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Chemical similarity: structuring risk and hazard assessment

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References

- [1] Military quotes, USMC General Lewis B. Chesty Puller Quotes, (n.d.). <https://www.military-quotes.com/chesty-puller.htm> (accessed July 6, 2021).
- [2] F. Aftalion, A history of the international chemical industry, Chemical Heritage Foundation, 2001.
- [3] Z. Wang, G.W. Walker, D.C.G. Muir, K. Nagatani-Yoshida, Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories, *Environmental Science and Technology*. 54 (2020) 2575–2584. <https://doi.org/10.1021/acs.est.9b06379>.
- [4] M. Bastian, S. Heymann, M. Jacomy, Gephi: An Open Source Software for Exploring and Manipulating Networks, Third International AAAI Conference on Weblogs and Social Media. (2009).
- [5] M. Jacomy, T. Venturini, S. Heymann, M. Bastian, ForceAtlas2, a continuous graph layout algorithm for handy network visualization designed for the Gephi software, *PLoS ONE*. 9 (2014). <https://doi.org/10.1371/journal.pone.0098679>.
- [6] C.W. Yap, PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints, *Journal of Computational Chemistry*. (2011). <https://doi.org/10.1002/jcc.21707>.
- [7] R. Todeschini, V. Consonni, H. Xiang, J. Holliday, M. Buscema, P. Willett, Similarity coefficients for binary chemoinformatics data: Overview and extended comparison using simulated and real data sets, *Journal of Chemical Information and Modeling*. 52 (2012) 2884–2901. <https://doi.org/10.1021/ci300261r>.
- [8] ECHA - European Chemicals Agency, Guidance for identification and naming of substances under REACH and CLP, 2017. <https://doi.org/10.2823/538683>.
- [9] Y. Djoumbou Feunang, R. Eisner, C. Knox, L. Chepelev, J. Hastings, G. Owen, E. Fahy, C. Steinbeck, S. Subramanian, E. Bolton, R. Greiner, D.S. Wishart, ClassyFire: automated chemical classification with a comprehensive, computable taxonomy, *Journal of Cheminformatics*. 8 (2016) 1–20. <https://doi.org/10.1186/s13321-016-0174-y>.
- [10] J. Ravichandran, B.S. Karthikeyan, P. Singla, S.R. Aparna, A. Samal, NeurotoxKb 1.0: Compilation, curation and exploration of a knowledgebase of environmental neurotoxicants specific to mammals, *Chemosphere*. 278 (2021). <https://doi.org/10.1016/j.chemosphere.2021.130387>.
- [11] F.I. Saldivar-González, C.S. Huerta-García, J.L. Medina-Franco, Chemoinformatics-based enumeration of chemical libraries: a tutorial, *Journal of Cheminformatics*. 12 (2020). <https://doi.org/10.1186/s13321-020-00466-z>.
- [12] European Parliament, Council of the European Union, REACH Regulation (EC/1907/2006), 2006.
- [13] European Commission, Chemicals Strategy for Sustainability - Towards a Toxic-Free Environment, 2020.
- [14] J. van Dijk, A. Leopold, H. Flerlage, A. van Wezel, T.B. Seiler, M.H. Enrici, M.C. Bloor, The EU Green Deal's ambition for a toxic-free environment: Filling the gap for science-based policymaking, *Integrated Environmental Assessment and Management*. 17 (2021) 1105–1113. <https://doi.org/10.1002/ieam.4429>.
- [15] European Parliament, Council of the European Union, CLP Regulation (EC/1272/2008), 2008.
- [16] C.J. van Leeuwen, T.G. Vermeire, Risk Assessment of Chemicals - An Introduction, Springer Science & Business Media, 2007.
- [17] C.A.M. van Gestel, F.G.A.J. van Belleghem, N.W. van den Brink, S.T.J. Droge, T. Hamers, J.L.M. Hermens, M.H.S. Kraak, A.J. Löhr, J.R. Parsons, A.M.J. Ragas, N.M. van Straalen, M.G.

- Suite for Microsoft Window, v4.1, (2012).
