

Inhalation
Sciences



The Power of Precision

A novel tool for generating and exposing aerosols
in precise, repeatable, controlled doses

White Paper

Precision dosing: A unique methodology

> Control your aerosol > Control your dose > Control your outcome

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"I broke with conventional dry powder technology — PreciseInhale is the only platform offering precision dosing!"

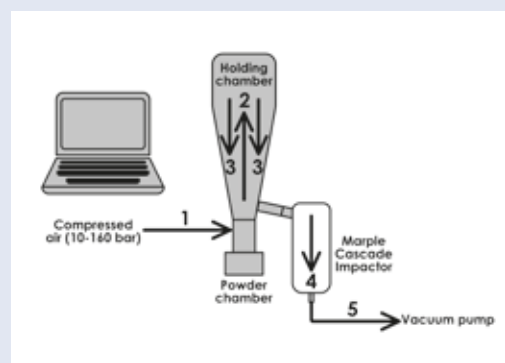
Dr Per Gerde, CSO

Two core innovations

#1

PreciseInhale separates aerosol generation and dispensing.

PreciseInhale generates aerosols using a high-power air jet of 10-160 bar pressure, de-agglomerating even tough substances. This energy is then siphoned off, leaving a plume of aerosol settling downwards. An adjustable air flow, via a vacuum pump, pulls this settling cloud into a fine, free-flowing stream of particulate aerosol that can be dispensed across a range of exposure modules.



#2

PreciseInhale's software monitors and measures the tailored aerosol in real time.

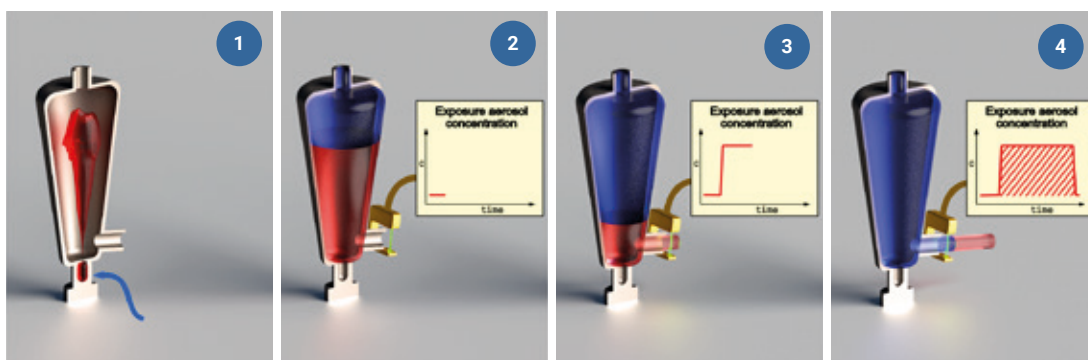
Automated software and a light-scattering device maps and measures the aerosol concentration and breathing pattern in real time. This enables researchers to customize their aerosol to their exact needs, and generates detailed PK data, including particle size distribution data and T_{max} and C_{max} curves.

What is precision dosing?

PreciseInhale aerosol generator is built around a methodology called 'precision dosing'. Using adjustable air pressure, settings can be optimized. The generated aerosol is precisely dosed as desired. The higher the air pressure, the finer the aerosol generated, meaning less particle agglomeration and smaller Mass Median Aerodynamic Diameter (MMAD) determined by Particle Sizing Distribution (PSD). Aerosols can

be sourced from dry powders, inhalers or nebulized solutions. As little as 100 milligrams of costly test substance can be enough to run a full PK study compared to 100g using conventional methods. The aerosol generated is a controllable, free-flowing, fine particulate stream that can be used in a wide range of exposures. It produces precise, predictive data with low Standard Deviation.

How does it work?



A jet of high pressure air is shot through the powder chamber, aerosolising the powder upwards into the holding chamber. The energy of the jet is siphoned off.

