

Consolidated octanol/water partition coefficients: Combining multiple estimates from different methods to reduce uncertainties in log K_{OW}



Monika Nendza¹, Verena Kosfeld², Christian Schlechtriem²
¹Analytisches Laboratorium, Luhnstedt, Germany, ²Fraunhofer IME, Schmallenberg, Germany



The octanol/water partition coefficient (K_{OW}) is a key parameter for assessing the environmental fate and effects of chemicals. It is a metric of their hydrophobicity, related to uptake and accumulation in organisms and specific tissues, and distribution in water, soil and sediments. The log K_{OW} can be determined experimentally, but more often it is calculated. Different methods can sometimes perform better and sometimes worse for different target chemicals, and no method is consistently superior. The variability may be caused by differences in the applicability domain related to, for example, training set coverage and descriptor relevance. Furthermore, ionisation, tautomerism, etc. can also have an effect. This study aims to contribute to the consolidation of log K_{OW} values needed for the assessment and regulation of chemical substances, e.g. their bioaccumulation potential.

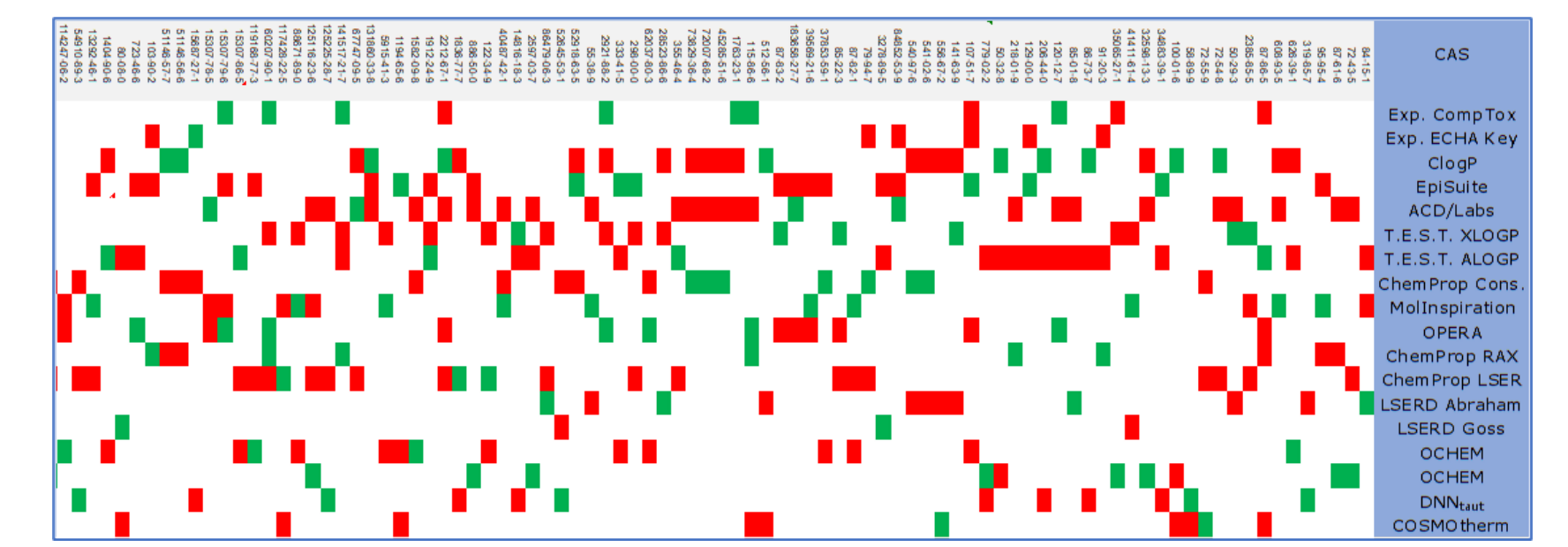
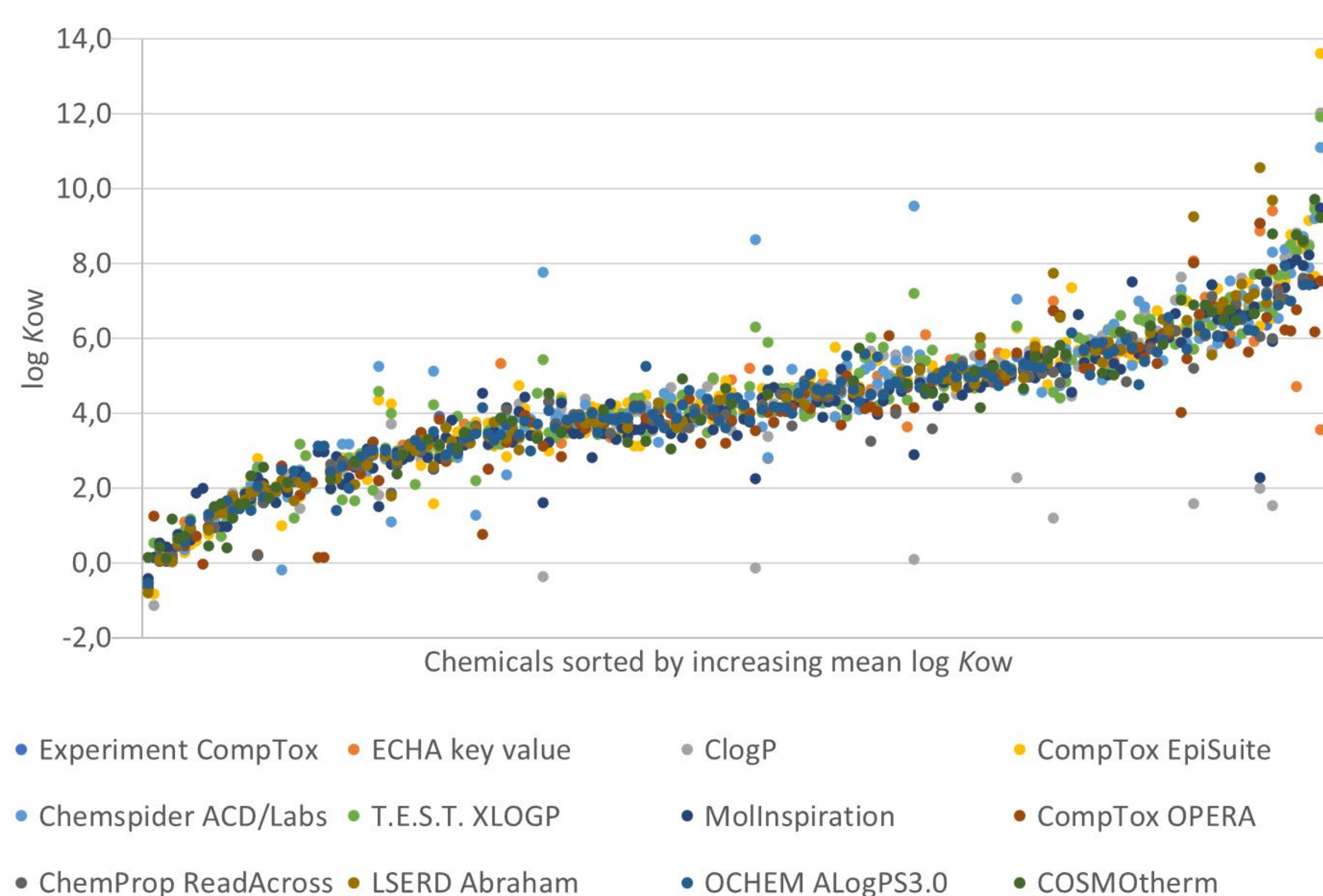