- [38] E. Rorije, E.M.J. Verbruggen, A. Hollander, T.P. Traas, M.P.M. Janssen, Identifying potential POP and PBT substances : Development of a new Persistence/Bioaccumulation-score (RIVM Report 601356001), (2011) 1–88.
- [39] R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, A. Worth, The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree, 2008.
- [40] P. Banerjee, A.O. Eckert, A.K. Schrey, R. Preissner, ProTox-II: A webserver for the prediction of toxicity of chemicals, Nucleic Acids Research. (2018). <https://doi.org/10.1093/nar/gky318>.
- [41] H. Yang, C. Lou, L. Sun, J. Li, Y. Cai, Z. Wang, W. Li, G. Liu, Y. Tang, AdmetSAR 2.0: Web-service for prediction and optimization of chemical ADMET properties, Bioinformatics. (2019). <https://doi.org/10.1093/bioinformatics/bty707>.
- [42] BIOVIA, TOPKAT (Toxicity Prediction by Komputer Assisted Technology), (n.d.). <https://www.3dsbiovia.com/products/datasheets/qsar-admet-and-predictive-toxicology-with-ds.pdf>.
- [43] MultiCase Inc, MultiCase, (n.d.). <http://www.multicase.com/>.
- [44] Leadslope, Leadslope, (n.d.). <http://www.leadslope.com/>.
- [45] DTU, Danish (Q)SAR Database, (2015). <http://qsar.food.dtu.dk/>.
- [46] ChemSec, Methodology for grouping the SIN List and development of the SINimilarity tool, (2015). <https://chemsec.org/publication/sin-list/methodology-for-grouping-the-sin-list-and-development-of-the-sinimilarity-tool/>.
- [47] ECHA - European Chemicals Agency, Screening Definition Document - Methodology for identifying (groups of) potential substances of concern for (further) regulatory action, 2019. https://echa.europa.eu/documents/10162/19126370/screening_definition_document_en.pdf/e588a9f8-c55e-4412-a760-49ddb7ac687.
- [48] R. Todeschini, V. Consonni, Molecular descriptors for chemoinformatics: volume I: alphabetical listing/volume II: appendices, references., John Wiley and Sons, 2009.
- [49] P. Willett, J.M. Barnard, G.M. Downs, Chemical similarity searching, Journal of Chemical Information and Computer Sciences. (1998). <https://doi.org/10.1021/ci9800211>.
- [50] C.L. Mellor, R.L. Marchese Robinson, R. Benigni, D. Ebbrell, S.J. Enoch, J.W. Firman, J.C. Madden, G. Pawar, C. Yang, M.T.D. Cronin, Molecular fingerprint-derived similarity measures for toxicological read-across: Recommendations for optimal use, Regulatory Toxicology and Pharmacology. (2019). <https://doi.org/10.1016/j.yrtph.2018.11.002>.
- [51] RIVM - National Institute for Public Health and the Environment, List of Dutch Substances of Very High Concern [in Dutch], (2018). <https://rvszoeksysteem.rivm.nl/ZZSlijst/Index> (accessed March 1, 2018).
- [52] ECHA - European Chemicals Agency, Biocidal Active Substances., (2018). <http://echa.europa.eu/web/guest/information-on-chemicals/biocidal-active-substances> (accessed May 23, 2018).
- [53] European Commission, EU Pesticides Database, (2018). <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN> (accessed May 23, 2018).
- [54] Daylight, SMILES - A Simplified Chemical Language, (2008). <http://www.daylight.com/dayhtml/doc/theory/theory.smiles.html> (accessed February 15, 2019).
- [55] G. Landrum, RDKit: Open-source Cheminformatics and machine-learning, <http://www.rdkit.org/>. (2019).
- [56] M. Floris, A. Manganaro, O. Nicolotti, R. Medda, G.F. Mangiatordi, E. Benfenati, A generalizable definition of chemical similarity for read-across, Journal of Cheminformatics. (2014). <https://doi.org/10.1186/s13321-014-0039-1>.
- [57] S. Wu, J. Fisher, J. Naciff, M. Laufersweiler, C. Lester, G. Daston, K. Blackburn, Framework

- for identifying chemicals with structural features associated with the potential to act as developmental or reproductive toxicants, Chemical Research in Toxicology. (2013). <https://doi.org/10.1021/tx400226u>.