The aerosol rises upwards in a plume, then settling downwards in the holding chamber where a controlled air flow "pulls" the API past a real-time aerosol monitor.

The real-time aerosol concentration and dose is logged.

The precise exposure is controlled.

A quality-not-quantity methodology

The precision dosing methodology creates big benefits from working on a meticulous scale. Tailoring each exposure, and using small, precise amounts, one-animal-at-a-time,

generates exceptionally accurate, reliable results—reducing the number of tests needed, and the amount of test substance required.



100 mg

As little as 100 mg or less of test substance can run a full PK study.



PreciseInhale® reduces development time by identifying the right candidate drug early on.



<10% SD

Generates data on precise dosing with a typical standard deviation of less than 10%.



iMAC

One aerosol across a range of exposure modules producing predictive, comparable data, with less translational issues.



<5 μm

Customized dose setting gives consistent particle size distribution from nano particles upwards.



3R

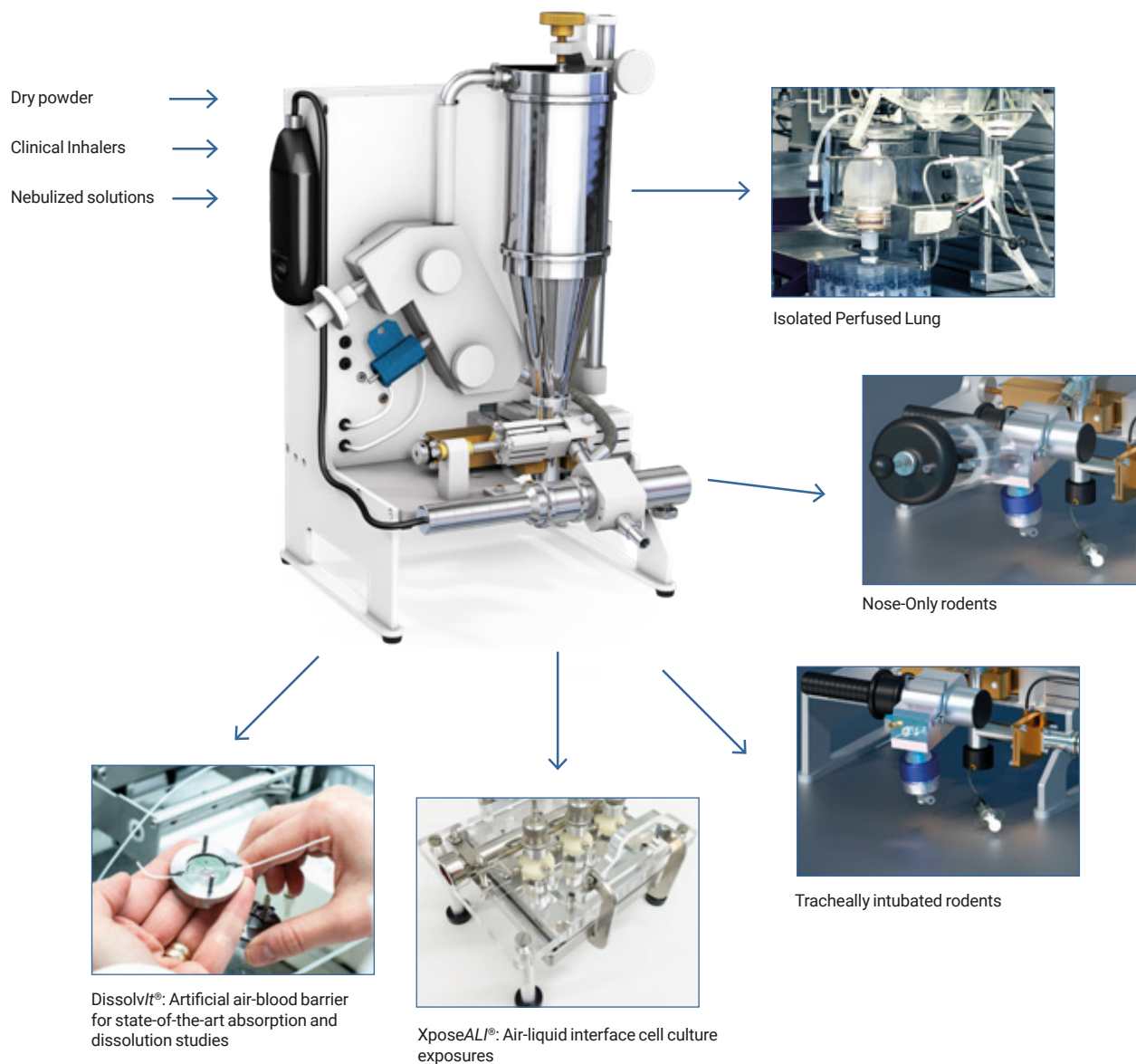
One-animal-at-a-time method plus *in vitro* capabilities reduces, refines & replaces animals.