Illustration of the variability of log K_{OW} estimates: Red dots indicate the methods that lead to the lowest and highest results per chemical. The green dots each mark the method whose result is closest to the mean value of all methods used: no method is consistently superior and any method can be the worst.

Determination of log K_{OW}

- **Experimental methods:** shake-flask, slow-stirring, chromatography, ...
- **Computational methods:** fragment (group contribution), read-across, LSER, deep learning, quantum-chemistry, ...
- **Variability:** training set coverage, descriptor relevance, (in)correct structure (ionisation, tautomerism, ...), ...
- **Limitations:** determination <0 and >6 subject to large uncertainties, strongly dependent on ionised fraction at ambient pH values, not adopted for inorganic pollutants, ...

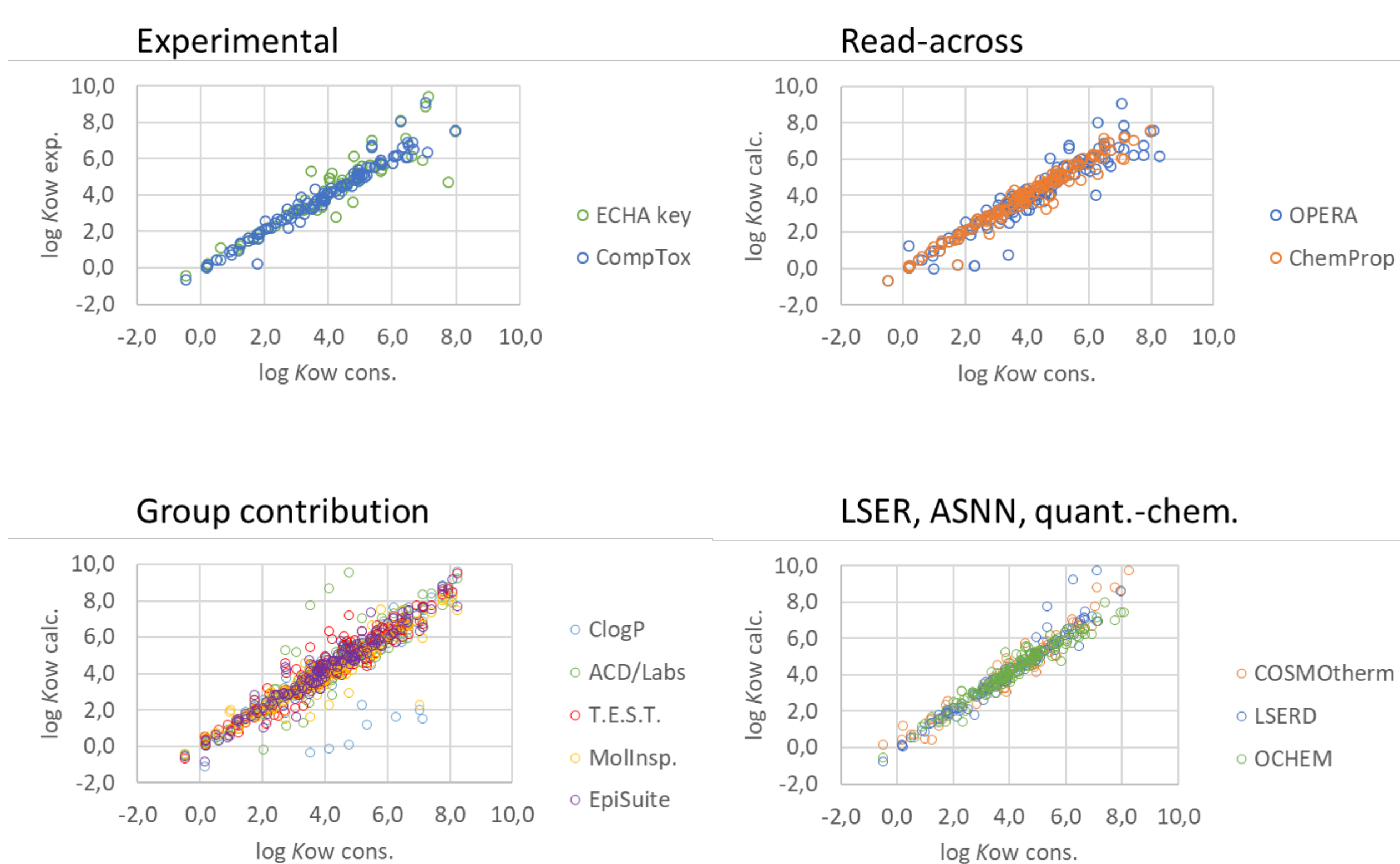
Variability of log K_{OW}



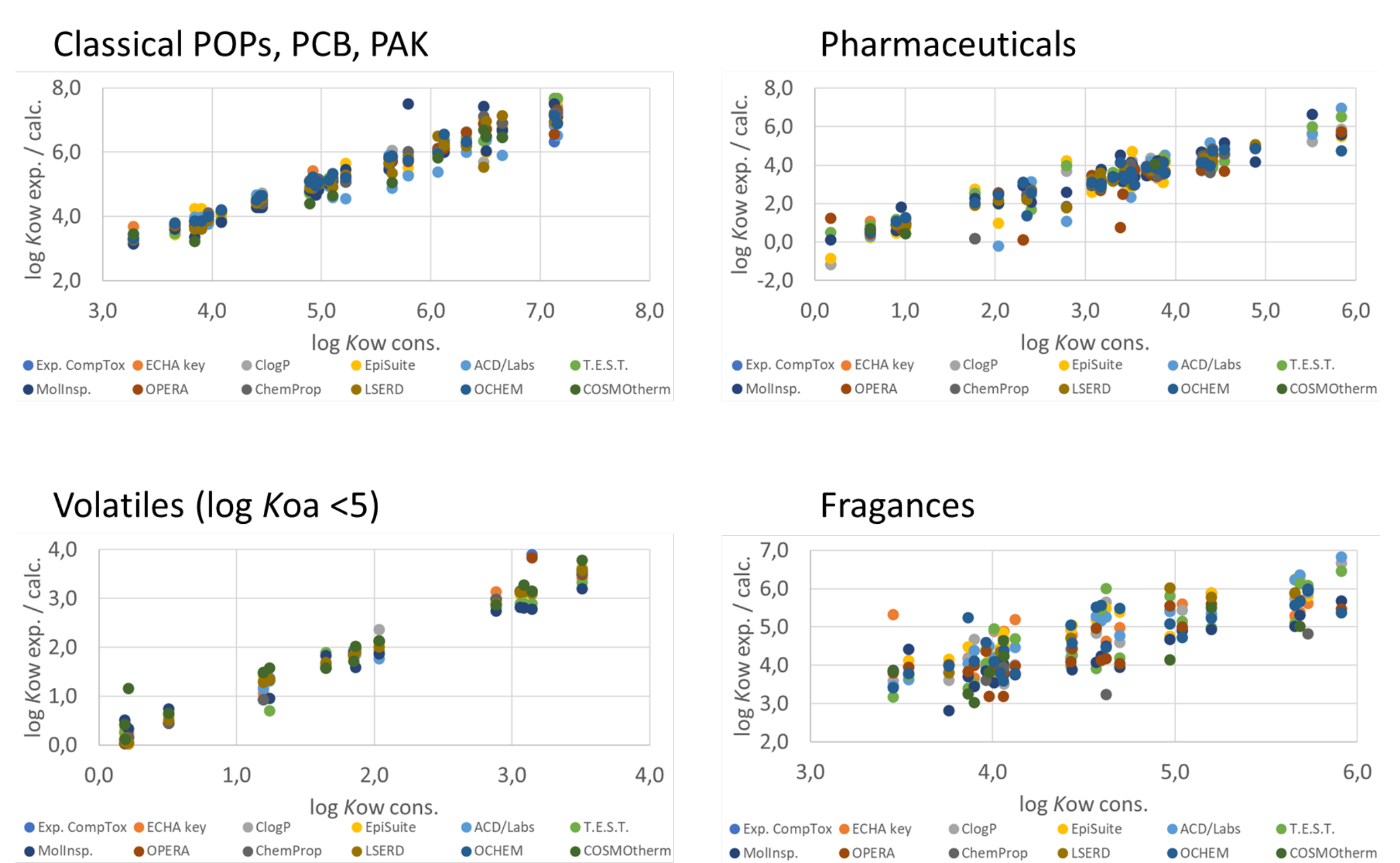
Comparison of log K_{OW}

- **Data set:** 260+ chemical substances (classical POPs, PCB, PAK, flame retardants, PFAS, siloxanes, pesticides, pharmaceuticals, fragrances, biocides, ...) with information on bioaccumulation potential from alternative, in vitro methods (e.g. Hybit, IVIVE).
- **Methods:** experimental: (CompTox, ECHA), calculated: group contribution (ClogP, EpiSuite, ACD/Labs, T.E.S.T., MolInspiration), read-across (Opera, ChemProp), LSERD, OCHEM, COSMOtherm.

by method:



by chemical class:



Results

- Experimental and calculated log K_{OW} can be highly variable ($> \pm 1$ log unit over the whole log K_{OW} range from <0 to >8).
