

Background data for repeated-dose inhalation toxicity studies in monkeys

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Objective

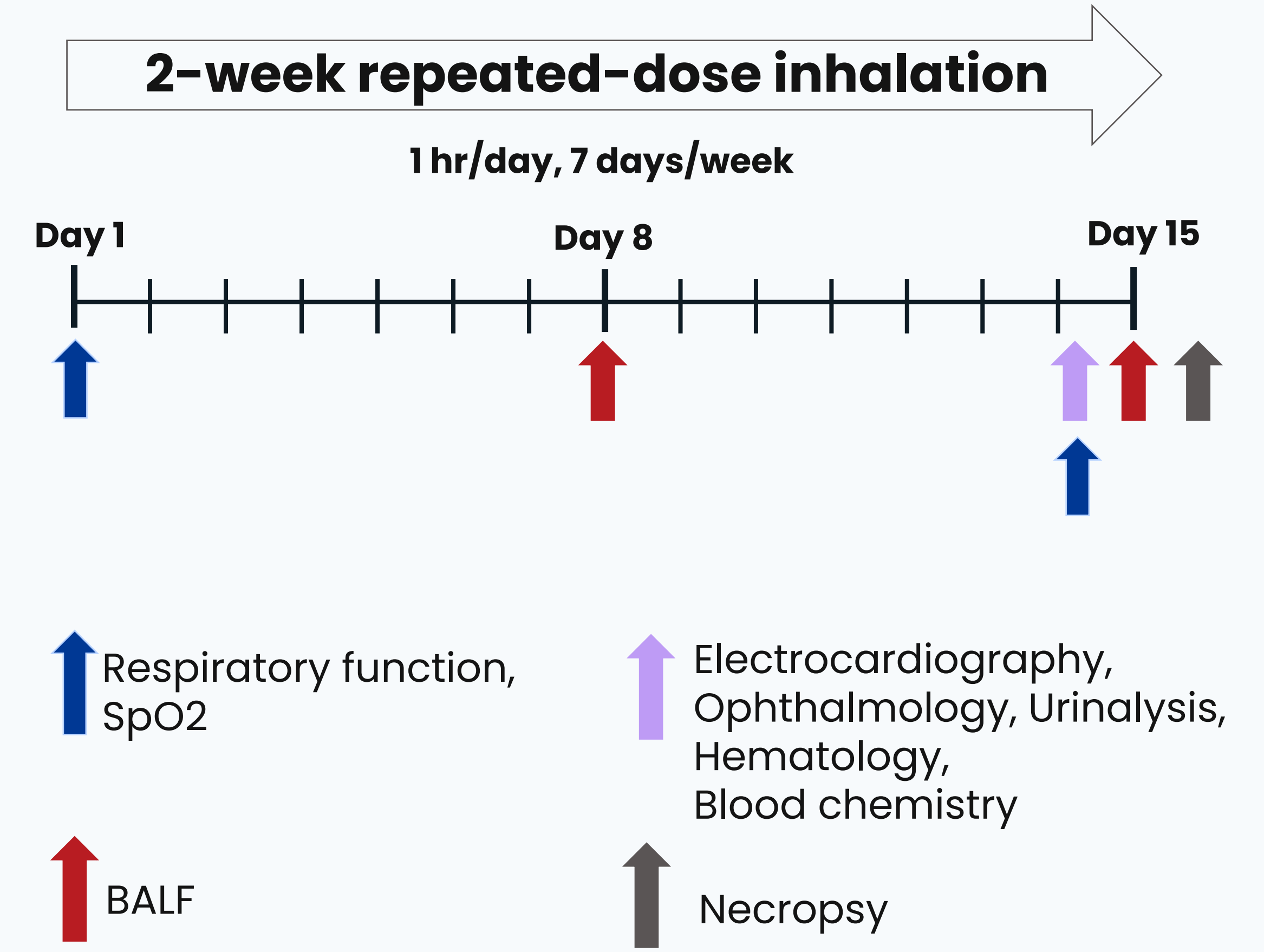
The inhalation route of drug delivery is effective for directly targeting the respiratory system, allowing for rapid systemic exposure while avoiding the first-pass effect. Recently, the outbreak of respiratory infections has heightened interest in the development of inhaled pharmaceuticals. However, there is limited information available regarding inhalation toxicity studies in non-rodents. This study aimed to collect background data for repeated-dose inhalation toxicity studies in cynomolgus monkeys using various vehicles.