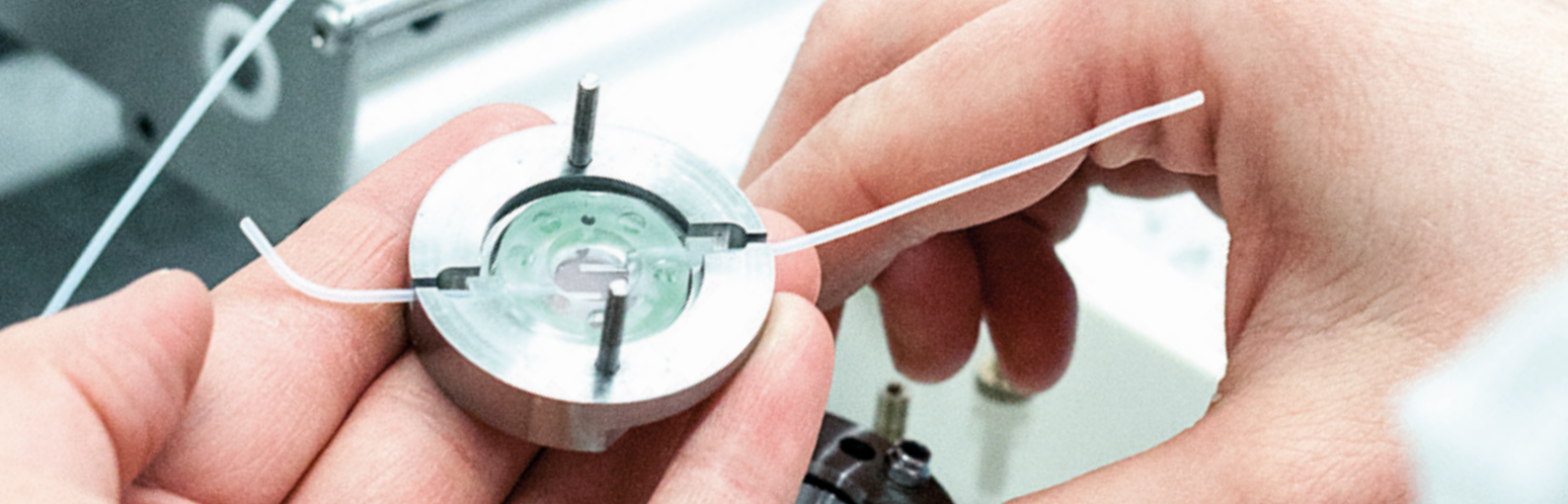
The aerosol switchboard

A wide range of exposure modules

Because the aerosol produced by PreciseInhale is controlled, it is easily exposed in a range of exposure modules. The aerosol can be sourced from dry powders, inhalers or nebulized solutions, optimizing conditions for a wide range

of substrates. PreciseInhale works as an exposure platform for small-scale inhalation experiments by precisely dosing animals *in vivo*, lungs *ex vivo*, and depositing material for *in vitro* exposure and dissolution testing.



