Comparative Assessment of Pharmacokinetics and Acute Lung Inflammation of Nicotine Dry Powder Aerosols Generated by PreciseInhale®

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Introduction

- Why are we looking at delivering nicotine in a dry powder?
- Nicotine-containing dry powder (Batch A) has been **successfully aerosolized and delivered intratracheally** via the PreciseInhale® system in previous studies (Sciuscio et al., 2019).
- Batch B was **produced for comparison** with Batch A.
- Both batches were synthesized via **spray-drying** and contained **2% nicotine and other excipients**.

Sciuscio, D. et al., 2019. Respirable aerosol exposures of nicotine dry powder formulations to *in vitro*, *ex vivo*, and *in vivo* pre-clinical models demonstrate consistency of pharmacokinetic profiles. Inhalation Toxicology, 31(6):248- 257.

Research Questions

(1) Will the **aerosol characteristics** and **nicotine pharmacokinetic (PK) profiles** of both batches be **comparable**?

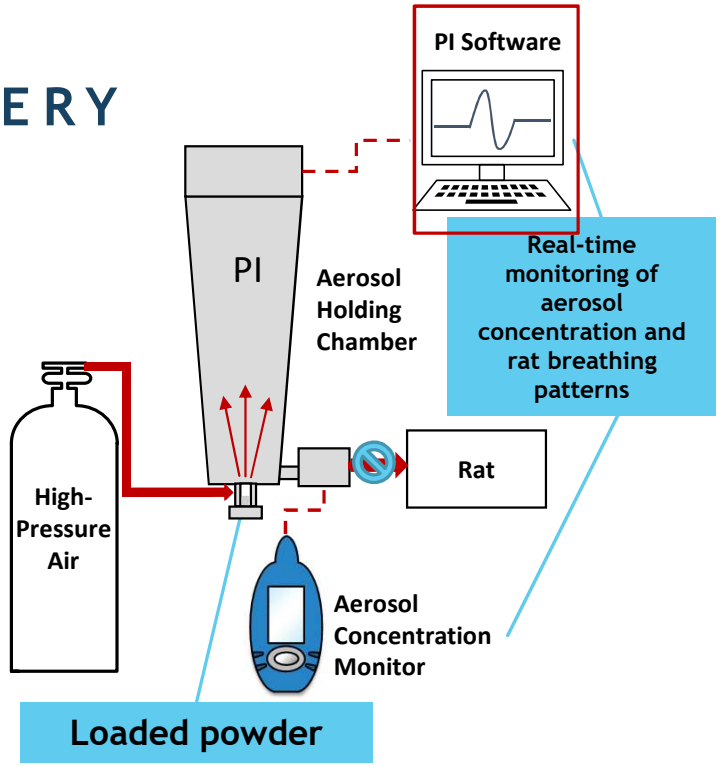
(2) Will these batches, when inhaled, cause **acute lung inflammation** in rats?

Methodology

AEROSOL GENERATION AND DELIVERY

- Dry powder aerosol was generated and **intratracheally delivered** to anaesthetized rats (~250 g body weight) by using PreciseInhale® (Inhalation Sciences).
- Cumulative target dose: **0.1 mg nicotine/kg body weight**

Intratracheally intubated rat connected to PreciseInhale®

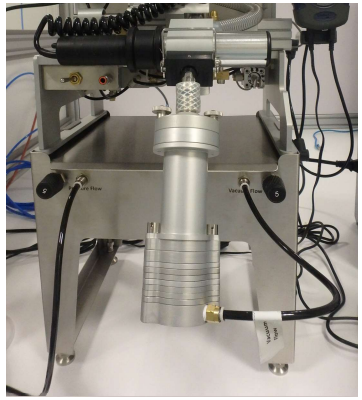


Schematic of the PreciseInhale® dry powder aerosol generation system

Methodology

PARTICLE SIZE ANALYSIS

- Particle size distribution (PSD) was determined by using an **8-stage Marple cascade impactor**.
- **Mass median aerodynamic diameter (MMAD)** and **geometric standard deviation (GSD)** of the aerosol's PSD were derived (Rubow et al., 1987).



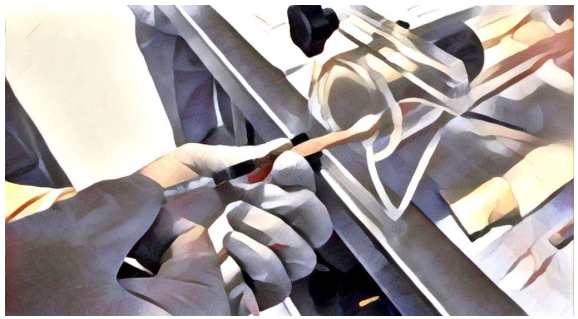
Marple cascade impactor connected to PreciseInhale®

Rubow, K.L. et al., 1987. A Personal Cascade Impactor: Design, Evaluation and Calibration. American Industrial Hygiene Association Journal. 48(6):532-538.

