Comment on "QSAR modeling is not 'Push a button and find a correlation': A case study of toxicity of (benzo-)triazoles on algae"

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In their manuscript, Gramatica et al. [1] develop a "case study of toxicity of (benzo)triazoles ((B)TAZs) to the algae *Pseudokirchneriella subcapitata* ... to discuss some problems and solutions in QSAR modeling, particularly in the environmental context." The authors make the following statements regarding the structural composition of their dataset: "the aquatic toxicity on algae of a set of triazoles and benzo-triazoles ((B)TAZs) was here studied ... Given the limited number of toxicity data for (benzo-)triazoles on algae (homogeneously determined on the same species using the same protocol) we also added other azo-aromatic compounds, including diazines, triazines and similar compounds, to enlarge the response and structural domain of the studied dataset." Similarly, in their Supporting Information, Table S1 has the following caption: "Table S1: Experimental (both modeled values and CADASTER measures), predicted and hat values for the 404 studied compounds (386 Triazoles and Benzotriazoles plus 18 additional azo-aromatic compounds)."

Benzotriazoles (**1**), triazoles (**2a** and **2b**), diazines (**3a**, **3b**, and **3c**), and triazines (**4a**, **4b**, and **4c**) have the general structures as presented in Figure 1. By this definition (and allowing for other so-called "azo-aromatic" compounds; e.g., pyridine, etc.), the following compounds studied by Gramatica et al. [1] do not appear to be benzotriazoles, triazoles, diazines, triazines, and/or other "azo-aromatic compounds" (list presented as compound number [CAS registry number] as taken from the Supporting Information in ref. [1]; CAS registry numbers from ref. [1] were converted to SMILES and two-dimensional structures using SPARC [http://archemcalc.com/sparc; October 2011 release w4.6.1691-s4.6.1687] and checked for additional structural consistency using the SPARC generated SMILES data [both original and unique SMILES strings where they differ] in the PubChem Sketcher [V2.4; http://pubchem.ncbi.nlm.nih.gov/edit2/index.html]): **12** [000932649]; **14** [000939071]; **16** [000944912]; **17** [000947853]; **25** [001468264]; **26** [001600619]; **28** [001704661]; **30** [002440224]; **32** [002683901]; **33** [003142425]; **34** [003147759]; **35** [003147760]; **36** [003232846]; **38** [003333628]; **50** [003846717]; **51** [003864991]; **52** [003896115]; **59** [005302272]; **62** [005516201]; **69** [006994510]; **72** [007532527]; **75** [010187845]; **77** [010187890]; **90** [019794935]; **94** [023711344]; **97** [025973551]; **110** [031701425]; **116** [036411526]; **117** [036437373]; **120** [038942517]; **165** [056881368]; **177** [063216864]; **178** [063251401]; **190** [068049832]; **193** [070321867]; **222** [080301640]; **227** [081518265]; **228** [081518276]; **229** [081518287]; **233** [081518378]; **234** [081518414]; **236** [083044897]; **237** [083044900]; **239** [083366669]; **314** [122836355]; **321** [128639021]; **323** [129909906]; **326** [139158240]; **327** [139158251]; **328** [139158262]; **359** [178928706]; and **396** [066753079].

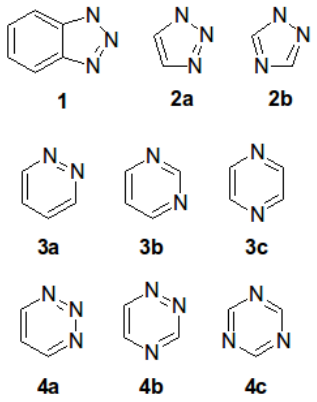

Figure 1: General structures of benzotriazoles (**1**), triazoles (**2a** and **2b**), diazines (**3a**, **3b**, and **3c**), and triazines (**4a**, **4b**, and **4c**).

Furthermore, in their Supporting Information, Gramatica et al. [1] show azafenidin (Figure S4-b), nefazodone (Figure S4-c), and bencarbazone (Figure S4-c) as having aromatic triazole rings. Because of the carbonyl moiety in the ring, these are not aromatic functional groups. Erroneously assigned aromatic groups may affect structural descriptors employed for QSAR development. The authors of ref. [1] should also publish all SMILES data for their database, and confirm their structural classification systems and the bases on which such classifications were made, so that readers may replicate the results of this

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work. This valuable information will also allow readers to confirm that various CAS databases (e.g., SPARC) contain accurate information.

References

[1] P. Gramatica, S. Cassani, P. Roy, S. Kovarich, C. Yap, E. Papa, QSAR modeling is not 'Push a button and find a correlation': A case study of toxicity of (benzo-)triazoles on algae, Molecular Informatics 31 (2012) 817–835.