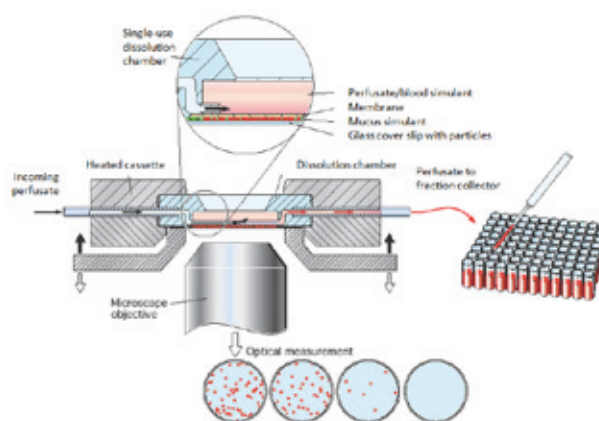


DissolvIt®

In vitro simulation of absorption and dissolution of particles in the lung epithelium.

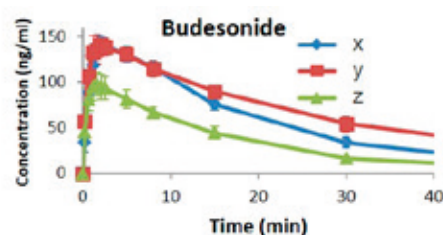
In the patented DissolvIt *in vitro* module dry powder particles are deposited on a glass surface by Preciselnhale. The particles are then brought into contact with a simulated lung/airway mucus and the dissolution is studied, from the 'luminal' side through optical microscopy and from the 'vascular' side by chemical analysis of a flow-past perfusion medium. The system consists of a dissolution chamber, a precision-controlled peristaltic pump and an inverted microscope with a high resolution camera. The dissolution chamber is perfused in single-pass mode after which the blood simulant is collected in a fraction collector. The entire system is thermostatted to 37° C. This artificial lung/blood barrier delivers state-of-the-art absorption and dissolution data.

How it works



Key and features:

- > Ranks substances according to solubility
- > Monitors absorption as well as dissolution
- > Identifies successful, effective Drug Candidates early on
- > Delivers exceptionally detailed data incl. C_{max} and T_{max} curves
- > Optical microscopy shows real-time dissolution of particles
- > Customizable, programmable Fraction Collector for flexible sampling