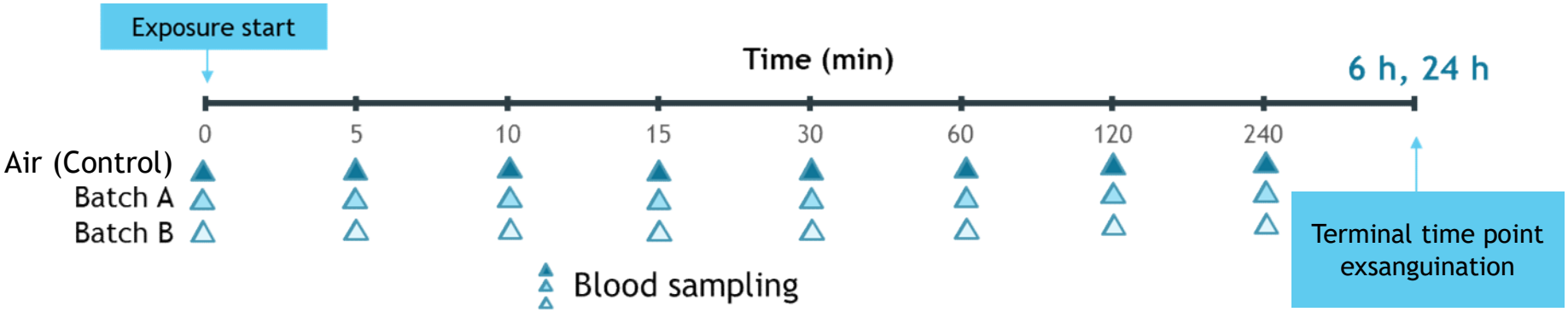
Methodology

PK ANALYSIS

- For **nicotine/cotinine quantification**, blood was sampled at timepoints (for 4 h from the start of exposure) via a tail-vein catheter.



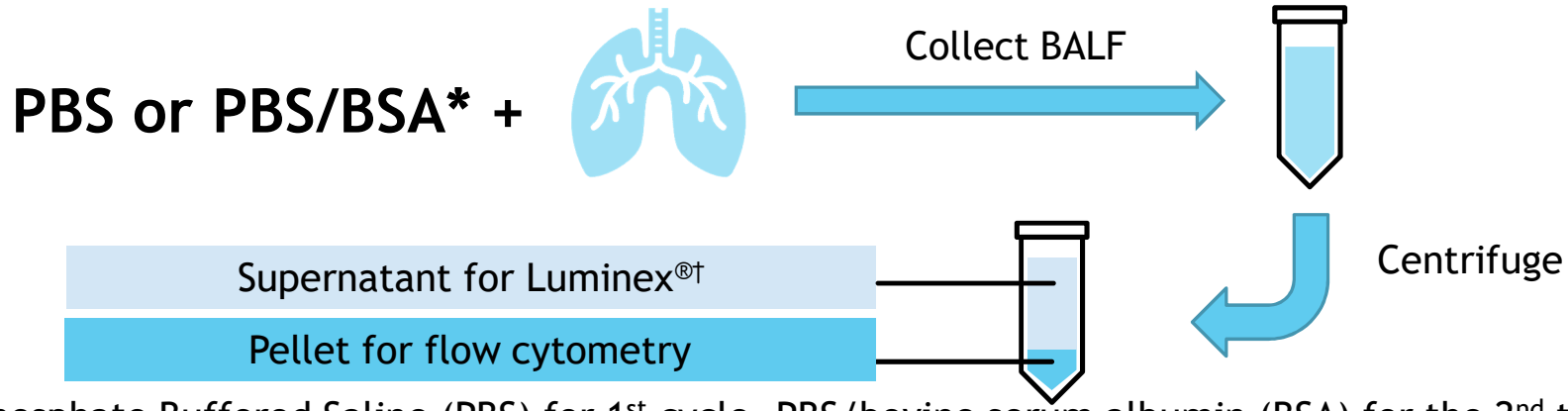
Blood draw from tail-vein catheter



Methodology

LUNG INFLAMMATION ANALYSIS

- Bronchoalveolar lavage fluid (BALF) was collected at terminal time points (6 h and 24 h).
- BALF was analyzed for **pro-inflammatory cytokines via Luminex®** and **differential cell count via flow cytometry**.



