Tiered testing approaches to assess substances that cause thyroid hormone imbalance in rodents

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INTRODUCTION

Overall, data from human observational studies are in support of a link between altered serum levels of thyroxine (T4) and/or thyroid stimulating hormone (TSH) in pregnant mothers and increased risk of neurodevelopmental impairment in their child. Criteria for the identification of endocrine disruptors have been in place for pesticides and biocides in the EU since 2018. Substances inducing thyroid histopathological and/or thyroid hormone (TH) effects in rodent studies are thus subject to regulatory evaluation if they fulfil the relevant criteria. Due to the complexity of the thyroid modality, which includes several potential molecular initiating events (MIE), limited facilities and a methodology to conduct valid and robust mechanistic studies, and uncertainties around adverse outcome pathways leading to neurodevelopmental toxicity, a conclusive testing and assessment scheme for compounds causing thyroid effects in rodents is not established. In addition, there are a number of known differences between humans and rats with respect to TH metabolism and excretion, in particular the increased breakdown of TH following liver enzyme induction in rats.

METHODOLOGY

An ECETOC Thyroid Task Force (TF) was established in 2018 to contribute to the development of a science-based testing strategy to identify whether a substance has the potential to elicit maternal thyroid hormone imbalance and subsequently neurodevelopmental effects in children. This includes exploring the relevance for humans of effects observed in rodent studies and an evaluation of whether thresholds for adverse effects associated with changes to thyroid hormones can be identified. The TF performed an extensive literature review of relevant human and animal studies and held a meeting with external regulatory and academic experts to identify which experimental data are key in order to determine whether a substance-mediated increase in liver enzymes and TH clearance does (or does not) result in impaired neurodevelopment. Four publications, which have been either published or are in preparation, focus on 1. human/epidemiological studies, 2. key events of relevant adverse outcome pathways, 3. case studies addressing a variety of thyroid-active substances (and dietary iodine deficiency) and parameters indicative for

neurodevelopmental impairment and 4. the proposal of a tiered testing and assessment scheme.

RESULTS

Rodent toxicity studies show that substances that affect the thyroid system often do so through liver enzyme induction (mainly uridine diphosphate glucuronosyltransferases (UGTs)), which leads, via increased TH conjugation, to increased TH clearance, decreased circulating TH, and ultimately possibly also to alterations in the thyroid gland itself. By contrast, the available human evidence does not allow such a clear causal link to be established. UGT is generally not collected in human observational studies, and thus is unavailable for comparison with the extensive laboratory rodent data. In the second publication, relevant key events in thyroid adverse outcome pathways were identified, and it was evaluated how they are being, or might be, addressed in rat toxicity studies and/or in-vitro assays. The third manuscript is assessing reproductive toxicity studies on compounds with different thyroid-related MIEs. The focus is on identifying thresholds for thyroid hormone imbalance in dams and offspring that are indicative of neurodevelopmental toxicity.

DISCUSSION

A proposal for a tiered testing and assessment scheme is currently under development. The scheme includes evaluation of thyroid effect data and potentially corresponding systemic toxicity, which could trigger the need for further mechanistic in-vitro and in-vivo studies in order to clarify the thyroid mode of action by conducting a thorough mode of action and human relevance framework, to assess potential species-related specificities and to further investigate the compound’s potential to induce neurodevelopmental toxicity in rats.