

OECD PRINCIPLES FOR THE VALIDATION, FOR REGULATORY PURPOSES, OF (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIP MODELS

These principles were agreed by OECD member countries at the 37th Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in November 2004. The principles are intended to be read in conjunction with the associated explanatory notes which were also agreed at the 37th Joint Meeting.

To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

- 1) a defined endpoint¹
- 2) an unambiguous algorithm²
- 3) a defined domain of applicability³
- 4) appropriate measures of goodness-of-fit, robustness and predictivity⁴
- 5) a mechanistic interpretation, if possible⁵

Notes

1. The intent of Principle 1 (defined endpoint) is to ensure clarity in the endpoint being predicted by a given model, since a given endpoint could be determined by different experimental protocols and under different experimental conditions. It is therefore important to identify the experimental system that is being modeled by the (Q)SAR. Further guidance is being developed regarding the interpretation of “defined endpoint”. For example, a no-observed-effect level might be considered to be a defined endpoint in the sense that it is a defined information requirement of a given regulatory guideline, but cannot be regarded as a defined endpoint in the scientific sense of referring to a specific effect within a specific tissue/organ under specified conditions.
2. The intent of Principle 2 (unambiguous algorithm) is to ensure transparency in the model algorithm that generates predictions of an endpoint from information on chemical structure and/or physicochemical properties. It is recognized that, in the case of commercially-developed models, this information is not always made publicly available. However, without this information, the performance of a model cannot be independently established, which is likely to represent a barrier for regulatory acceptance. The issue of reproducibility of the predictions is covered by this Principle, and will be explained further in the guidance material.
3. The need to define an applicability domain (Principle 3) expresses the fact that (Q)SARs are reductionist models which are inevitably associated with limitations in terms of the types of chemical structures, physicochemical properties and mechanisms of action for which the models can generate reliable predictions. Further work is recommended to define what types of information are needed to define (Q)SAR applicability domains, and to develop appropriate methods for obtaining this information.

4. The revised Principle 4 (appropriate measures of goodness-of-fit, robustness and predictivity) includes the intent of the original Setubal Principles 5 and 6. The wording of the principle is intended to simplify the overall set of principles, but not to lose the distinction between the internal performance of a model (as represented by goodness-of-fit and robustness) and the predictivity of a model (as determined by external validation). It is recommended that detailed guidance be developed on the approaches that could be used to provide appropriate measures of internal performance and predictivity. Further work is recommended to determine what constitutes external validation of (Q)SAR models.
5. It is recognised that it is not always possible, from a scientific viewpoint, to provide a mechanistic interpretation of a given (Q)SAR (Principle 5), or that there even be multiple mechanistic interpretations of a given model. The absence of a mechanistic interpretation for a model does not mean that a model is not potentially useful in the regulatory context. The intent of Principle 5 is not to reject models that have no apparent mechanistic basis, but to ensure that some consideration is given to the possibility of a mechanistic association between the descriptors used in a model and the endpoint being predicted, and to ensure that this association is documented.