Materials and Methods

Animals

Cynomolgus monkey, Male, 6 to 13 years old

Experimental Design



Group Composition

Vehicle	Exposure conc. (mg/L)	Number of animals
Sham	0	3
Distilled water (DW)	–	3
Saline	44.4	3
0.1% Tween 80	47.8	3

The exposure concentrations in saline and Tween were set to the maximum levels achieved in the inhalation exposure system used in this study. DW was exposed under conditions similar to those of these vehicles.

Observations and Measurements

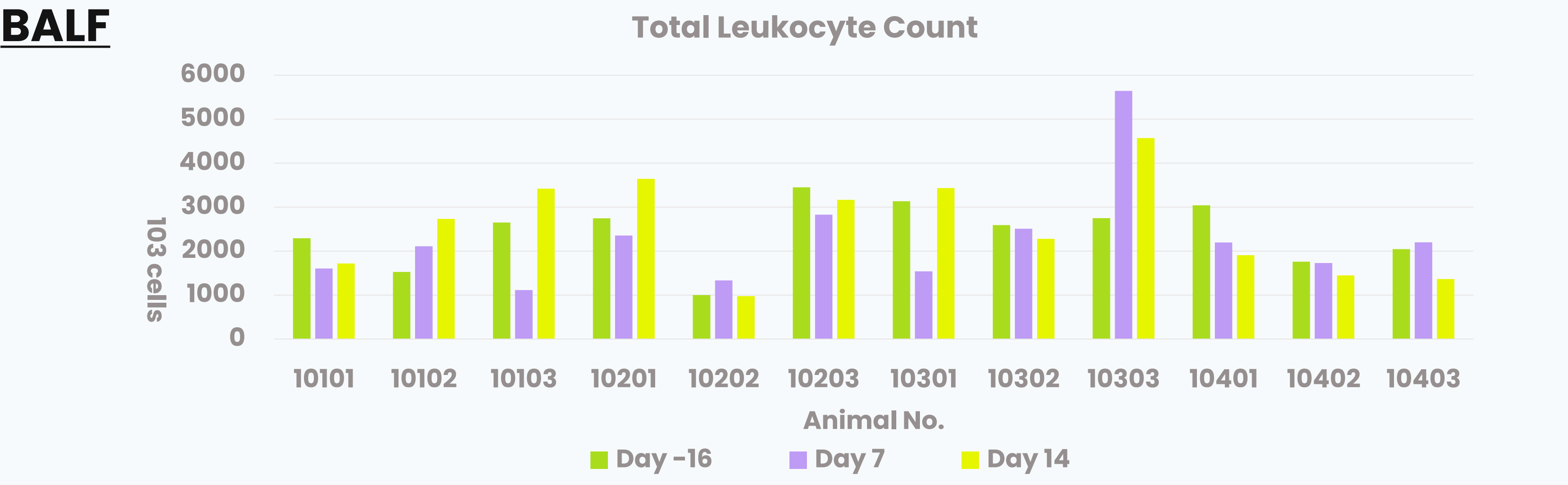
Clinical signs, Body weight, Food consumption, Respiratory function, Electrocardiography, Ophthalmology, Urinalysis, Hematology, Blood chemistry, Bronchoalveolar lavage fluid (BALF)*, Necropsy, Organ weight, and Histopathology

*: BALF was collected from the right middle lobe via bronchoscopy.
Examined items: Total protein (TP), lactate dehydrogenase (LDH), total leukocyte count, and differential leukocyte ratio and count

