Abstract for 3R symposium 2018

Transition towards animal-free safety assessment of chemicals

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Abstract

Background: Knowledge on sensitive endocrine effects on male reproductive health for the currently ~352 EU-approved pesticides is scarce. There is an urgent need to improve non-animal test strategies that can help in predicting pesticides' adverse effects on male reproductive health. The development of the male reproductive system strongly depends on androgens produced by the fetal testes, and hence the fetus is a target for compounds capable of interfering with the synthesis of these hormones or by antagonizing the androgen receptor.

Methods: Our strategy combines androgen-related activity of pesticides on human cells with physiologically-based kinetic modeling. Here, in vitro data pinpoints compounds with a potential in vivo activity by identifying their critical internal fetal exposure, while the kinetic model simulates the maternal doses necessary to reach critical levels in the fetus.

Results: We have developed a proof-of-principle showing that adverse effects on anogenital distance in male offspring, which is a unique and non-invasive marker for male reproductive health effects in animals and humans, can be predicted for selected pesticides. We investigated this strategy on 11 pesticides and selected 6 compounds – fludioxonil, cyprodinil, dimethomorph, procymidone, vinclozolin and linuron – for in vivo 'validation' of the alternative approach. Predicted levels in the fetuses were within a factor of 2.5 from measured concentrations, and all compounds showed a shorthened AGD in vivo as predicted by the alternative approach.

Conclusion: We have obtained the first proof-of-principle that our approach is viable and may have the potential in the long term to reduce unnecessary animal testing in risk assessment of chemically-induced male reproductive disorders.