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# Comment on “Towards rational molecular design for reduced chronic aquatic toxicity [Voutchkova et al., *Green Chem.*, 2012, 14, 1001]”

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5 In their article, Voutchkova et al.<sup>1</sup> develop “property-based guidelines for the design of chemicals with reduced chronic aquatic toxicity to multiple standardized species and endpoints by exploring properties associated with bioavailability, narcotic toxicity and reactive modes of action, such as electrophilic interactions.” The authors claim to use a dataset of “865 neutral organic compounds,” and then proceed to calculate “38 physicochemical properties” such as “molecular weight, number of freely rotatable bonds, partition coefficients for octanol-water (log  $P_{o-w}$ ), water-gas (log  $P_{w-g}$ ), and octanol-gas (log  $P_{o-g}$ ),  
15 aqueous solubility, solvent accessible surface area (SASA), polar surface area (PSA), globularity, molecular volume, number of H-bonds, and others” using QikProp. Furthermore, Voutchkova et al.<sup>1</sup> also state that “HOMO and LUMO energies were computed using two semiempirical molecular orbital (SMO) methods, AM1  
20 and PM3, and a density functional method (B3LYP) using the 6-311+G(d,p) basis set.”

Voutchkova et al.<sup>1</sup> do not list all 865 purportedly “neutral organic compounds” that they conducted their molecular modeling  
25 exercises on. However, one reasonably assumes it is the same 865 purportedly “neutral organic compounds” from their prior study.<sup>2</sup> The supporting information from ref. <sup>2</sup> appears to provide a small subset of CAS # molecular identifiers for some of the compounds considered. A large number of the compounds examined by these  
30 authors are not “neutral organic compounds” as the authors claim, but rather have basic and/or acidic ionizable functionalities (such as aliphatic and aromatic amines, phenols, etc.) with  $pK_a$  values such that these molecules would be substantially or, in many cases, effectively entirely ionized in aqueous solutions at the pH  
35 values relevant to the aquatic toxicity endpoints being modeled against. For example, in the supporting information of Voutchkova et al.,<sup>2</sup> the small subset of CAS # identifiers they list yields the following compounds with toxicologically and environmentally relevant experimental or estimated  $pK_a$  values:  
40 hexamethylenetetramine (CAS 100970), 6.2;<sup>3</sup> 5,5-dimethyl-2,4-imidazolidinedione (CAS 77714), 8.88;<sup>4</sup> 2,2',2''-nitrotrisetanol (CAS 102716), 7.76-7.92;<sup>5</sup> 1-piperazineethanol (CAS 103764), 9.57;<sup>4</sup> 2,2'-iminobisethanol (CAS 111422), 9.37;<sup>4</sup> 1,4-bis(3-aminopropyl)piperazine (CAS 7209383), 10.17;<sup>4</sup> 4-morpholine  
45 ethanol (CAS 622402), 6.91;<sup>4</sup> 1-amino-2-propanol (CAS 78966), 9.81;<sup>4</sup> 1-methylpiperazine (CAS 109013), 9.14;<sup>6</sup> 2-methylpiperazine (CAS 109079), 9.57;<sup>6</sup> N-(2-aminoethyl)piperazine (CAS 140318), 9.89;<sup>4</sup> 2-aminoethanol (CAS 141435), 9.62;<sup>7</sup> 2-(diethylamino)ethanol (CAS 100378),  
50 9.87;<sup>8</sup> triethylenediamine (CAS 280579), 8.92;<sup>9</sup> 2-

(ethylamino)ethanol (CAS 110736), 10.24;<sup>4</sup> 1,3-propanediamine (CAS 109762), 10.6;<sup>10</sup> 5-chlor-2-pyridinol (CAS 4214793), 9.51;<sup>4</sup> N-(3-hydroxyphenyl)acetamide (CAS 621421), 9.36;<sup>4</sup> 1,2-propanediamine (CAS 78900), 9.82;<sup>11</sup> 5,6-dimethyl-1,2,4-triazin-  
55 3-amine (CAS 17584122), 4.90;<sup>4</sup> 2-methylpyridine (CAS 109068), 6.00;<sup>11</sup> N-ethylethanamine (CAS 109897), 10.85;<sup>4</sup> N-(4-hydroxyphenyl)acetamide (CAS 103902), 9.48;<sup>4</sup> 2,2'-(phenylimino)bisethanol (CAS 120070), 4.36;<sup>4</sup> N,N-bis(2,2-diethoxyethyl)methylamine (CAS 6948863), 6.09;<sup>4</sup> 2-chlor-3-  
60 pyridinol (CAS 6636788), 6.97;<sup>4</sup> 1,1-dimethylhydrazine (CAS 57147), 7.21;<sup>12</sup> 2-hydroxybenzaldehyde (CAS 90028), 8.28;<sup>13</sup> 1-octanamine (CAS 111864), 10.65;<sup>11</sup> 1-nonanamine (CAS 112209), 10.64;<sup>11</sup> 2-octanamine (CAS 693163), 10.37;<sup>4</sup> and 4-hydroxy-3,5-diiodobenzonitrile (CAS 1689834), 3.9.<sup>14</sup>

In addition, the supporting information from ref. <sup>1</sup> contains a small subset of CAS # molecular identifiers for some of the 865 compounds considered (presumably part of the same total set also employed in ref. <sup>2</sup>). The following compounds in the supporting  
70 information of Voutchkova et al.<sup>1</sup> also have toxicologically and environmentally relevant experimental or estimated  $pK_a$  values: N,N-diethylbenzenamine (CAS 91667), 5.69;<sup>4</sup> 1,2-benzenediamine (CAS 95545), 4.55;<sup>15</sup> 2-methylbenzenamine (CAS 95534), 4.55;<sup>4</sup> 3,4-dimethylbenzenamine (CAS 95647),  
75 5.31;<sup>4</sup> aniline (CAS 62533), 4.87;<sup>11</sup> 2,3-dimethylbenzenamine (CAS 87592), 4.76;<sup>4</sup> quinoline (CAS 91225), 4.90;<sup>11</sup> 2-nitrophenol (CAS 88755), 7.23;<sup>11</sup> 2-chlorophenol (CAS 95578), 8.56;<sup>11</sup> and chloroacetic acid (CAS 79118), 2.87.<sup>11</sup>

80 Because a substantial proportion of the compounds that Voutchkova et al.<sup>1,2</sup> do provide molecular identifiers for in their supporting information are not “neutral organic compounds” as the authors claim, one must reasonably conclude that the true set of ionizable compounds among the total dataset of 865 molecules  
85 is likely larger than presented herein. Properties such as the molecular weight, partitioning coefficients between various matrices (where at least one of the matrices is water), aqueous solubility, solvent accessible surface area, polar surface area, molecular volume, number of H-bonds, HOMO/LUMO energies,  
90 etc., are all pH dependent (i.e., speciation dependent) for ionizable compounds. Since Voutchkova et al.<sup>1</sup> appear to have conducted all their molecular modeling efforts on the neutral forms of all compounds, the authors appear to have obtained molecular descriptors for speciations of the compounds that are  
95 not relevant for the toxicological properties being modeled against.

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## Notes and references

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