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FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

ISOLATED PERFUSED RAT LUNG (IPL) FOR ABSORPTION KINETICS STUDIES

The ex-vivo model "Isolated Perfused Rat Lung" (IPL) allows simulation of whole-organ exposure to inhalable substances. Due to this proximity to the in-vivo situation, the isolated perfused rat lung is an attractive tool for preclinical testing of new drug candidates and formulations as well as for acute toxicity testing of chemicals.

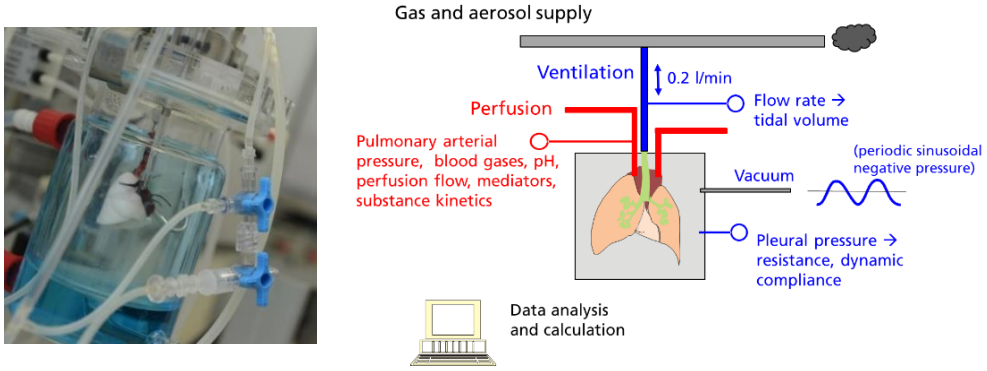

Fig. 1: Experimental setup of the isolated perfused rat lung

At Fraunhofer ITEM, the IPL has recently been established as a tool for investigations into the systemic uptake of inhaled substances through the lung. To this end, lungs from rats are ventilated and perfused with a physiologic buffer solution. Respiratory parameters, such as tidal volume, dynamic compliance, and pulmonary arterial pressure (VT, Cdyn, PAP), are measured online for monitoring of pulmonary viability.

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For investigations into mass transfer processes through the lung, IPLs are exposed to rat-respirable aerosols. The concentration profile of the substance is subsequently analyzed in the perfusate.

Studies at Fraunhofer ITEM have shown that the analysis of such concentration profiles for small molecules delivered to the lungs as aerosols enables a qualitative ranking in regard to the transfer velocity through the lung into the systemic circulation, which is in good agreement with data from human clinical trials.

These experiments as well as further studies performed at Fraunhofer ITEM show a strong potential of the model for systematic investigations of mass transfer through the lung for different substances, though a quantitative comparison to the human situation and in this context between different products has not been carried out yet. In the context of absorption studies, the IPL model is also useful for further mechanistic investigations, such as the elucidation of transport-relevant mechanisms through the alveolar-epithelial membrane.

Fig. 2 shows an example of substance uptake for two different substances.

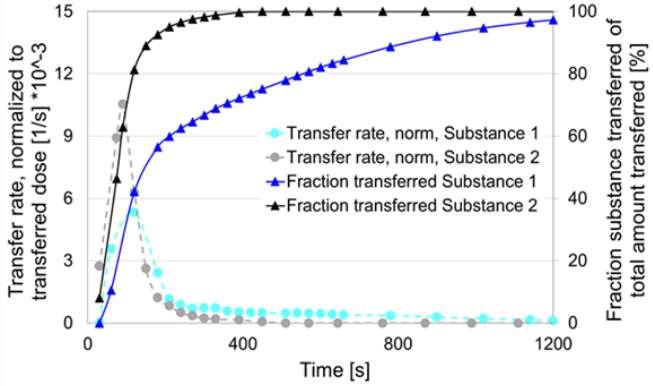

Fig. 2: Substance transfer rate into perfusate, normalized to the transferred dose, and fraction of substance transferred of total amount of substance transferred as a function of time after one minute inhalation exposure of the IPL to aerosols containing the substances.

Analysis options

Test substances can be from any source (medications, chemicals, environmental pollutants etc.) and aerosol generation can be performed for both solid and liquid materials. Besides the relevant inhaled substances, biomarkers can be analyzed in bronchoalveolar lavage fluid and lung perfusate.

Lung function

- Ex-vivo measurement of dynamic compliance (C_{dyn}), lung resistance (R_L), and pO_2 in perfusate
- Analysis of lung weight (edema, atelectasis formation)
- Perfusion flow, pulmonary artery/venous pressure

Imaging

- Conventional staining and tissue pathohistology/conventional microscopy
- Immunohistochemistry/fluorescence microscopy
- Confocal microscopy
- Electron microscopy

Chemical analysis

- HPLC
- LC/GC-MS