- [58] R Core Team, R: A Language and Environment for Statistical Computing, (2019).
 - [59] M. Kuhn, R package, caret: Classification and Regression Training. Version 6.0-81, CRAN. (2018).
 - [60] Y. Cao, A. Charisi, L.C. Cheng, T. Jiang, T. Girke, ChemmineR: A compound mining framework for R, Bioinformatics. (2008). <https://doi.org/10.1093/bioinformatics/btn307>.
 - [61] J. Tuszyński, caTools: Tools: moving window statistics, GIF, Base64, ROC AUC, etc. R package version 1.17.1.1, CRAN. (2018).
 - [62] T. Sing, O. Sander, N. Beerenwinkel, T. Lengauer, ROCR: Visualizing classifier performance in R, Bioinformatics. (2005). <https://doi.org/10.1093/bioinformatics/bti623>.
 - [63] R. Guha, Chemical Informatics Functionality in R, Journal of Statistical Software. (2007). <https://doi.org/10.18637/jss.v018.i05>.
 - [64] MACCS, Molecular ACCess System (MACCS) keys. MDL Information Systems - As interpreted by CDK, (n.d.).
 - [65] Daylight, Fingerprints - Screening and Similarity, (2008). <http://www.daylight.com/dayhtml/doc/theory/theory.finger.html> (accessed February 15, 2019).
 - [66] Å. Bergman, J. Heindel, S. Jobling, K. Kidd, R. Zoeller, Endocrine Disrupting Chemicals - 2012, 2013.
 - [67] D. Rogers, M. Hahn, Extended-connectivity fingerprints, Journal of Chemical Information and Modeling. (2010). <https://doi.org/10.1021/ci100050t>.
 - [68] ECHA - European Chemicals Agency, EFSA - European Food Safety Authority, JRC - Joint Research Centre, Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, EFSA Journal. (2018). <https://doi.org/10.2903/j.efsa.2018.5311>.
 - [69] International Agency for Research on Cancer, Glyphosate Monograph, 2015.
 - [70] J. V. Tarazona, D. Court-Marques, M. Tiramani, H. Reich, R. Pfeil, F. Istace, F. Crivellente, Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC, Archives of Toxicology. (2017). <https://doi.org/10.1007/s00204-017-1962-5>.
 - [71] ECHA - European Chemicals Agency, Search for Chemicals, (2019). <https://echa.europa.eu/en/information-on-chemicals> (accessed September 20, 2019).
 - [72] M. Woutersen, M. Beekman, M.E.J. Pronk, A. Muller, J.A. de Knecht, B.C. Hakkert, Does REACH provide sufficient information to regulate mutagenic and carcinogenic substances?, Human and Ecological Risk Assessment. (2018). <https://doi.org/10.1080/10807039.2018.1480351>.
 - [73] P.N.H. Wassenaar, E. Rorije, N.M.H. Janssen, W.J.G.M. Peijnenburg, M.G. Vijver, Chemical similarity to identify potential Substances of Very High Concern – An effective screening method, Computational Toxicology. 12 (2019). <https://doi.org/10.1016/j.comtox.2019.100110>.
 - [74] B. Settles, Active Learning Literature Survey - Computer Sciences Technical Report 1648. University of Wisconsin–Madison, 2010.
 - [75] X. Yang, Y. Wang, R. Byrne, G. Schneider, S. Yang, Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery, Chemical Reviews. (2019). <https://doi.org/10.1021/acs.chemrev.8b00728>.
 - [76] ECHA - European Chemicals Agency, Registered substances, (2019). <https://echa.europa.eu/en/information-on-chemicals/registered-substances> (accessed May 17, 2019).
 - [77] D. Gadaleta, A. Lombardo, C. Toma, E. Benfenati, A new semi-automated workflow for chemical data retrieval and quality checking for modeling applications, Journal of

- DSSTox QSAR Ready File. , (2018). <https://doi.org/10.23645/epacomptox.6253679.v1>.
- [111] K. Mansouri, Standardization workflow for QSAR-ready chemical structures pretreatment., (2020). <https://github.com/kmansouri/QSAR-ready> (accessed March 10, 2021).
