Figure 5.5a shows the comparison results of the four prediction models for Mixture 1~~,~~ and the EC_{50} ratio mixture, ~~consisting~~which consisted of ten components (five herbicides, four fungicides, and one insecticide). The best prediction capability was found in the results of the QSAR-TSP model (R^2_{test} = 0.947, RSS = 3.70E+02) for Mixture 1~~. The~~, with the CA model ~~showed~~showing a ~~less predictive capability~~weaker result (R^2_{test} = 0.749, RSS = 1.76E+03~~) than the QSAR-TSP model.~~). Interestingly, the conventional TSP model did not estimate the mixture toxicity correctly (R^2_{test} = 0.158, RSS = 5.89E+03). This result implies that ~~incorrect~~correct MoAs of a test organism might be unavailable for the TSP model ~~because all~~, corroborated by the fact that none of the MoAs listed in Dataset 1 ~~did not originate~~originated from the test organism, *V. fischeri*. The IA model had a negative R^2_{test} value (RSS = 9.58E+03), which would be equivalent to having no explained variation at all (Mittlböck, 2002). The QSAR-TSP and CA models overestimated the toxicity of Mixture 1 in the high effect range (> 40%~~). By contrast, both the models had underestimation~~%), yet underestimated it in the low effect range (< 40%). However, in the whole effect range, the deviation between observed and predicted values from the QSAR-TSP model was relatively ~~smaller~~small as compared to the CA model~~, as well as~~. Also, the ~~modeled~~modelled values of the QSAR-TSP model ~~was~~were located within the standard deviation (SD) ~~area~~range.

Figure 5.5b illustrates the comparison results for Mixture 2, which is the EC_{10} ratio mixture of the same components as in Mixture 1. For Mixture 2, the QSAR-TSP model had the highest prediction capability (R^2_{test} = 0.923, RSS = 5.39E+02~~). The~~), but the CA model also predicted the toxicity of Mixture 2 well (R^2_{test} = 0.876, RSS = 8.68E+02). The conventional TSP model, which again was based on incorrect MoAs that did not originate from the test organism~~, *V. fischeri*~~, and the IA model did not correctly calculate the toxicity of Mixture 2. The TSP and IA models showed much lower R^2_{test}s (0.337 ~~for the TSP model,~~ and 0.034 ~~for the IA model~~, respectively) and higher RSSs (4.64E+03 ~~for the TSP model~~ and 6.76E+03 ~~for the IA model) as compared to~~, respectively) than the QSAR-TSP and CA models. The CA model underestimated the toxicity of Mixture 2 in the effect range of up to 30%, but overestimated it ~~in the effect range of~~at 30% or more. ~~In the case of~~For the QSAR-TSP model, the toxicity of Mixture 2 was underestimated in the overall effect range.

Figure 5.4c shows the comparison results for Mixture 3, a realistic pesticide mixture composed of 23 chemicals with ~~eight~~8 different MoAs ~~originated~~originating from the test organism, *S. vacuolatus*. Since the PCA- and RF-based clustering methods

註解 [Editor1]:
Golden English Editing
Life Sciences
Pharmacology & Toxicology
Sample of work

註解 [Editor2]:

CHECK: This sentence is slightly unclear—incorrect MoAs being unavailable would surely aid the accuracy for the TSP model. The edit assumes that the authors meant “correct”; please revise this sentence if not.

provided different results ~~on~~for the best number of clusters for Mixture 3~~, as shown in~~ (Table 5.4~~,~~), the QSAR-TSP model was applied to estimate the toxicity of Mixture 3 on the basis of ~~not only~~both two ~~clusters determined by the PCA-based methods, but also~~and three clusters, as derived by the PCA- and RF-based methods~~.~~, respectively. The best prediction performance was ~~placed on~~achieved by the CA model (R^2_{test} = 0.985, RSS = 2.42E+02). The QSAR-TSP model with two clusters (R^2_{test} = 0.973, RSS = 4.46E+02), QSAR-TSP with three clusters (R^2_{test} = 0.974, RSS = 4.32E+02), and conventional TSP (R^2_{test} = 0.979, RSS = 3.45E+02) models ~~excellently predicted~~gave excellent predictions on the toxicity of Mixture 3 as well. All the QSAR-TSP models with two and three clusters showed very similar prediction results for Mixture 3. The TSP model was based on ~~the~~ correct ~~MoAs originated~~MoA information originating from the target organism~~,~~ (*S. ~~Vacuolatus~~,vacuolatus*) for Dataset 2~~, yielded a~~; this was most likely responsible for the model's much better prediction result~~, as compared to its result~~ than for Dataset 1. ~~Similar to~~Along the lines of this result for Mixture 3, some previous studies had ~~presented~~argued that the TSP model, based on reliable MoAs, might ~~has~~have better predictions for estimating mixtures of pesticides, nitrobenzenes, industrial organic compounds, or wastewater treatment plant effluents (Junghans *et al.*, 2004; Altenburger *et al.*, 2005; Ra *et al.*, 2006; Wang *et al.*, 2009). For Mixture 3, the IA model ~~performed~~achieved a good prediction ~~of~~for mixture toxicity (R^2_{test} = 0.874, RSS = 2.10E+03), ~~unlike the cases of~~quite dissimilar to its poor performance for Mixtures 1 and 2. The IA and conventional TSP models showed a tendency ~~for~~of the deviations between the predicted and observed data on Mixture 3 ~~to increase~~increasing gradually ~~along~~concomitantly with the development of effective ~~concentration~~concentrations in the effect range of 30% or more. Table 5.5 summarizes the RSSs and R^2_{test}s from the QSAR-TSP, TSP, CA, and IA models for the three mixtures in the ~~validation~~validations of Datasets 1 and 2.

3.4 Evaluation of the QSAR-TSP model

This section addresses the advantages and disadvantages of the QSAR-TSP model by comparing the PLS-IAM with the other models used in this study ~~using~~from three perspectives: model performance, data availability, and application coverage ~~perspectives. Firstly~~. First, from the perspective of model performance on predicting the mixture toxicity of the three mixtures in this study, it ~~could be~~was evaluated that the QSAR-TSP model, overall, showed excellent prediction power for all ~~the~~ datasets (Table 5.5). The CA model also presented high prediction performance for Mixtures 2 and 3, but these mixture types, ~~including~~which included different MoAs, were

~~basically against~~essentially contrary to the model assumption. In the case of the conventional TSP model, it was shown that ~~the~~ incorrect information on MoAs ~~originated in a~~ , which ideally should originate from reference data of the target organism for each mixture component, did not perform well for estimating the toxicity of the mixture in this study. When it comes to the performance of the clustering algorithms in the QSAR-TSP model applied in this study, the *k*-means-based methods showed ~~relatively~~ higher average silhouettes than the PAM-based methods did. Among the methods, the *k*-means via PCA method presented not only the quickest computation, but also the largest overall average silhouette width, ~~indicating~~the size of which indicates how well the number of