Ethyl cyclopentenolone

Ethyl Cyclopentenolone (ECP) is one of these chemicals where no or little data is available regarding their endocrine disruptor effect and mutagenicity. A screening of Ethyl Cyclopentenolone for estrogen receptor binding activity using the algorithm described in the toolbox is explained below step by step.

**Step 1: Substance identification**

Identifiers on ECP have been obtained from the most recent reliable sources chemfinder, chemexper and chemspider which are listed in step 1. Unfortunately no IUCLID data is available for this chemical. The smiles notation for ECP was obtained from the chemspider source (see the attached sheet). These identifiers are shown in Table 1 below.

<table>
<thead>
<tr>
<th>Identifier of ECP</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINECS or ELINCS number</td>
<td>244-606-5</td>
</tr>
<tr>
<td>CAS name and CAS number</td>
<td>21835-01-8</td>
</tr>
<tr>
<td>Name(s) in the IUPAC nomenclature or other international chemical name(s)</td>
<td>2-Cyclopenten-1-one, 3-ethyl-2-hydroxy-2-Hydroxy-3-ethyl-2-cyclopenten-1-one</td>
</tr>
<tr>
<td>Other names (usual name, trade name, abbreviation)</td>
<td>3-Ethyl-2-hydroxycyclopent-2-en-1-one</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C₇H₁₀O₂</td>
</tr>
<tr>
<td>Structural formula</td>
<td><img src="image" alt="Structural formula of ECP" /></td>
</tr>
<tr>
<td>Smiles Notation</td>
<td>O=C1C(O)=C(CC)CC1</td>
</tr>
</tbody>
</table>

**Table 1: ECP identification parameters.**
Step 2: Data needed for the assessment

These are divided into the followings:

- Data on binding affinity of the chemical to receptor
- Data on Effects in Wildlife
- Data on human Health effects
- Data on the exposure of humans and wildlife to the chemical

Step 3: Collecting the available information and identifying the data gap

Conducting searches in the endocrine disruptor sources and databases listed in step 3 of the algorithm for ECP revealed no citation in this topic. In other word, no data related to ECP binding affinity, endocrine disruption effects in human health and wildlife was found.

Step 4: Using (Q)SAR models

In this step the ability of ECP to be a potential endocrine disruptor was predicted. This ability to bind to the estrogen receptor was first predicted using the SAR models (1 and 2) developed by Tong et al. Multicase expert system software was then used through the Danish (Q)SAR database. The results from all three (Q)SAR models were combined to reach a conclusion.

1- Results obtained by using Tong et al SAR models:

Figures 1 and 2 show the application of SAR principles developed by Tong et al. to predict the ability of ECP to bind to ER. Both models predict that ECP is unlikely to be ER binder; i.e. inactive.
Figure 1: Application of SAR model 1 (Tong et al.) for ECP. The red line shows the prediction path for ECP.
Figure 2: Application of SAR model 2 (Tong et al.) for ECP. The red line shows the prediction path for ECP.

2- Results obtained from Danish (Q)SAR database

The Danish (Q)SAR report for ECP is shown below (Figure 3) with some comments. This output contains predictions for physical-chemical, environmental and human health endpoints, however, as we are only interested in estrogenicity endpoints these are highlighted in blue in the report. The text that is highlighted in blue indicates the values predicted using Multicase software. The prediction output of ECP by multicase cannot be provided for commercial purposes, only the final prediction is shown. As a result, interpretation of the result is not be possible, however, it is known that the program aims to discover substructures or biophores that appear mostly in active molecules and may therefore be responsible for the observed activity. Details of the methodology of MultiCASE can be found elsewhere (Klopman, 2003).
Figure 3: Danish(Q)SAR report for ECP.

By comparing the predicted values obtained from SAR models with the Danish(Q)SAR database (Multicase), we could conclude that ECP was unlikely to be an ER binder. In the next step, an in vitro test had to be conducted to cross validate its result with the QSAR finding and reach a final conclusion.
Step 5: carrying out in vitro tests

According to ER Calux \textit{in vitro} test, this chemical does not contain estrogenic activity, with a range of concentration tested from $1.10^{-1}$ to $1.10^{-9}$ M as shown in Figure 4.

![Figure 4: Dose response curve for 3-Ethyl-2-hydroxy-2-cyclopenten-1-one. No estrogenicity is observed.](image)

Step 6: Is the information I have sufficient to identify the hazard?

Identifying the hazard of ECP being an endocrine disruptor potential was based on the ability of the chemical to bind to ER. This endpoint was first predicted using the SAR models (Tong \textit{et al.}) and Danish database. Both models estimated that ECP was unlikely to be an ER binder. Additional support for the prediction was obtained by assessing the estrogenic activity of ECP using ER Calux \textit{in vitro} assay. In agreement with the predicted data, this study showed that ECP does not contain estrogenic activity.

As a conclusion, based on the prediction and measured data, ECP is not considered to bind to ER and is not a potential endocrine disruptor.

Summary

This report presents the preliminary results from a (Q)SAR and \textit{in vitro} tests to identify the hazard of ECP being potential endocrine disruptor. This quick screening was only for estrogen receptor binding activity using free (Q)SAR software and models and ER Calux \textit{in vitro} test. Endocrine effects to human or wildlife were not considered due to the lack of these test data. It is highly recommended to use the commercial (Q)SAR software such as QSAR
with CoMFA to get better prediction. As mentioned in the algorithm that estrogen receptor (ER) binding data alone is not sufficient to characterize a compound as an ED but provides valuable information for priority setting of chemicals for more costly and time consuming in vivo assays.