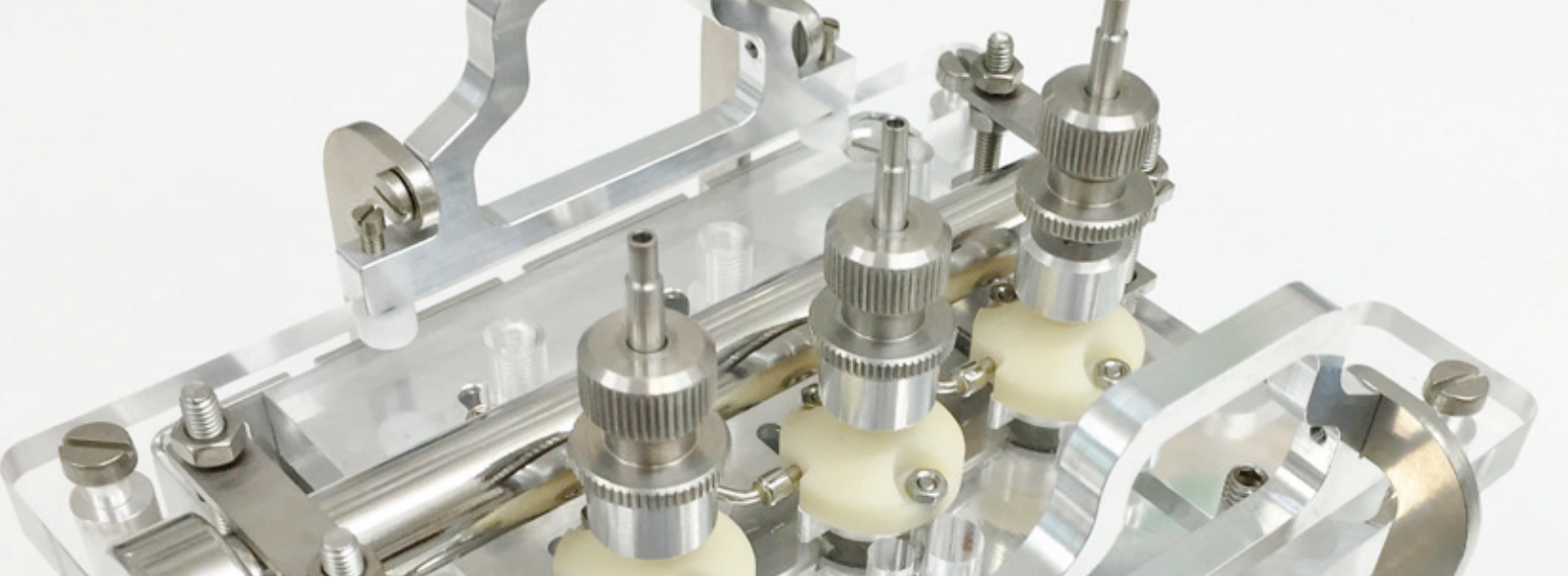


C_{max} and T_{max} displayed for three different budesonide formulations



"ISAB's in vitro dissolution capabilities are excellent, in fact, leading."

Professor Ben Forbes, King's College London, Institute of Pharmaceutical Science



XposeALI®

3D *in vitro* cell exposure

XposeALI/ 3D cell exposure module combines aerosol capability with 3D cell models cultured in an Air Liquid Interface (ALI). It enables studies of cellular effects induced by airborne particles.

XposeALI/ uses Preciselnhale for exposing cells with respirable size aerosols without the aerosol reaching the cell media or contamination the transwell walls. The cells are in contact with the media from below during the entire exposure. After aerosol exposure, the cells are brought back to the incubator for an appropriate time period, so the aerosol exposure induced cellular effects can be studied by analyzing the cells, or its media.

Key and features:

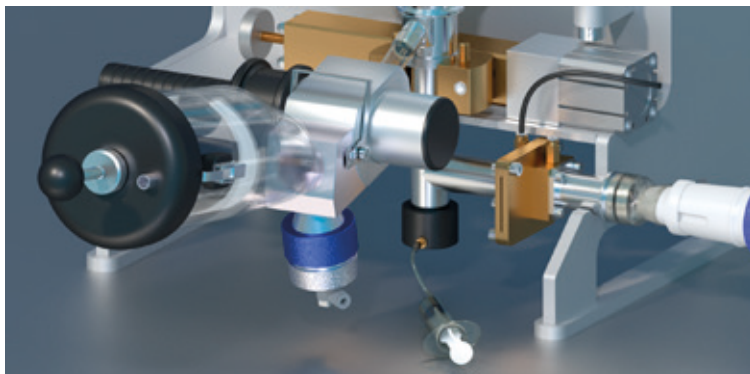
- > Lung-like conditions during cell exposure
- > Defined aerosol exposure of cells
- > Enables studies of cellular effects induced by airborne particles



"Culturing the 3D-models in ALI mimics the uptake of substances in the lung in vivo more exactly than conventional cell culturing. We are confident that XposeALI will play an even greater role in cell culturing research in the future."