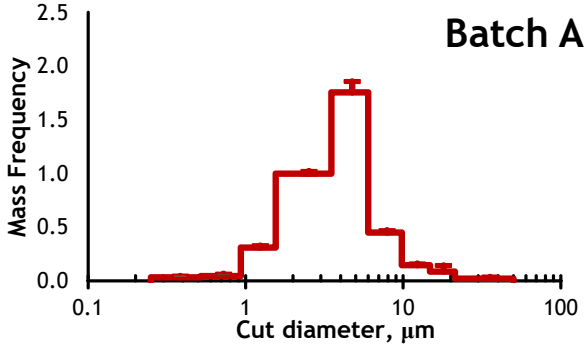
* Phosphate Buffered Saline (PBS) for 1st cycle, PBS/bovine serum albumin (BSA) for the 2nd to 5th cycle.

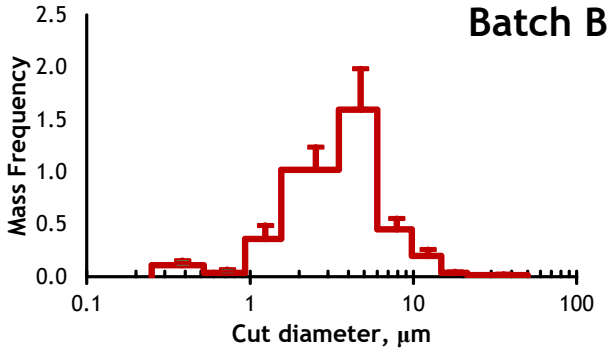
† BALF from the 1st cycle only.

Results - PSD

- Dry powder aerosols generated from both batches had a **similar MMAD of ~4 µm and GSD ~1.8**.
- Aerosols were determined to be **inhalable** by using the Multiple-Path Particle Dosimetry (MPPD) 3.04 software (Applied Research Associates, Inc.).

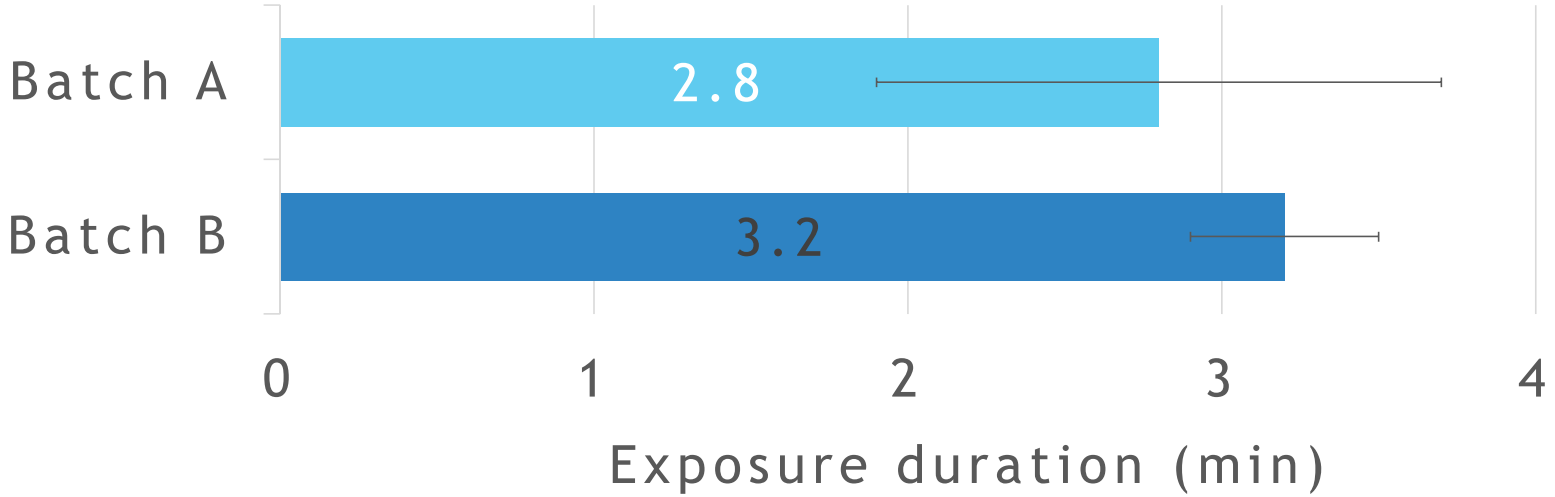
Batch	MMAD (µm)	GSD	Weighted Theoretical Lung Deposition Percentage (%)	n
A	3.83 ± 0.08	1.75 ± 0.03	58 ± 1	3
B	3.60 ± 0.62	1.84 ± 0.09	56 ± 5	3