- [112] R Core Team, R: A Language and Environment for Statistical Computing. (2021).
- [113] M. Kuhn, R package, caret: Classification and Regression Training. Version 6.0-90, CRAN. (2021). <https://CRAN.R-project.org/package=caret> (accessed December 6, 2021).
- [114] J. Tuszynski, caTools: Tools: Moving Window Statistics, GIF, Base64, ROC AUC, etc. R package version 1.18.2, CRAN. (2021). <https://CRAN.R-project.org/package=caTools> (accessed December 6, 2021).
- [115] G. Landrum, RDKit: Open-source Cheminformatics and machine-learning. <http://www.rdkit.org/>. (2021).
- [116] ECHA - European Chemicals Agency, Guidance on information requirements and chemical safety assessment (Chapter R.7c: Endpoint specific guidance), 2017. <https://doi.org/10.2823/43472>.
- [117] JRC - Joint Research Centre, Review of available criteria for non-aquatic organisms within PBT/vPvB frameworks - Part I: Bioaccumulation assessment, 2014. <https://doi.org/10.2788/11347>.
- [118] OECD - Organisation for Economic Co-operation and Development, OECD Guidelines for the Testing of Chemicals - Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD TG 305), 2012.
- [119] H.J. Geyer, G.G. Rimkus, I. Scheunert, A. Kaune, K.-W. Schramm, A. Kettrup, M. Zeeman, D.C.G. Muir, L.G. Hansen, D. Mackay, Bioaccumulation and Occurrence of Endocrine-Disrupting Chemicals (EDCs), Persistent Organic Pollutants (POPs), and Other Organic Compounds in Fish and Other Organisms Including Humans, in: Bioaccumulation – New Aspects and Developments, 1987. https://doi.org/10.1007/10503050_1.
- [120] ECHA - European Chemicals Agency, Evaluation under REACH: Progress Report 2017 - 10 years of experience, 2017. <https://doi.org/10.2823/76886>.
- [121] F. Grisoni, V. Consonni, S. Villa, M. Vighi, R. Todeschini, QSAR models for bioconcentration: Is the increase in the complexity justified by more accurate predictions?, Chemosphere. (2015). <https://doi.org/10.1016/j.chemosphere.2015.01.047>.
- [122] J. Nichols, K. Fay, M.J. Bernhard, I. Bischof, J. Davis, M. Halder, J. Hu, K. Johanning, H. Laue, D. Nabb, C. Schlechtriem, H. Segner, J. Swintek, J. Weeks, M. Embryc, Reliability of in vitro methods used to measure intrinsic clearance of hydrophobic organic chemicals by rainbow trout: Results of an international ring trial, Toxicological Sciences. (2018). <https://doi.org/10.1093/toxsci/kfy113>.
- [123] C. Schlechtriem, S. Kampe, H.J. Bruckert, I. Bischof, I. Ebersbach, V. Kosfeld, M. Kotthoff, C. Schäfers, J. L'Haridon, Bioconcentration studies with the freshwater amphipod *Hyalella azteca*: are the results predictive of bioconcentration in fish?, Environmental Science and Pollution Research. (2019). <https://doi.org/10.1007/s11356-018-3677-4>.
- [124] J. Sanz-Landaluze, M. Pena-Abaurrea, R. Muñoz-Olivas, C. Cámera, L. Ramos, Zebrafish (*danio rerio*) eleutheroembryo-based procedure for assessing bioaccumulation, Environmental Science and Technology. (2015). <https://doi.org/10.1021/es504685c>.
- [125] J.A. Arnot, F.A. Gobas, A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals in aquatic organisms, Environmental Reviews. (2006). <https://doi.org/10.1139/a06-005>.
- [126] NITE - National Institute of Technology and Evaluation, The biodegradation and bioconcentration data under CSCL have been published, (2018). https://www.nite.go.jp/en/chem/kasinn/cscl_data.html (accessed April 10, 2018).
- [127] T.F. Parkerton, J.A. Arnot, A. V. Weisbrod, C. Russom, R.A. Hoke, K. Woodburn, T. Traas, M. Bonnell, L.P. Burkhard, M.A. Lampi, Guidance for evaluating in vivo fish bioaccumulation data, Integrated Environmental Assessment and Management. (2008). <https://doi.org/10.1002/ieam.2045>.