Assoc. Prof. Lena Palmberg, Institute of Environmental Medicine, Karolinska Institutet

In vivo module: Nose-Only inhalation



Key and features:

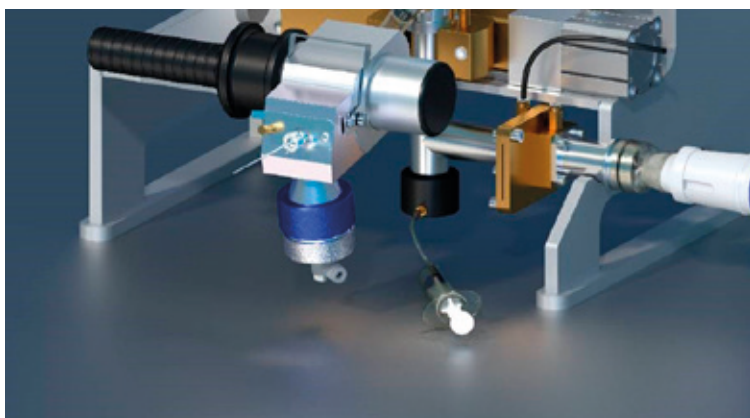
- > Individual exposure monitoring & dosing
- > Low inter-individual variation of exposures, typically +/- 10% SD in rats
- > Low substance consumption
- > Repeated exposures optimal

The module for Nose-Only inhalation exposures of rodents, one-at-a-time, to respirable aerosols by PreciseInhale makes it possible to reduce Standard Deviation, obtain highly reliable, repeatable PK data and is of particular benefit when repeated exposures are required.

PreciseInhale reduces both the variability of exposure between animals, and test substance consumption—due to individual precision dosing. It allows the study of the distribution

of inhaled drugs to blood and other tissues, as well as metabolism and clearance.

In vivo module: Intratracheal intubation



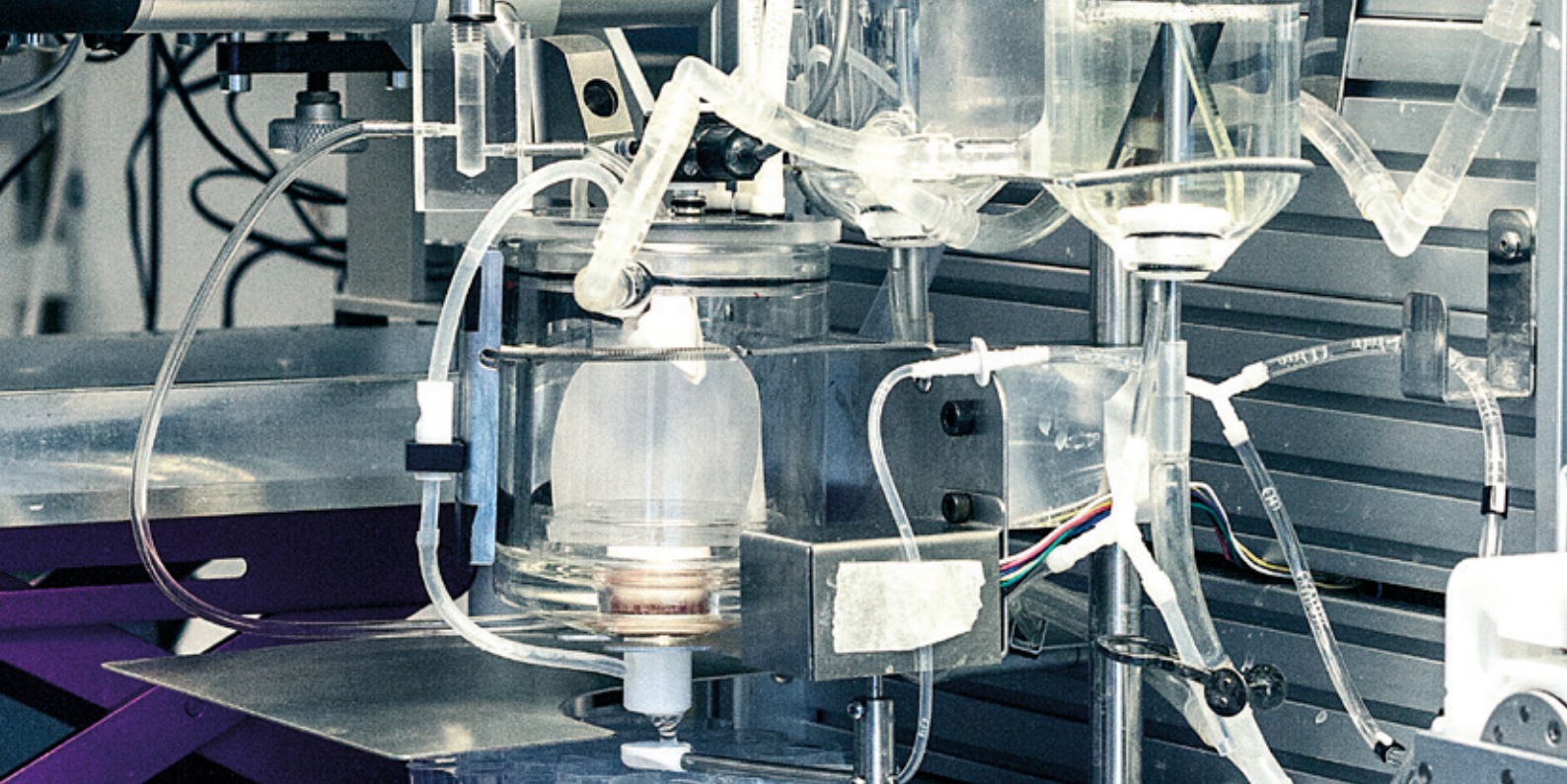
Key and features:

