Toward new alternatives to animal testing

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A novel alternative approach that can identify chemicals which affect male reproductive health without the use of animal tests has been developed in a research project led by the Technical University of Denmark.

For many years, researchers at the National Food Institute, Technical University of Denmark, have studied the harmful effects of chemicals and developed methods to best and most effectively investigate their harmful effects. Of the many thousands of chemical substances to which humans can be exposed, the majority has not been adequately examined in terms of their ability to harm human reproductive health.

The institute's researchers have now developed a novel approach based on in vitro methods (experiments at the cellular level) and computational models, which makes it possible to identify chemicals that have a detrimental effect on male reproductive health. Such harmful effects include imbalances in male sex hormones and the inability to father a child.

In vitro methods integrated with computational models can replace animal tests

The new approach is based on selected in vitro models that measure the ability of pesticides to block the receptor for the male sex hormone, testosterone, and the pesticides' ability to inhibit testosterone production. The in vitro methods are integrated with computational models that have been fed large data sets on how the body absorbs, metabolizes, distributes and excretes the chemicals.

Results from the cell-based assays are uploaded in the computer models (so-called physiologically-based kinetic models). The models can thereby calculate the concentration of a given substance that must be present in a fetus in order for a harmful effect to occur in the fetus. That calculation can be used to assess how much of the chemical a human would need to consume (e.g. via the diet) before a harmful effect in the fetus occurs.

Traditionally, experiments with e.g. pregnant rats have been used to assess the amount of a given chemical that is passed on to the rat's fetus. The new study from the National Food Institute shows promising results when using the alternative approach, as the computational models were able to predict relatively accurately the exposure of the fetus.

To increase confidence in this novel method, researchers have validated their predictions by conducting animal tests on selected pesticides. For the validation, the researchers used both EU-approved pesticides and model pesticides, which the EU has banned due to their harmful effects on reproductive health.

In the tests, the animals were exposed to doses that were equivalent to the doses, which the computational models had predicted would cause harmful effects. This comparison showed a surprisingly good correlation between the predicted and the measured effects.

Better use of resources

The researchers' vision is usage of their approach on all EU-approved pesticides for which there is a lack of studies on male reproductive health. They propose that the new approach be used to classify chemicals as being either positive or negative.

Chemicals predicted positive should be handled and potentially regulated by the authorities based on these predictions, while those that are negative would require in vivo tests to determine if they are actually negative. Such an approach would save resources.

The work is described in further detail in a scientific article in the journal *Environmental Health Perspectives*: "Quantitative in Vitro to in Vivo Extrapolation (QIVIVE) for Predicting Reduced Anogenital Distance Produced by Anti-Androgenic Pesticides in a Rodent Model

for Male Reproductive Disorders."

More information: Martin Scholze et al. Quantitative in Vitro to in Vivo Extrapolation (QIVIVE) for Predicting Reduced Anogenital Distance Produced by Anti-Androgenic Pesticides in a Rodent Model for Male Reproductive Disorders, *Environmental Health Perspectives* (2020). DOI: 10.1289/EHP6774

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