- org/10.1897/IEAM_2007-057.1.
- [128] OECD - Organisation for Economic Co-operation and Development, QSAR Toolbox, (2019). <https://qsartoolbox.org/>.
- [129] US EPA - United States Environmental Protection Agency, ECOTOX, (2018). <https://cfpub.epa.gov/ecotox/> (accessed April 10, 2018).
- [130] R. Froese, D. Pauly, FishBase, (2019). www.fishbase.org (accessed February 12, 2019).
- [131] J. Pinheiro, D. Bates, S. DebRoy, D. Sarkar, the R.C. Team, The nlme Package: Linear and Nonlinear Mixed Effects Models, R-Project. (2018).
- [132] K.P. Burnham, D.R. Anderson, Model selection and multimodel inference: a practical information-theoretic approach, Second Edition, 2002.
- [133] R. Carlson, A. Oyler, E. Gerhart, R. Caple, K. Welch, H.B.D. and S.D. Kopperman, Implications to the aquatic environment of polynuclear aromatic hydrocarbons liberated from Northern Great Plains coal, 1979.
- [134] H. Wang, Y. Li, X. Xia, X. Xiong, Relationship between metabolic enzyme activities and bioaccumulation kinetics of PAHs in zebrafish (*Danio rerio*), Journal of Environmental Sciences (China). (2018). <https://doi.org/10.1016/j.jes.2017.03.037>.
- [135] W. Larisch, K.U. Goss, Uptake, distribution and elimination of chemicals in fish – Which physiological parameters are the most relevant for toxicokinetics?, Chemosphere. (2018). <https://doi.org/10.1016/j.chemosphere.2018.07.112>.
- [136] J.W. Nichols, J.M. McKim, M.E. Andersen, M.L. Gargas, H.J. Clewell, R.J. Erickson, A physiologically based toxicokinetic model for the uptake and disposition of waterborne organic chemicals in fish, Toxicology and Applied Pharmacology. (1990). [https://doi.org/10.1016/0041-008X\(90\)90338-U](https://doi.org/10.1016/0041-008X(90)90338-U).
- [137] D. Schlenk, M. Celander, E.P. Gallagher, S. George, M. James, S.W. Kullman, P. Van Den Hurk, K. Willett, Biotransformation in fishes, in: The Toxicology of Fishes, 2008. <https://doi.org/10.1201/9780203647295>.
- [138] M. Ferreira, J. Costa, M.A. Reis-Henriques, ABC transporters in fish species: A review, Frontiers in Physiology. (2014). <https://doi.org/10.3389/fphys.2014.00266>.
- [139] P.N. Fitzsimmons, G.J. Lien, J.W. Nichols, A compilation of in vitro rate and affinity values for xenobiotic biotransformation in fish, measured under physiological conditions, Comparative Biochemistry and Physiology - C Toxicology and Pharmacology. (2007). <https://doi.org/10.1016/j.cbpc.2006.12.011>.
- [140] J.A. Arnot, D. Mackay, T.F. Parkerton, M. Bonnell, A database of fish biotransformation rates for organic chemicals, Environmental Toxicology and Chemistry. (2008). <https://doi.org/10.1897/08-058.1>.
- [141] I. Bischof, J. Köster, H. Segner, C. Schlechtriem, Hepatocytes as in vitro test system to investigate metabolite patterns of pesticides in farmed rainbow trout and common carp: Comparison between in vivo and in vitro and across species, Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology. (2016). <https://doi.org/10.1016/j.cbpc.2016.05.003>.
- [142] G.I. Petersen, P. Kristensen, Bioaccumulation of lipophilic substances in fish early life stages, Environmental Toxicology and Chemistry. (1998). [https://doi.org/10.1897/1551-5028\(1998\)017<1385:BOLSIF>2.3.CO;2](https://doi.org/10.1897/1551-5028(1998)017<1385:BOLSIF>2.3.CO;2).
- [143] P. Kristensen, N. Nyholm, Bioaccumulation of Chemical Substances in Fish Flow-Through Method: Ring-Test Programme 1984 - 1985, 1987.
