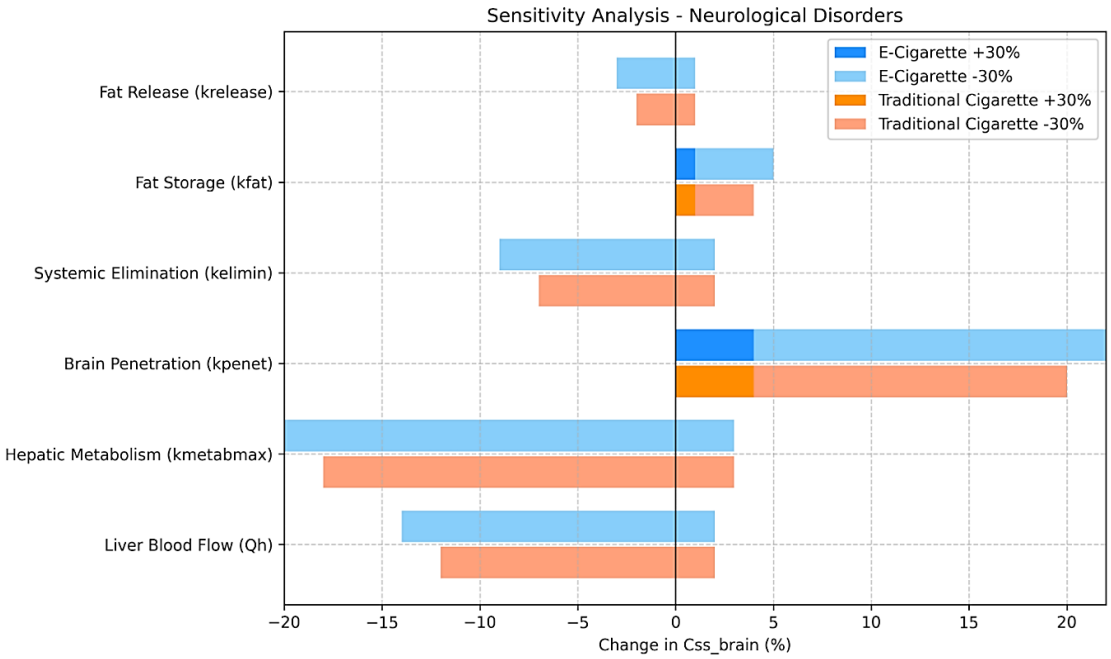

Figure 13. Sensitivity Analysis - Neurological Disorders (E-Cigarette vs Traditional Cigarette).

Source: Authors' own.

This heatmap visualization (Fig. 14) highlights the disease- and delivery-specific sensitivity patterns, emphasizing the need for individualized pharmacokinetic modeling in populations with comorbid conditions or altered physiology.

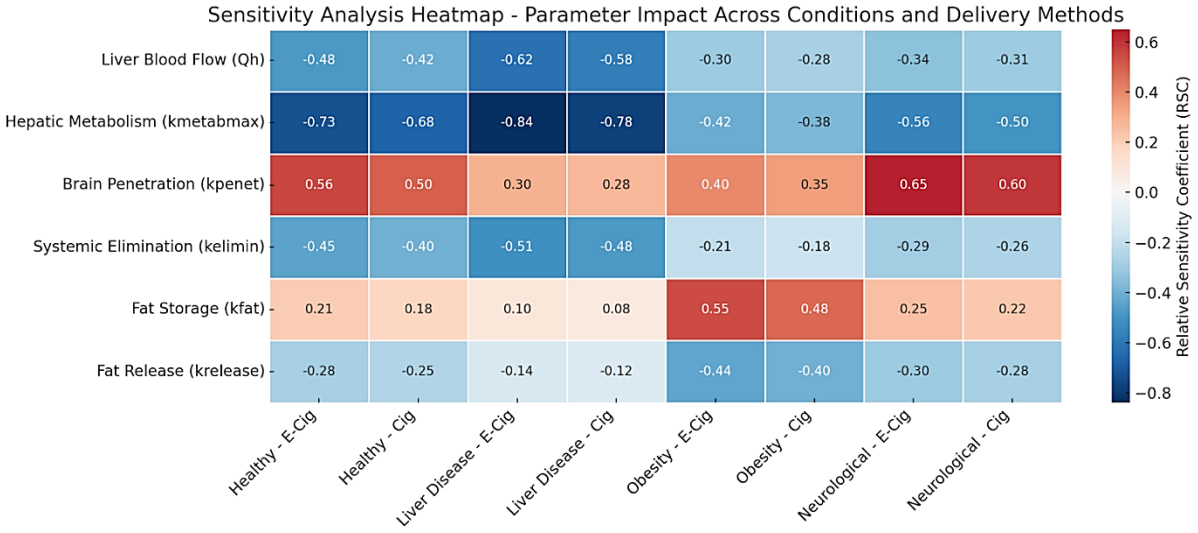

Figure 14. Sensitivity Analysis Heatmap – Relative Sensitivity Coefficients (RSC) Across Health Conditions and Delivery Methods.