- Variabilities > 1 log unit are the rule rather than the exception.
- No method (experimental or computational) is consistently superior.
- Lack of (experimental) reference values for e.g. PFAS, siloxanes, surfactants, etc. compromises calibration of modelling results.
- No substantial differences of results between commercial and freely available / public domain tools.

Conclusions

Consolidated log K_{OW} : The search for the one and only best method for estimating log K_{OW} may be futile. Instead, multiple estimates can be combined in the sense of a WoE or averaging approach, which, while not solving any of the problems about "correctly" determining log K_{OW} , allows one to become independent of the limitations of any particular model by consolidating all available data and deriving a consensus for log K_{OW} .

Recommended procedure:

1. verify chemical identity (2D and 3D structure, not only CAS),
2. calculate multiple log K_{OW} (**unionised** chemical) with different independent methods,
3. analyse results for outliers, eliminate obvious misestimates,
4. apply WoE or averaging approach,
5. use pKa for log D adjustment.

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References: ECHA <https://echa.europa.eu/information-on-chemicals/registered-substances>, CompTox Chemicals Dashboard <https://comptox.epa.gov/dashboard/>, ChemSpider <https://www.chemspider.com/>, T.E.S.T. <https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test>, ChemProp <https://www.ufz.de/ecochem/chemprop>, LSERD <http://www.ufz.de/lserd>, OCHEM <https://ochem.eu/>, MolInspiration <https://www.molinspiration.com/services/loggp.html>