QSAR models for the prediction of endocrine disruption potentials of brominated flame retardants: a classification approach

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INTRODUCTION

Increasing concern is shown by the scientific community, regulators, and the public, about endocrine-disrupting chemicals (EDCs) that are adversely affecting human and wildlife health through a variety of mechanisms of toxicity. The potential activity as endocrine disruptors (EDs) of Brominated Flame Retardants (BFRs), has already been experimentally demonstrated and deserves particular attention since the production and use of potential EDs will be strictly regulated through the authorization process of the REACH regulation. To overcome the problem of insufficient experimental data necessary to complete the toxicological profile of these chemicals, the QSAR/QSPR approach can be applied to predict the missing information [2]. In this study QSAR classification models were developed, according to the OECD principles, to predict endocrine disrupting potentials of BFRs.

ENDPOINTS and Classes

Classification criteria according to Hamers et al., 2004 [2].

New CLASSIFICATION models were developed for different endpoints related to the endocrine potency of BFRs.

The proposed models were selected by balancing:
- number of false negatives FN (highest Sn)
- external predictivity (NREtest)
- simplicity and interpretability of descriptors

The most dangerous compounds and/or important structural alerts were identified for each ED activity (i.e., nAOH, F04(0-B)).

According to literature P < 0.05, ED activity of BFRs (DR/ER/AR/PR) T4-TTR compiled (E2SULT Bà) is strongly increased by the presence of -OH group on the aromatic ring.

The variability of interactions of the studied chemicals with different receptors prevented us from defining a general ranking based on their ED potency.

The here proposed classification models are simple tools, with defined Applicability Domains, which can be applied to screen BFRs in relation to their ED activity and, for identification of safer alternatives. This is in agreement with requirements of REACH regulation (Title VII, Chapter 1, Article 57-f).

VALIDATION and Applicability Domain (AD) Data were split into training set (development of the models) and prediction set (validation of the models) by random selection (30%). Models were developed taking into account the OECD principles for QSAR validation for regulatory purposes [9].

- Internal and external validation: Sn (sensitivity), Sp (specificity), NER (non-error rate), NER test,
- Applicability Domain (AD%) for 243 BFRs verified by descriptor’s range.

CONCLUSIONS

- New CLASSIFICATION models were developed for different endpoints related to the endocrine potency of BFRs.
- The proposed models were selected by balancing:
  - number of false negatives FN (highest Sn)
  - external predictivity (NREtest)
  - simplicity and interpretability of descriptors
- The most dangerous compounds and/or important structural alerts were identified for each ED activity (i.e., nAOH, F04(0-B)).
- According to literature P < 0.05, ED activity of BFRs (DR/ER/AR/PR) T4-TTR compiled (E2SULT Bà) is strongly increased by the presence of -OH group on the aromatic ring.
- The variability of interactions of the studied chemicals with different receptors prevented us from defining a general ranking based on their ED potency.
- The here proposed classification models are simple tools, with defined Applicability Domains, which can be applied to screen BFRs in relation to their ED activity and, for identification of safer alternatives. This is in agreement with requirements of REACH regulation (Title VII, Chapter 1, Article 57-f).

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REFERENCES