- > Active control of the dose delivered
- > Particle Size Distribution in the lungs closely resembling clinical data
- > Eliminates substance losses in the nose
- > Low substance consumption
- > Reduces and refines the number of animals used in research
- > Typically +/- 10% SD in rats

The intratracheal inhalation exposure module bypasses the nose, ensuring inhalation direct to the lung.

It avoids the risk of substance losses in the nose, or secondary gastro-intestinal exposure. Produces Particle Size Distribution closely resembling that obtained during

clinical exposures. It also enables the study of the distribution of inhaled drugs to the blood and other tissues, as well as metabolism and clearance.



Isolated perfused and ventilated lung

Ex vivo module

This isolated perfused and ventilated lung (IPL) system is a specially tailored version of IPL designed for exposures of respirable aerosols from PreciseInhale. IPL delivers low standard deviation dosing rates, typically <10%, and high-resolution data.

IPL is a well-established experimental model in toxicological and pharmacological studies. With this model of IPL it is possible to study the effects of different agents in an intact organ, with physiological cell-to-cell contacts and a native intracellular matrix. It enables the study of lung-specific effects of toxicants and drugs, as it does not involve recirculation of blood from distal compartments. Additional aspects of lung physiology like airway resistance, vascular resistance and gas exchange can be monitored at the same time.

The IPL perfused in a single pass mode is especially advantageous for PK studies of inhaled drugs and toxicants. In our tailored IPL system, the perfusate is collected throughout the perfusion period using a fraction collector, which also makes it possible to monitor the perfusate flow rate. The perfusion system can also be converted to a recirculation mode to facilitate detection of an accumulating substance or its metabolites in a smaller perfusate volume.

Key and features:

- Characterization of lung absorption and retention in detail (up to 2 hr sample collection).
- <10% standard deviation in dosing.
- Total mass balance control, no losses.
- Detect possible acute organ toxicity at the earliest time point.



Contact us

TSE Systems GmbH

Louisenstr. 65

61348 Bad Homburg, Germany

Phone: +49-6172-789-0

E-Mail: info@TSE-systems.com

Web: www.TSE-Systems.com



TSE Systems GmbH

Louisenstr. 65
61348 Bad Homburg
Germany

Phone: +49-6172-789-0
E-Mail: info@TSE-systems.com
Web: www.tse-systems.com