Source: Authors' own.

4. Discussion

Physiologically-Based Pharmacokinetic (PBPK) modeling has gained popularity in recent years for studying nicotine pharmacokinetics in different delivery systems and physiological conditions (Schroeder, 2014; World, 2024). The models enable researchers to model how nicotine moves through the body by simulating its ADME processes. This study applies an in silico PBPK framework to simulate how nicotine is absorbed, distributed, metabolized, and eliminated in individuals with varying physiological and pathological conditions. By explicitly modeling organ-level functions, such as hepatic clearance, pulmonary uptake, adipose tissue storage, and neural barrier transport, the approach provides mechanistic insight into the functional alterations of key human organs under disease.

Rostami et al. (Prasad, 2024) provided a major contribution through their application of an extended conventional PBPK framework to forecast nicotine pharmacokinetics from acute and repeated nicotine delivery product exposure including combustible cigarettes, smokeless tobacco, ENDS, and nicotine inhalers. The model included anatomically detailed representations of nicotine absorption pathways, particularly through the buccal mucosa, upper airways, and lower respiratory tract. Moreover, it accurately reproduced plasma nicotine concentration-time profiles and tissue-specific distribution by integrating region-specific deposition and diffusion parameters, thus highlighting the influence of route-specific absorption on systemic exposure. Rostami's results are in agreement with the present study findings which show that nicotine retention and metabolic clearance are route-dependent. E-cigarette use was found to result in longer systemic exposure compared to conventional cigarette smoking which produced higher peak plasma concentrations.

Prasad et al. (Rostami, 2022) developed a machine learning–augmented PBPK model specifically for e-cigarette users. The approach enabled personalized pharmacokinetic predictions through user-specific variables including puffing patterns and device parameters. Our data supports these findings by showing that e-cigarette users especially those with hepatic insufficiency or obesity experience prolonged systemic nicotine retention which supports the need for individualized PBPK modeling to evaluate nicotine exposure risk.

The initial research by Robinson et al. (Schneider, 1996) presented a nine-compartment PBPK model which included both nicotine and its main metabolite cotinine. The tissue-to-blood partition coefficients derived from this model served as a foundation for future modeling research. Our research extends the existing framework through disease-specific modifiers including hepatic impairment which leads to longer nicotine half-life. The findings from our study confirm Robinson's conclusion that PBPK models require individual metabolic capacity data to achieve better predictive accuracy.

Noteworthy, Guo et al. (Guo, 2022) performed an open-label crossover clinical trial to assess nicotine delivery profiles in Chinese adult smokers who used both e-cigarettes and combustible cigarettes. The researchers observed that e-cigarettes delivered nicotine at a steady rate which differed from the fast nicotine peaks that occur during conventional smoking. Our results match the results from Guo's study and show that e-cigarettes maintain steady nicotine levels in the body while traditional cigarettes create sudden pharmacokinetic effects because of their combustion process.

The blood-brain barrier (BBB) interaction with nicotine functions as a primary factor which determines how the substance affects the central nervous system (CNS). Tega et al. (Robinson, 1992) showed that nicotine changes BBB permeability through modifications in tight junction proteins ZO-1 and claudin-3 which leads to disrupted junctional integrity. Our research supports this mechanistic understanding because people with neurological disorders show different brain nicotine exposure patterns especially when using e-cigarettes since their BBB integrity is already compromised by disease-related pathology.

The National Academies of Sciences, Engineering, and Medicine study (Yuki, 2024) on the public health impacts of e-cigarette usage concludes that e-cigarette aerosols have a lower toxicant load than traditional tobacco products. However, it also highlights the paucity of understanding concerning long-term health consequences, particularly in patients with pre-existing respiratory disorders such as chronic obstructive pulmonary disease (COPD). Our findings support this conclusion, implying that e-cigarette users with pulmonary comorbidities may have distinct patterns of nicotine absorption and retention, which could accelerate disease progression or make illness treatment more challenging. Our findings are congruent with this assessment, suggesting that e-cigarette users with pulmonary comorbidities may experience altered nicotine absorption and retention dynamics, potentially exacerbating disease progression or complicating management strategies.