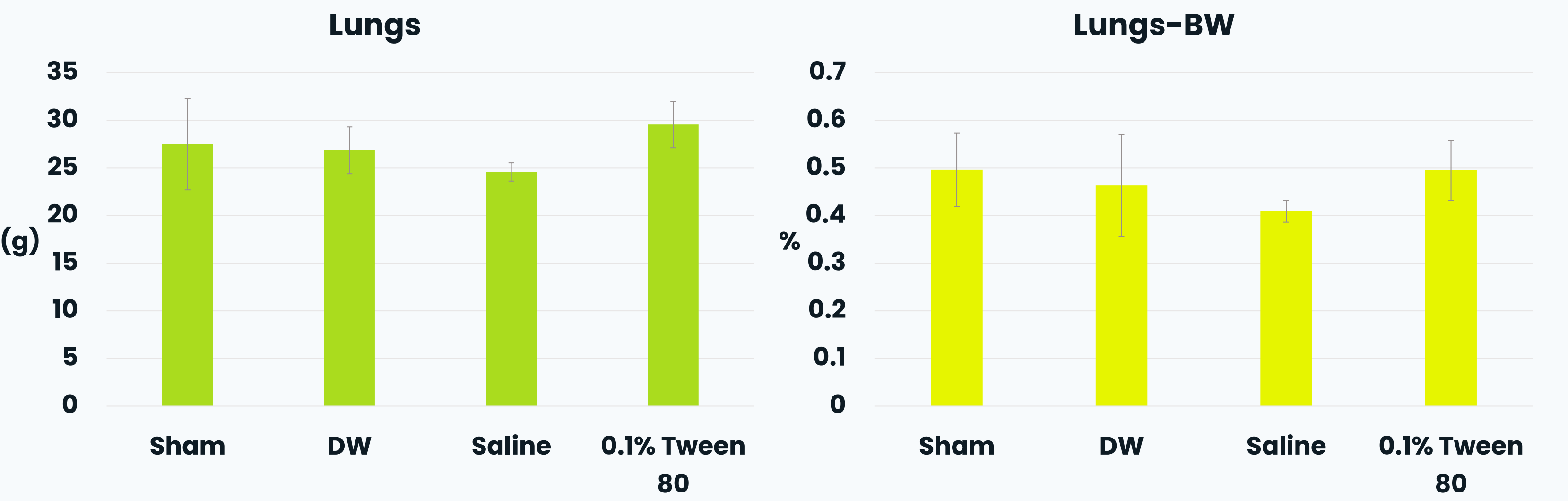
Results

Observations and measurements	Exposure-related changes (vs. sham)
Survival/ Clinical signs	None
Body weight/ Food consumption	None
Respiratory function/ ECG	None
Ophthalmology	None
Urinalysis	None
Hematology	None MCV: Statistically significant increase in the saline group, but within pre-exposure range.
Blood chemistry	None

