

## **DRAFT MUT/2011/10**

### **COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS**

#### **Applicability of QSAR analysis to evaluation of mutagenicity**

##### **Introduction**

1. The COM briefly considered initial assessments of potential mutagenicity of drinking water chemicals as illustrative examples of how QSAR approaches could be potentially applied to aid in hazard assessment.
2. Members had a number of reservations regarding the approach used MUT/2011/04 and requested more information on the models which had been used. A copy of the minutes of the discussion is appended (Annex 1) for ease of reference. The generic guidance from COM is that if *'there are no available genotoxicity data on a chemical substance, then at least publicly available QSAR modelling should be used to aid an initial assessment of potential mutagenicity'*.
3. The objective of this paper is to provide members with background information on the two publicly available models which have been selected. Members are asked to advise on the guidance which has been proposed for applying these models.

##### **Scientific report produced for EFSA prepared by Computation Toxicology Group, Joint Research Centre, Ispra, Italy.**

4. The JRC developed a framework for assessing the usefulness of QSAR models based on published guidance adopted for use under REACH and also guidance published by the OECD. A review of publicly available and commercial models was conducted across all toxicology end points. A standardised documentation for demonstrating model validity has been adopted (QSAR Model Reporting Format QMRF). The framework analysis for CAEAR and Toxtree are appended as Annex 1 to this document. The JRC undertook a survey of national regulatory bodies and international advisory organisations (in the field of food safety) to assess how QSAR approaches are used. There were responses from 38 organisations. 60% of the organisations didn't use QSAR, in most cases the reason for this was lack of appropriate technical expertise. The most commonly used were (Commercial; Derek, Multicase. Public ;OECD Toolbox and Toxtree). The most highly developed models were for genotoxicity. The JRC undertook an assessment of commercial and publicly available genotoxicity models using a structurally diverse data set of 700 chemicals with genotoxicity test data. The correct identification of Ames test data was highly reproducible. The JRC concluded that pairwise combinations of increase the overall sensitivity and reduce the false negative rate. Further work could involve optimising data interpretation schemes.

## JRC Assessment of genotoxicity QSAR models

5. A copy of the chapter from the JRC report detailing the assessment of genotoxicity models is appended as Annex 2. Three data sets were used i) A data set of 181 pesticides, ii) an external heterogeneous dataset of 748 chemicals (DSSTox CPD) and iii) 113 classified mutagens (from EU harmonised process).

6. CAESAR (Computer Assisted Evaluation of industrial chemical Substwas developed as an EU funded project and is a statistical based model developed using 4225 compounds from the Kazius-Bursi mutagenicity database. The correct classification rates were 92.3% and 83.2% for the training and test sets.

7. Toxtree was developed by the JRC as an EU project. It is a rule based approach using Benigni-Bossa rule base (an expansion of the Ashby super mutagen model) and the Tox Mic rulebase for the *in vivo* MN prediction. It has a reported accuracy of 78% for mutagenicity and 59% for *in vivo* micronucleus prediction.

8. A combination of CAESAR and Toxtree has a false negative rate of 11%. The JRC used a cut off of 20% FN rate for the assessment of combined models.

9. A brief tabulation of the performance of CESAR and Toxtree compared to two commercial models is given below. Full details can be found in Annex 2. The purpose of this tabulation is to show that publicly available and commercial models have very similar performance for genotoxicity assessment. The lowest sensitivity was reported for the pesticide data set and reflects the small number of chemicals in the dataset which were shown to be mutagenic in experimental test systems

Data set	CAESAR	Toxtree	Derek	TOPKAT
Pesticides: 181 chemicals, 11 mutagenic, 170 inactive	64% (sens)	55%	60%	64%
	76% (spec)	69%	87%	72%
DSSTox 748 chemicals, 368 mutagenic, 310 inactive	86%	85%	83%	83%
	80%	70%	89%	85%
Classified mutagens 113 Chemicals	73%	87%	73%	58%

## Generic approach to QSAR application

10. The JRC provided some generic guidance which has been used by the secretariat to develop an approach to using QSAR data. The following steps are proposed which should be applied on a case-by-case basis.