- [144] K.M. Kleinow, M.J. Melancon, J.J. Lech, Biotransformation and induction: Implications for toxicity, bioaccumulation and monitoring of environmental xenobiotics in fish, Environmental Health Perspectives. (1987).
- [145] K. Monostori, K. Jemnitz, L. Vereczkey, Xenobiotic metabolizing enzymes in fish: diversity, regulation and biomarkers for pollutant exposure, Acta Physiologica Hungarica. (1996).

- [146] D. Chabot, R. Koenker, A.P. Farrell, The measurement of specific dynamic action in fishes, *Journal of Fish Biology.* (2016). <https://doi.org/10.1111/jfb.12836>.
- [147] A. Tandler, F.W.H. Beamish, Apparent specific dynamic action (SDA), fish weight and level of caloric intake in largemouth bass, *Micropterus salmoides Lacepede, Aquaculture.* (1981). [https://doi.org/10.1016/0044-8486\(81\)90017-X](https://doi.org/10.1016/0044-8486(81)90017-X).
- [148] D. Randall, Control and co-ordination of gas exchange in water breathers, in: Springer (Ed.), *Vertebrate Gas Exchange,* Berlin, 1990.
- [149] R. Yang, C. Brauner, V. Thurston, J. Neuman, D.J. Randall, Relationship between toxicant transfer kinetic processes and fish oxygen consumption, *Aquatic Toxicology.* (2000). [https://doi.org/10.1016/S0166-445X\(99\)00050-8](https://doi.org/10.1016/S0166-445X(99)00050-8).
- [150] M. Adolfsson-Erici, G. Åkerman, M.S. McLachlan, Measuring bioconcentration factors in fish using exposure to multiple chemicals and internal benchmarking to correct for growth dilution, *Environmental Toxicology and Chemistry.* (2012). <https://doi.org/10.1002/etc.1897>.
- [151] N.B. Metcalfe, T.E. Van Leeuwen, S.S. Killen, Does individual variation in metabolic phenotype predict fish behaviour and performance?, *Journal of Fish Biology.* (2016). <https://doi.org/10.1111/jfb.12699>.
- [152] C. Toms, D. Echevarria, D. Jouandot, A Methodological Review of Personality-Related Studies in Fish: Focus on the Shy-Bold Axis Behaviour, *International Journal of Comparative Psychology.* (2010). <https://doi.org/10.1016/j.socscimed.2010.01.002>.
- [153] P.A. Biro, N.J. Dingemanse, Sampling bias resulting from animal personality, *Trends in Ecology and Evolution.* (2009). <https://doi.org/10.1016/j.tree.2008.11.001>.
- [154] L. Böhm, R.A. Düring, H.J. Bruckert, C. Schlechtriem, Can solid-phase microextraction replace solvent extraction for water analysis in fish bioconcentration studies with highly hydrophobic organic chemicals?, *Environmental Toxicology and Chemistry.* (2017). <https://doi.org/10.1002/etc.3854>.
- [155] J.L. Van Geest, D.G. Poirier, K.R. Solomon, P.K. Sibley, A comparison of the bioaccumulation potential of three freshwater organisms exposed to sediment-associated contaminants under laboratory conditions, *Environmental Toxicology and Chemistry.* (2011). <https://doi.org/10.1002/etc.456>.
- [156] W. de Wolf, M. Comber, P. Douben, S. Gimeno, M. Holt, M. Léonard, A. Lillicrap, D. Sijm, R. van Egmond, A. Weisbrod, G. Whale, Animal use replacement, reduction, and refinement: development of an integrated testing strategy for bioconcentration of chemicals in fish., *Integrated Environmental Assessment and Management.* (2007). [https://doi.org/10.1897/1551-3793\(2007\)3\[3:AURRAR\]2.0.CO;2](https://doi.org/10.1897/1551-3793(2007)3[3:AURRAR]2.0.CO;2).
- [157] European Parliament, Council of the European Union, Directive 2010/63/EU on the protection of animals used for scientific purposes, *Official Journal of the European Union.* (2010).
- [158] R.J. Quann, Modeling the chemistry of complex petroleum mixtures, in: *Environmental Health Perspectives,* 1998. <https://doi.org/10.1289/ehp.98106s61441>.