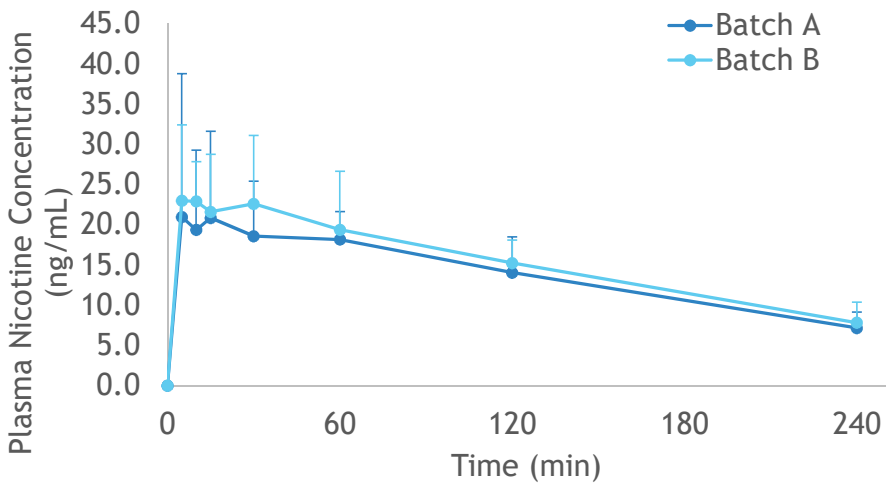
Results — Exposure Duration

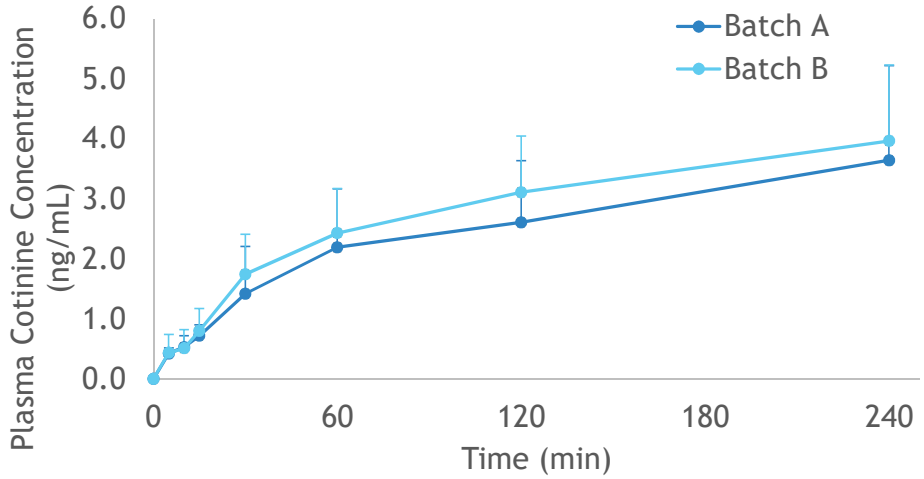
- From both batches, 0.1 mg nicotine/kg body weight was delivered within **short exposure durations** (<5 min).



Results — PK Analysis

- Plasma **nicotine and cotinine PK profiles and parameters** for both batches were **similar**.