i) *Is chemical under evaluation within the scope of model?*

CAESAR provides a prompt when the chemical is outside the domain of applicability. Toxtree applies set rules for evaluation but doesn't provide information or an alert when novel structures not covered by the rulebase are evaluated. The combined use of these two models gives the widest possible domain of applicability (see Venn diagram appended as Annex 3.)

ii) *Is the defined endpoint suitable for the regulatory purpose?*

CAESAR provides a QSAR estimate for mutagenicity in the Ames test which is an end point commonly used in regulatory assessments. Toxtree provides an estimate for mutagenicity in Salmonella TA100, MN formation in rodents and prediction of genotoxic carcinogenicity which are end points commonly used in regulatory assessments.

iii) *How well does the chemical predict chemicals similar to the chemical of interest?*

CAESAR provide estimates for 6 structural analogues within the database. These can be used to provide informed assessment of the chemical of interest. Thus if there is doubt over the validity of the assessments made for structural analogues, this might limit extrapolation to the chemical of interest. Chemical analogues have to be identified and then separately entered for Toxtree.

iv) *Is model estimate reasonable taking into account other information?*

The JRC stress the need for weight of evidence assessment regarding the chemical of interest and structural analogues. Actual test data for chemical of interest and analogues should overrule any QSAR estimation.

## COM Discussion

11. The secretariat proposes to use a combination of CAESAR and Toxtree using a case-by-case approach for chemicals where no other genotoxicity data are available and there is a need to provide an estimation of potential genotoxicity. CAESAR and Toxtree are freely available simple to use and provide data for defined endpoints and have similar performance to commercial models. Great care is needed in the interpretation of results. The JRC advised that similar predictions from different models enhanced the weight that could be attached to predictions.

12. Members are asked for their comments on the proposed approach.



## **ITEM 8: QSARS. INITIAL ASSESSMENT OF POTENTIAL MUTAGENCY OF DRINKING WATER CHEMICALS (MUT/2011/04)**

7. The Health Protection Agency (HPA) is responsible for advising the Drinking Water Inspectorate (DWI) on the health risks of chemicals. In this regard the HPA advises the DWI on the approval of products used for Public water supply. The DWI is the regulatory body responsible for such products.

8. As part of the approval process, products are tested for the potential migration of chemicals into drinking water (e.g. for degradation products, reaction products, contaminants etc). In associated risk assessments, a number of chemicals have been detected migrating at low concentrations with no genotoxicity data. The HPA has considered whether publicly available Quantitative Structure Activity Relationships (QSARs) could be used in an initial assessment of potential mutagenicity.

9. The COM had not previously provided advice on the potential practical use of QSARs to Government Department/Agencies. For illustrative purposes, the HPA provided some example drinking water product chemicals, where the initial use of QSARs has been investigated. The use of QSARs had not yet been adopted by the HPA, but they may be useful where there is no or very little available genotoxicity data.

10. According to the COM Guidance, if there is no available genotoxicity data, then at least publicly available QSAR modelling should be used to aid an initial assessment of potential mutagenicity.

11. The use of CAESAR and Toxtree models for predicting potential mutagenicity were suggested as two such models. The combined use of CAESAR and Toxtree was considered to provide a false negative rate of 11% . This combination may be the preferred option since it combines two freely available tools of which one (CAESAR) is statistically based and the other is knowledge based. This was the conclusion reached in an independent review of models undertaken by the EU Joint Research Centre (JRC) of the Institute for Health and Consumer Protection (IHCP) for the European Food Safety Authority (EFSA).

12. Members were requested to provide comments on the examples provided, which may be of help in adopting a generic approach to the assessment of such chemicals.

13. The committee considered that they needed to have more information on the basis of the two QSAR models suggested before being able to provide answers to questions outlined in the paper. However, members agreed that for chemicals where there was a positive *in vitro* comet result and negative predictions from QSAR models along with a negative Ames test result, that the chemical should be regarded as potentially mutagenic in the absence of additional data (i.e. *in vitro* genotoxicity test data overrules QSAR)

14. The secretariat suggested that it could bring this item back at a later meeting with some further background of the EU JRC review. One member

agreed to forward further detailed comments on some of the QSAR estimations provided in the draft discussion paper.