- [159] D. Salvito, M. Fernandez, K. Jenner, D.Y. Lyon, J. de Knecht, P. Mayer, M. MacLeod, K. Eisenreich, P. Leonards, R. Cesnaitis, M. León-Paumen, M. Embry, S.E. Déglon, Improving the Environmental Risk Assessment of Substances of Unknown or Variable Composition, Complex Reaction Products, or Biological Materials, *Environmental Toxicology and Chemistry.* 39 (2020) 2097–2108. <https://doi.org/10.1002/etc.4846>.
- [160] S.S. Kutsarova, D.G. Yordanova, Y.H. Karakolev, S. Stoeva, M. Comber, C.B. Hughes, E. Vaipoulou, S.D. Dimitrov, O.G. Mekyan, UVCB substances II: Development of an endpoint-nonspecific procedure for selection of computationally generated representative constituents, *Environmental Toxicology and Chemistry.* (2019). <https://doi.org/10.1002/etc.4358>.
- [161] CONCAWE, REACH - Roadmap for Petroleum Substances, 2019.
- [162] CONCAWE, Environmental risk assessment of petroleum substances: the hydrocarbon block

- method - report no. 96/52, 1996.
- [163] ECHA - European Chemicals Agency, Candidate List of substances of very high concern for Authorisation, (2020). <https://echa.europa.eu/en/candidate-list-table> (accessed June 11, 2020).
- [164] InfoCuria, Action brought on 21 March 2019 – Exxonmobil Petroleum & Chemical v ECHA (Case T-177/19), 2019.
- [165] C.B. Hughes, D.M. Brown, L. Camenzuli, A.D. Redman, J.S. Arey, D. Vione, N. Wang, E. Vaiopoulou, Can a chemical be both readily biodegradable AND very persistent (vP)? Weight-of-evidence determination demonstrates that phenanthrene is not persistent in the environment, Environmental Sciences Europe. 32 (2020). <https://doi.org/10.1186/s12302-020-00427-1>.
- [166] D.M. Pampanin, M.O. Sydnes, Chapter 5: Polycyclic aromatic hydrocarbons a constituent of Petroleum: Presence and influence in the aquatic environment, in: Hydrocarbon, 2013.
- [167] S.A. Stout, S.D. Emsbo-Mattingly, G.S. Douglas, A.D. Uhler, K.J. McCarthy, Beyond 16 Priority Pollutant PAHs: A Review of PACs used in Environmental Forensic Chemistry, Polycyclic Aromatic Compounds. (2015). <https://doi.org/10.1080/10406638.2014.891144>.
- [168] OECD - Organisation for Economic Co-operation and Development, OECD Guidelines for the Testing of Chemicals - Aerobic and Anaerobic Transformation in Soil (OECD TG 307), 2002.
- [169] OECD - Organisation for Economic Co-operation and Development, OECD Guidelines for the Testing of Chemicals - Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD TG 308), 2002.
- [170] OECD - Organisation for Economic Co-operation and Development, OECD Guidelines for the Testing of Chemicals - Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test (OECD TG 309), 2004.
- [171] ECHA - European Chemicals Agency, Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7b: Endpoint specific guidance), 2017. <https://doi.org/10.2823/84188>.
- [172] K.K. Sjøholm, H. Birch, A. Dechesne, A.P. Loibner, P. Mayer, Temperature dependency of biodegradation kinetics in environmental surface waters across Europe, in: SETAC SciCon - Poster, 2020.
- [173] CONCAWE, PETRORISK version 7.0 Public: Manual, 2016.
- [174] OECD - Organisation for Economic Co-operation and Development, BCF Estimation Tool v2, (2019).
- [175] D.T.H.M. Sijm, M.E. Verberne, W.J. De Jonge, P. Pärt, A. Opperhuizen, Allometry in the Uptake of Hydrophobic Chemicals Determined in Vivo and in Isolated Perfused Gills, Toxicol Appl Pharmacol. 131 (1995) 130–135. <https://doi.org/10.1006/taap.1995.1054>.