BALF



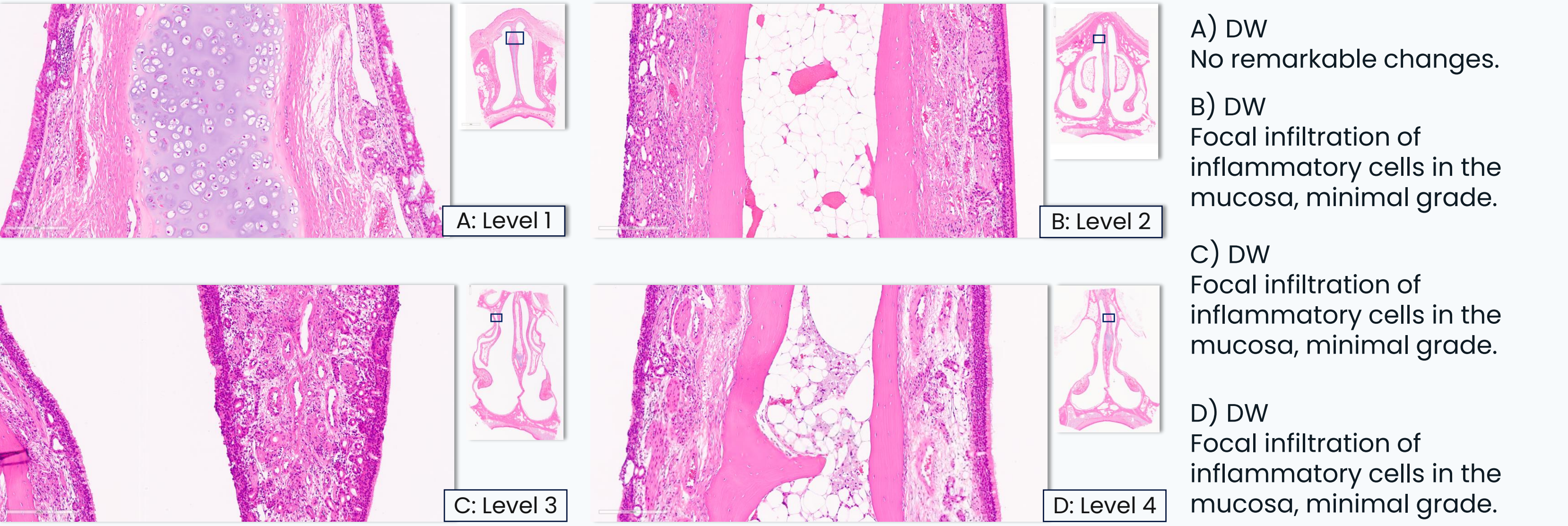
Organ Weight



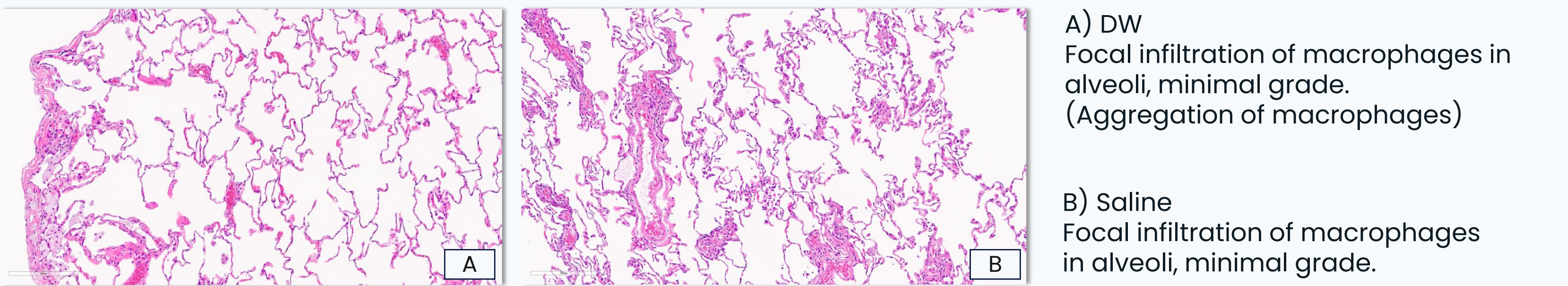
Histopathological Examination

Organs/Tissues	Sham	DW	Saline	0.1% Tween 80
Nasal cavity				
Infiltrate, Inflammatory cell, Mucosa, Focal Minimal	0	2	0	0
Trachea				
Infiltrate, Inflammatory cell, Mucosa Minimal	1	1	0	0
Lungs (and bronchus)				
Fibrosis, Pleura, Focal Minimal	1	0	0	0
Infiltrate, Macrophage, Alveolar, Focal Minimal Mild	0 1	2 0	1 0	0 0
Optic nerve	–	–	–	–
Eye	–	–	–	–

Nasal Cavity



Lungs (and bronchus)



Characteristic changes were observed in the respiratory tract, including the nasal cavity and lungs; however, these were spontaneous in monkeys and not related to exposure.

Discussion and Conclusion

This study demonstrated that none of the three vehicles commonly used in nonclinical toxicity studies caused any significant toxicological findings in 14-day inhalation studies in cynomolgus monkeys. These results provide valuable background data for future inhalation toxicity studies.

Presenting Author: HOTTA Keisuke, Mediford corporation; The authors have no financial relationship to disclose.
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