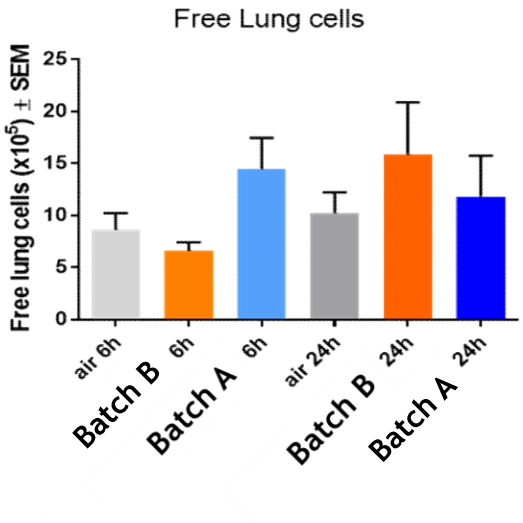


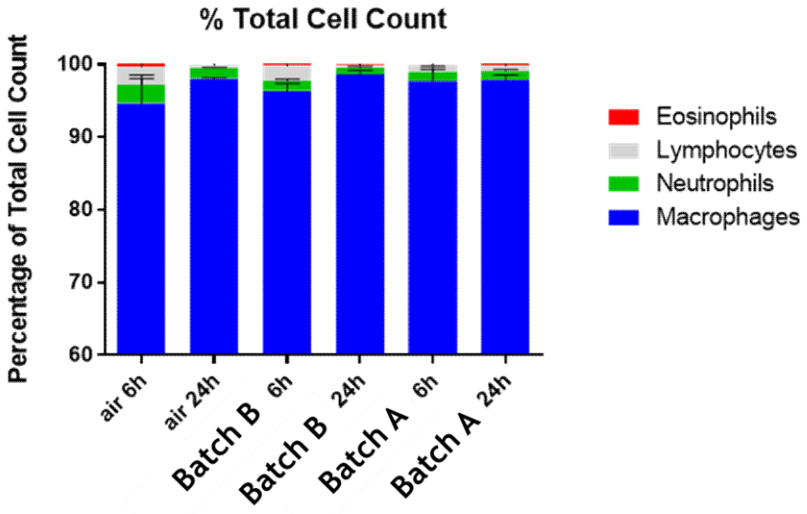
Batch	$t_{1/2}$ (min)	t_{max} (min)	C_{max} (ng/mL)	C_{last} (ng/mL)	AUC_{last} (min*ng/mL)	MRT_{last} (min)
A	132.8	5	20.97	7.186	3341	96.19
B	138.1	5	23.01	7.844	3670	95.44

Batch	t_{max} (min)	C_{max} (ng/mL)	C_{last} (ng/mL)	AUC_{last} (min*ng/mL)	MRT_{last} (min)
A	240	3.642	3.964	595.8	147.1
B	240	3.964	3.964	679.1	145.1

Results — Flow Cytometry Differential Cell Count

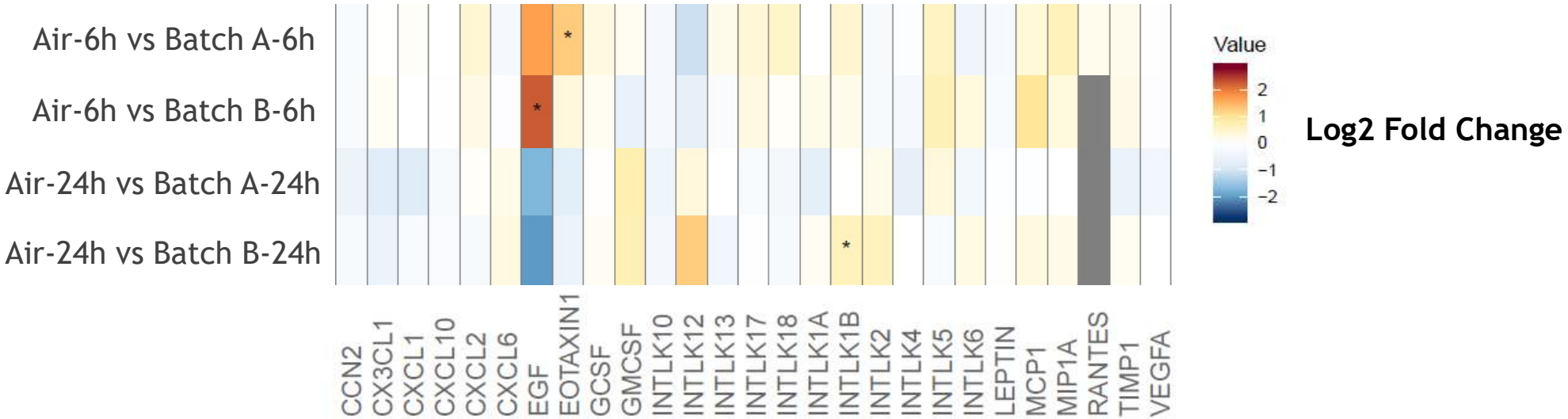
- Batches A and B **did not cause significant increase in total lung cell count** ($p > 0.05$) relative to air (control).
- Batches A and B **did not cause significant increase in % cell count for any of the immune cell groups** ($p > 0.05$) relative to air (control).





Results - Luminex® Pro-Inflammatory Cytokine Measurements

- Overall, Batches A and B **caused little to no significant increase in pro-inflammatory cytokine expression** relative to air (control).



Conclusion

- Nicotine can be **delivered into rat systemic circulation** via inhalation of **nicotine-containing dry powder aerosol**.
- Dry powder aerosols generated from both batches have **similar PSD**, were delivered within **similar exposure durations**, and produced **similar nicotine/ cotinine PK profiles**.
- Dry powder aerosols generated from both batches **caused no acute lung inflammation** in rats up to 24 h post exposure.

Acknowledgements

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Thank you

Questions?

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