RESEARCH NEWS

Toxicological risk assessment for chemicals

Avoiding animal experimentation

It is still the case that data from animal studies is required in order to evaluate the safety of a substance for humans. However, the Fraunhofer Institute for Toxicology and Experimental Medicine ITEM has teamed up with 39 partners from 13 countries on a range of projects, all of which have a common aim: to bring about a paradigm shift – away from animal experimentation and towards a deeper understanding of how chemical substances work.

In Germany, the number of test animals has broadly remained the same for a number of years now. According to the German Federal Ministry of Food and Agriculture (BMEL), a total of 2,825,066 animals were used in animal experiments in 2018. Dr. Sylvia Escher, head of the Department of In-silico Toxicology at Fraunhofer ITEM in Hannover, is seeking to develop alternatives to animal testing. "At our institute, we work with various groups on new concepts for chemical risk assessment," the chemist explains. The two examples she names are the EXITOX and EU-ToxRisk projects. Both of these aim to develop test strategies based on human cell lines and organ sections, which are intended to reduce and, in the long term, replace animal experiments.

A better and more conservative alternative

The objective is to develop an alternative that is not only more conservative but also better. In conventional animal testing, scientists observe for the onset of toxic effects, such as inflammation or tissue changes in the relevant organ, following administration of the test substance. In particular, they seek to determine whether continuous exposure to a substance damages the organism or whether a low concentration, such as that absorbed daily from the air, remains uncritical. "In EU-ToxRisk and EXITOX, we're investigating the mode of action that leads to the observed toxic effect. And given that we're using human test systems rather than animal testing, we very much hope that the results will be more relevant to humans," says Escher, pointing out the benefits of this approach.

A number of working groups from Fraunhofer ITEM are involved in three of the nine case studies being conducted as part of the EU-ToxRisk project. Dr. Tanja Hansen, head of the Working Group on In-vitro Test Systems, is currently investigating the toxicology of volatile compounds, using diketones as an example. The best-known representative of this substance group is diacetyl, a chemical compound naturally found in butter. An industrially produced version is used to give a butter flavor to popcorn, for example.

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Simulations with human tissue

What happens when people inhale diacetyl? Can it damage the lungs? To answer these questions, Escher and Hansen use an apparatus that was developed at Fraunhofer ITEM: the P.R.I.T.® ExpoCube®. This enables them to simulate the effect of volatile substances on cells and tissue.

In order to simulate the situation in the lung, the scientists use human bronchial epithelial cells that are cultivated on membranes at the air–liquid interface. Gaseous diacetyl is passed over the surface of these cells by means of the P.R.I.T.® ExpoCube®. Biochemical methods are then employed to examine the effect on the cells. Following a comprehensive analysis of gene expression, researchers can identify which genes the cells have activated or deactivated. They then use this data to determine which signal pathways were activated within the cell. These might be signal pathways that lead to the production of messenger substances that cause inflammation.

In the next step, the investigation progresses to the organ level. Here, researchers use living tissue sections cultivated from human lungs, which possess many functions of the actual organ. As with the cell cultures, the lung sections are now exposed to diacetyl in the P.R.I.T.® ExpoCube® and then analyzed.

To simulate the behavior of inhaled substances in the body, the project partners use complex calculation models known as "in silico methods." These computer-aided models are able to reproduce to a high degree of accuracy how an organism absorbs, distributes and excretes an inhaled substance. "In combination, in vitro and in silico data provides a more accurate picture of how substances such as diacetyl damage the lungs," Escher explains.

Using data from similar substances

A first step towards incorporating alternative methods in risk assessment is the read-across approach. If a new chemical is to be approved in accordance with this method, the first task is to seek out similar substances for which toxicological data from animal testing already exists. In the read-across approach, this data is then applied to the new chemical. "This approach is already in use. In practice, however, it is still proving difficult to demonstrate that two chemicals are so similar that they indeed have the same toxicity," says Escher. "This is why read-across approaches are often not accepted by the regulatory authorities."

In the case studies, project teams investigated groups of closely related substances and gathered comprehensive in vitro and in silico data. On the strength of these investigations, they were able to show that the alternative methods are perfectly capable of determining the toxicity of structurally related materials.

Consultation with regulatory authorities

The EU-ToxRisk project involves not only universities, research institutes and companies but also regulatory authorities. Close consultation with toxicologists working for regulatory bodies is vital if these new integrated test strategies are to be a success. For it is only if national and EU authorities approve these newly developed processes for assessing toxicity that animal testing can be replaced.

More information:
http://www.eu-toxrisk.eu/

Picture 1: Developed by Fraunhofer ITEM, the P.R.I.T.® ExpoCube® enables exposure to various classes of inhalable substances and their testing with high reproducibility and with the requisite dosage control.

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Picture 2: Read-across hypotheses can be derived from existing in vivo data.

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