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E18

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) ANALYSIS OF DISINFECTION BY-PRODUCTS IN DRINKING WATER

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INTRODUCTION

The discovery and application of public water disinfection treatment in 1908 was so significant, that it is now labelled as one of the greatest public health achievements of the 20th Century. However, it was not discovered until 1974, that the reaction between the disinfectant and precursors (organic and inorganic matter) in the water created disinfection by-products (DBPs). Subsequent studies showed that some of the DBPs showed toxic characteristics. Data analysis of the toxicity results outputted by a T.E.S.T (QSAR) model was performed to determine whether QSAR models are sufficient predictors of DBP toxicity.

DISINFECTION BY-PRODUCTS (DBPs)

Disinfection by-products occur due to a reaction between a disinfectant and precursors. Halogenated DBPs are formed by the disinfectants having the ability to oxidize a precursor into simpler moieties, which then react with additional disinfectants acting as a halogen substitution agent. The research project collected 64 DBPs from 9 DBP classes, all produced by chlorine disinfection.

QSAR

Quantitative Structure-Activity Relationship (QSAR) models have the ability to predict the toxicity of a compound by relating the molecular structure of the compound with its chemical activities. They work on the basis of two principles:

- Structurally similar compounds behave comparably under similar environmental conditions
- Behavioural differences among compounds are linked to structural and compositional variations

Predicted Mutagenicity for 75-25-2 from Consensus method

Prediction results

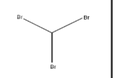
Endpoint	Experimental value (CAS=75-25-2) Source: Toxicity Benchmark	Predicted value[a]
Mutagenicity value	1.00	0.49
Mutagenicity result	Mutagenicity Positive	Mutagenicity Negative

[a]Note: the test chemical was present in the training set. The prediction does not represent an external prediction

Individual Predictions

Method	Predicted value
Hierarchical clustering	0.79
FDA	0.36
Nearest neighbor	0.33

Test chemical



Descriptor values for test chemical

Figure 1: T.E.S.T predicted mutagenicity result of chloroform

The United States Environmental Protection Agency (US EPA) created the Toxicity Estimation Software Tool (T.E.S.T), a QSAR model, to predict the toxicity of chemicals. It was developed to allow easy estimation of different toxicity endpoints, using a variety of QSAR methodologies. There are 7 toxicity endpoints which the model can output shown in Table 1.

DATA ANALYSIS

Correlation analysis and P-value analysis was performed, shown in Table 1, to understand if any trends could be established between the data from the experimental studies and T.E.S.T model outputs. The Ames mutagenicity, oral rat LD50 and bioaccumulation endpoints showed strong positive correlations. The P-values showed that only the oral rat LD50 and bioaccumulation endpoints were statistically significant. The top 10 most toxic DBPs predicted by the model are shown in Figure 4. the list was obtained by ranking the total toxicity sum for all the model endpoints for the DBPs.

Table 1: Model endpoint data analysis

Model endpoint	Correlation	P-Value
Fathead Minnow LC_{50}	0.28	0.504
Daphnia Magna LC_{50}	0.29	0.705
Tetrahymena Pyriformis IGC_{50}	0.23	0.428
Oral rat LD_{50}	0.91	0.002
Bioaccumulation	0.75	0.0015
Developmental toxicity	N/A	
Ames mutagenicity	-0.56	0.342

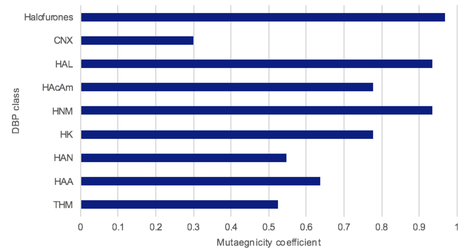


Figure 2: DBP class model mutagenicity values

DBP CLASS MUTAGENICITY RANKING

The mutagenicity value of each DBP class was obtained by taking the average of all the compounds in that class, this can be seen in Figure 2. The relative ranking was compared with experimental studies from Plewa et al. (2008). It was found to follow a similar ranking structure of the cytotoxicity studies.

DBP COMPOSITION ANALYSIS

The toxicity of the chemical composition of DBPs were examined, in order to understand whether toxicity was related to the composition of the compound. The study was split into Chloro-, Bromo- and Iodo-DBPs. Figure 3 and Plewa et al. (2008) showed that Bromo-DBPs are more toxic than Chloro-DBPs. Our study revealed that Iodo-DBPs are the least toxic unlike experimental studies which found that they are in fact the most toxic.

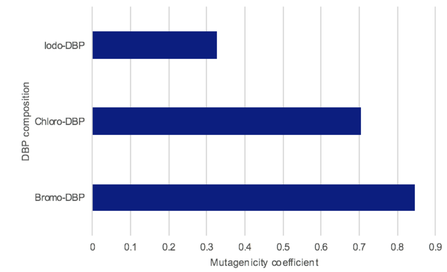
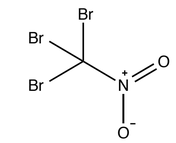
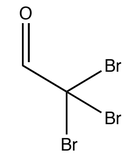


Figure 3: DBP composition model mutagenicity values

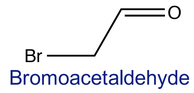
TOP 10 TOXIC DBPs



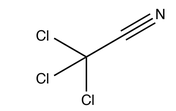
Tribromonitromethane



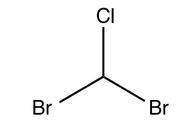
Tribromoacetaldehyde



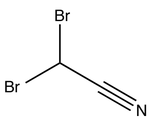
Bromoacetaldehyde



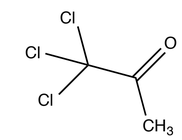
Trichloroacetonitrile



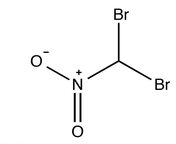
Dibromochloronitromethane



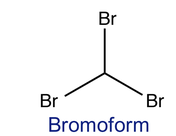
Dibromoacetonitrile



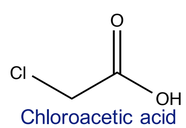
1,1,1-Trichloroacetone



Dibromonitromethane



Bromoform



Chloroacetic acid

Figure 4: DBP toxicity ranking

CONCLUSION

Data analysis studies showed that the outputs from the T.E.S.T model produced toxicity results which showed poor correlations with the experimental data. It is important to take into consideration that the poor correlation could be caused by the accuracy of the experimental data and not just due to the precision of the model output. Toxicity of DBPs in drinking water is a function of both toxicity and occurrence levels. The potentially toxic DBPs have been highlighted, however, the occurrence levels are not part of the scope of this project and is advised to be the next step in toxicity analysis to truly understand their public health importance. The rank order of DBP class is shown below.

HAN>HAL>HNM>HAA>Hk>HAcAm>THM>Halofurones>CNX

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REFERENCES

Plewa, M. J., Wagner, E. D., Muellner, M. G., Hsu, K. & Richardson, S. D. (2008) Comparative mammalian cell toxicity of N-DBPs and C-DBPs. *Urbana.* 5161801.