MUT/2023/09

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COM)

COM guidance on the use of QSAR models to predict genotoxicity.

1. During revision of the COM overarching Guidance Document (A strategy for testing of chemicals for genotoxicity) members requested that a separate Guidance Statement be prepared regarding the use of QSAR models to evaluate the potential genotoxicity of chemicals, to allow more frequent updates to be made to a fast-moving area. The Guidance Statement was drafted in 2018 and amended versions were presented to COM on several occasions, with the last presentation given at the COM meeting in February 2021 (MUT/202/05).
2. At the meeting in February 2021, members suggested that the most likely use of QSAR would be to assess the genotoxic potential of impurities and, as such, a summary of text from the QSAR Gudance Statement should be included in the COM Guidance statement 'Genotoxicity assessment of impurities in chemical substances', which was also being updated. It was agreed that a sub-group of interested COM members would be identified to facilitate progress of the QSAR Guidance Statement, going forwards.
3. The following provides a summary of discussions of the first meeting of the COM QSAR subgroup, held on the 7th September 2023, concerning further development of the draft Guidance Statement regarding the current use of QSAR models to predict the genotoxic potential of chemicals.

- The primary focus of the QSAR Guidance Statement is to outline COM recommendations for an evaluation of genotoxicity using QSAR model(s), including how the findings should be presented and explained. One or more 'real-life' case studies were considered to be a useful inclusion, for illustrative purposes, this could be from the use of QSARs to evaluate impurities or other risk assessments.

    - The Guidance Statement should outline how different QSAR models have been built and are curated/updated, to evaluate the basis on which decisions are made, as this will differ between models. It should also be noted that the development of many of the current QSARs will have been driven from a pharmacology perspective.

    - Ames data are commonly used as an endpoint in currently available QSAR models. Members considered that there should also be some consideration of the inclusion of signals for clastogenicity, as EU regulators have begun to request this endpoint. At present though, inclusion of signals for clastogenicity generates a large number of alerts and so advice should be included on how to deal with these.

- The QSAR Guidance Statement also needs to include discussion of whether the TTC approach, which is currently used to evaluate the safety of food additives, is also safe with regards to evaluating chemical impurities. Based on this information, COM should provide a clear statement as to its views.

- Further considerations to be discussed in the QSAR Guidance Statement include the use of read-across, justification for the QSAR models used and how to evaluate 'out of domain' predictions.

- It is intended that the QSAR Guidance Statement will support the COM overarching Guidance Statement which refers to the use of QSARs in Stage 0 testing, as no separate COM guidance on QSAR currently exists. Members of the subgroup emphasised the importance of justifying QSAR use in the overarching Guidance document.

- It was agreed that a summary of information from the QSAR Guidance Statement will be added to the COM Guidance on impurities and other areas of application may become apparent during development of the QSAR Guidance Statement.

4. Following discussions, members agreed that the first step towards defining the content of the QSAR Guidance Statement on impurities would be to collate a list of current guidance on the use of QSAR models, from international bodies. Where possible, the key statements regarding how/which type of QSAR models should be used will be highlighted. A number of sources were suggested by the subgroup members, with others being identified through general literature searches:
   - European Food Safety Authority (EFSA).
   - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) M7 guideline.
   - International Workshops on Genotoxicity Testing (IWGT).
   - Scientific Committee on Consumer Safety (SCCS).
   - Organisation for Economic Co-operation and Development (OECD).

Once this has been completed a more general QSAR statement / Guidance will be developed if necessary.

Members are asked to consider the following questions:

a) Do members have any comments on the proposed steps?

b) Do members have other sources that should be considered?

c) Do members agree that there should also be some consideration of the inclusion of signals for clastogenicity?

Secretariat
September 2023