# Advanced Non-animal Models in Biomedical Research:

## Respiratory Tract Diseases|

***Respiratory diseases*** *are a leading cause of death and disability worldwide. Research on human diseases relies extensively on animal models, however, effective* ***new therapies*** *for serious respiratory conditions are still lacking. One reason for this is that animal models often poorly represent human physiology and pathology. The European Commission's Joint Research Centre (JRC) has carried out an extensive review of advanced non-animal models being used for basic and applied research on respiratory tract diseases. Researchers characterised and catalogued almost* ***300 models*** *to make them more accessible for human relevant studies that avoid the use of animals.*

"3 million people die from chronic obstructive pulmonary disease (COPD) each year, making it the third leading cause of death worldwide"

*Forum of International Respiratory Societies, 2017*

### RESPIRATORY TRACT DISEASES

Respiratory tract diseases, such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer, are one of the leading causes of **morbidity and mortality globally**. Animal models are extensively used in research although their scientific relevance is a matter of debate.

### LEGISLATIVE FRAMEWORK

**Directive 2010/63/EU** on the protection of animals used for scientific purposes sets out clear legal requirements for the implementation of the 'Three Rs' principles of **Replacement**, Reduction and Refinement of animal procedures. The final goal is that animal testing should be phased out and replaced by scientifically valid non-animal alternatives.

### LACK OF EFFECTIVE NEW THERAPIES

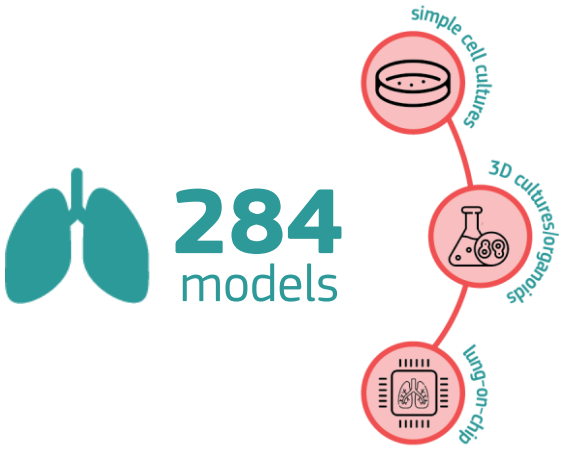
According to the latest statistics, in 2017 the European Union used approximately 10 million animals in experimental procedures with about 70% of those being used for disease related research.

However, there is still a **lack of effective new therapies** for serious respiratory conditions. Over 90% of new drugs fail to progress to market due mainly to a lack of efficacy or unexplained toxicity.

This suggests that reliance on animal models is failing to identify novel therapies. In this context, the JRC's EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) carried out a study to produce a unique **knowledge base** that contains detailed descriptions of non-animal models being used for respiratory disease research.

### KNOWLEDGE BASE OF ADVANCED NON-ANIMAL MODELS

About 21,000 scientific papers were screened for relevant human-based models of respiratory diseases and from those a total of **284 models** were identified as being the most representative and promising.

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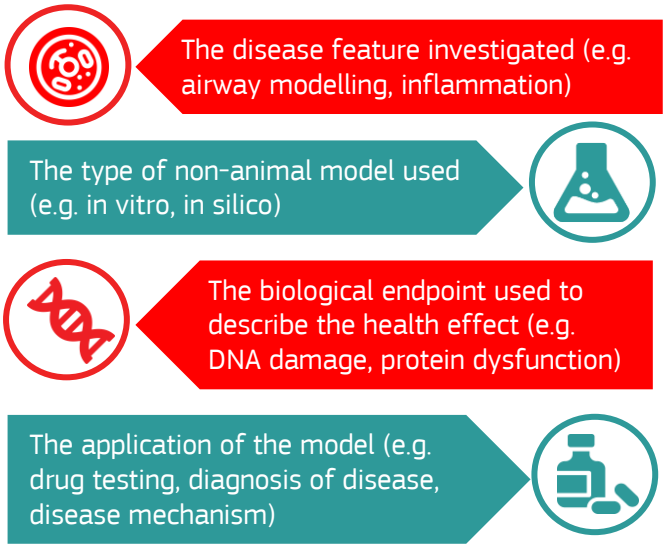
This collection of models is freely available for download from the **JRC Data Catalogue** in an easy-to-use spreadsheet format. This knowledge base is complemented by a **Technical Report**, which provides an in-depth meta-analysis of the approaches being used and a separately published **Executive Summary** intended for the general reader.

## THE META-ANALYSYS OF THE MODELS

In this meta-analysis the selected models are characterised according to:




The collection shows that simple models such as cell cultures are still prominent since they are inexpensive and quick to implement. However, research is shifting towards more sophisticated bioengineering approaches that better recapitulate lung development, anatomy and physiological functions in cell-based (in vitro) systems.

The emerging use of more **human-relevant models**, e.g. 3D human tissue cultures, spheroids, organoids, and microfluidic/'lung-on-a-chip' systems shows immense promise for the development of model systems that more accurately mimic human respiratory diseases.

## WHO IS THIS KNOWLEDGE FOR?

This review and model catalogue represent a valuable resource for **scientists** and **funding bodies,** as well as various actors involved in the application of **Directive 2010/63**, such as Animal Welfare Bodies, Competent Authorities, National Committees and National Contact Points.

The knowledge gathered can also be introduced into **education and training programmes** to inform a new generation of researchers about the non-animal models currently available and to stimulate innovative approaches in biomedical research.

## Non-animal models for pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a respiratory disease in which scars are formed in the lung tissues, resulting in stiffness and difficulty in breathing.

A non-animal model to study the efficacy of IPF drugs, known as a '**pulmosphere**', can be grown from tissue obtained from a lung biopsy. Pulmospheres are 3D multicellular spheroids composed of lung cells from individual patients that contain all the various cell types found in a human lung. Pulmospheres simulate the microenvironment in the lung and serve as a personalised and predictive model for assessing responsiveness to drugs in patients affected by IPF.

Microfluidic co-cultures also offer new opportunities for faithfully modelling human disease of pulmonary fibrosis. Lab-grown lung cells (epithelial cells, fibroblasts, and macrophages) are placed upon a chip and interconnected by channels to mimic the in vivo lung tissue – this is the **lung-on-a-chip** technology. A protein is then introduced in the system to cause contraction and stiffening of the engineered lung tissue. In this way, it is possible to mimic the scars of the lung tissue observed in people who suffer from the IPF. This system recapitulates the critical changes characteristic of pulmonary fibrosis.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