Finally, in the research of Perry et al. (Schroeder, 2014), the authors examine PBPK modeling applications and growth and challenges in different therapeutic contexts. The paper shows that PBPK-related research is increasing rapidly and is becoming more important in drug development and clinical pharmacology. PBPK modeling is especially useful for simulating drug behavior in different populations such as pediatrics, geriatrics, and individuals with organ impairment as well as for predicting complex drug-drug interactions. These findings support our study's focus on the need to adapt smoking cessation therapies to individuals' pharmacokinetic profiles and health state, acknowledging that differences in nicotine metabolism and exposure require different therapeutic approaches.

Our study provides extremely interesting results, however, it is not without its limitations. The research delivers important information about nicotine pharmacokinetics across user groups and delivery systems but faces multiple research constraints. The PBPK modeling framework produces reliable results but its accuracy depends on the precision of the physiological and biochemical parameters that it uses. The reliability of model results may be

impacted by the restricted and inconsistent information found in literature sources which was used to develop input data for specific subpopulations including patients with advanced hepatic or pulmonary disease. The research fails to consider behavioral differences among individuals who use nicotine products through their consumption methods including puffing patterns and inhalation depths and device-specific features like power settings and e-liquid composition especially for e-cigarette users.

The simulation's cross-sectional design prevents researchers from directly studying the long-term health impacts of chronic nicotine exposure. The model successfully reproduces short-term pharmacokinetic patterns but requires longitudinal verification to determine complete health implications from long-term nicotine use particularly when comorbid conditions exist. The model's predictions receive limited external validation because there is no empirical biomarker data (e.g., plasma cotinine levels) available for real-world users. The study investigates major disease states but it does not evaluate how pharmacogenomic factors like CYP2A6 polymorphisms affect nicotine metabolism and individual variability.

Finally, the generalizability of these findings may be limited by the model's focus on adult populations; adolescents, pregnant individuals, and elderly users—each with different physiological characteristics and vulnerability profiles—were not explicitly modeled. Future research should attempt to extend the PBPK framework to include these populations and incorporate real-world usage data to increase translational relevance.

5. Summary and Conclusions

The research provides an extensive analysis of nicotine pharmacokinetics in e-cigarette and combustible cigarette users through Physiologically-Based Pharmacokinetic (PBPK) modeling which analyzes absorption distribution metabolism and elimination across different health statuses. The research shows that nicotine retention and clearance rates differ widely between people which indicates the requirement for individualized approaches in smoking cessation and harm reduction programs.

The main outcome of this research demonstrates that different nicotine delivery systems generate distinct pharmacokinetic patterns. The plasma nicotine levels from combustible cigarettes increase quickly but e-cigarettes maintain steady systemic nicotine exposure. The distinctions become more pronounced in people who have metabolic or physiological conditions. Hepatic dysfunction leads to longer nicotine half-life especially among e-cigarette users because their products provide continuous nicotine delivery. The fat-attracting properties of nicotine in obese people result in its storage within adipose tissue which extends the time needed for nicotine elimination.

The research examines how lung diseases affect the process of nicotine absorption. Traditional cigarette smokers with respiratory problems experience decreased systemic nicotine levels but e-cigarette users with similar conditions show higher plasma nicotine concentrations. The study demonstrates how delivery methods influence nicotine exposure in disease-related situations. Neurological disorders that modify blood-brain barrier (BBB) permeability could impact how nicotine reaches the brain thus affecting addiction potential and withdrawal symptoms between different delivery systems.

The findings have significant consequences for translation. Because nicotine metabolism is not linear and does not remain stable across health conditions, uniform quitting strategies may not be optimum for all populations. Individualized quitting techniques that take into account metabolic capability, comorbid disorders, and chosen nicotine delivery systems are more likely to increase therapy efficacy. Pharmacological medications such as Nicotine Replacement Therapy (NRT), bupropion, and varenicline may require dosage changes or alternate formulations in populations with altered pharmacokinetics.

The research results question the common assumption that e-cigarettes represent a completely safer choice than combustible tobacco products from a public health and regulatory perspective. E-cigarettes lower combustion-related toxicant exposure but their pharmacokinetic profile leads to prolonged systemic nicotine retention which creates specific risks for people with cardiovascular disease and hepatic or metabolic conditions. The obtained results require a thorough reevaluation of harm reduction policies especially for vulnerable population groups, including youth.

Future research needs to focus on following medically compromised populations through time to understand the long-term consequences of e-cigarette use. PBPK modeling will become more accurate for exposure prediction and risk assessment through improvements that include real-world vaping behaviors and device-specific parameters and nicotine salt pharmacodynamics. This research demonstrates how nicotine pharmacokinetics interacts with delivery methods and health conditions of individual patients. The research findings support the need for precise cessation treatments and detailed regulatory approaches while encouraging ongoing multidisciplinary studies to reduce nicotine-related health problems in diverse population groups.

Acknowledgements

Financed by a subvention from the Ministry of Science and Higher Education Poland to the Academy of Silesia in Katowice.

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