- [176] P.N.H. Wassenaar, E.M.J. Verbruggen, E. Cieraad, W.J.G.M. Peijnenburg, M.G. Vijver, Variability in fish bioconcentration factors: Influences of study design and consequences for regulation, Chemosphere. (2020). <https://doi.org/10.1016/j.chemosphere.2019.124731>.
- [177] E.M.J. Verbruggen, M. Beek, J. Pijnenburg, T.P. Traas, Ecotoxicological environmental risk limits for total petroleum hydrocarbons on the basis of internal lipid concentrations, Environmental Toxicology and Chemistry. 27 (2008) 2436–2448. <https://doi.org/10.1897/07-597.1>.
- [178] European Commission, Technical Guidance for Deriving Environmental Quality Standards - Guidance Document no. 27, 2018.
- [179] A.P. Roberts, M.M. Alloy, J.T. Oris, Review of the photo-induced toxicity of environmental contaminants, Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology. (2017). <https://doi.org/10.1016/j.cbpc.2016.10.005>.
- [180] B.L. Boese, J.O. Lamberson, R.C. Swartz, R.J. Ozretich, Photoinduced toxicity of fluoranthene

- Archives of Environmental Contamination and Toxicology. (1998). <https://doi.org/10.1007/s002449900311>.
- [213] ECHA - European Chemicals Agency, C&L Inventory, (2021). <https://echa.europa.eu/information-on-chemicals/cl-inventory-database> (accessed January 20, 2021).
- [214] D.L. Elmendorf, C.E. Haith, G.S. Douglas, R.C. Prince, Relative rates of biodegradation of substituted polycyclic aromatic hydrocarbons, Bioremediation Chlorinated Polycyclic Aromat. Hydrocarbon Compd. (1994).
- [215] G. Jonsson, R.K. Bechmann, S.D. Bamber, T. Baissant, Bioconcentration, biotransformation, and elimination of polycyclic aromatic hydrocarbons in sheepshead minnows (*Cyprinodon variegatus*) exposed to contaminated seawater, Environmental Toxicology and Chemistry. (2004). <https://doi.org/10.1897/03-173>.
- [216] NITE - National Institute of Technology and Evaluation, Biodegradation and Bioconcentration data under CSCL, (2020). https://www.nite.go.jp/en/chem/kasinn/cscl_data.html (accessed March 2, 2020).
- [217] H. Lin, G.D. Morandi, R.S. Brown, V. Snieckus, T. Rantanen, K.B. Jørgensen, P. V. Hodson, Quantitative structure-activity relationships for chronic toxicity of alkyl-chrysenes and alkyl-benz[a]anthracenes to Japanese medaka embryos (*Oryzias latipes*), Aquatic Toxicology. (2015). <https://doi.org/10.1016/j.aquatox.2014.11.027>.
- [218] W.H. Shin, X. Zhu, M.G. Bures, D. Kihara, Three-dimensional compound comparison methods and their application in drug discovery, Molecules. 20 (2015) 12841–12862. <https://doi.org/10.3390/molecules200712841>.
- [219] A. Nicholls, G.B. McGaughey, R.P. Sheridan, A.C. Good, G. Warren, M. Mathieu, S.W. Muchmore, S.P. Brown, J.A. Grant, J.A. Haigh, N. Nevins, A.N. Jain, B. Kelley, Molecular Shape and Medicinal Chemistry: A Perspective, Journal of Medicinal Chemistry. 53 (2010) 3862–3886. <https://doi.org/10.1021/jm900818s>.
- [220] P.W. Finn, G.M. Morris, Shape-based similarity searching in chemical databases, Wiley Interdisciplinary Reviews: Computational Molecular Science. 3 (2013) 226–241. <https://doi.org/10.1002/wcms.1128>.
- [221] M. Cruz-Monteagudo, J.L. Medina-Franco, Y. Pérez-Castillo, O. Nicolotti, M.N.D.S. Cordeiro, F. Borges, Activity cliffs in drug discovery: Dr Jekyll or Mr Hyde?, Drug Discovery Today. 19 (2014) 1069–1080. <https://doi.org/10.1016/j.drudis.2014.02.003>.
- [222] M.D.M. AbdulHameed, R. Liu, P. Schyman, D. Sachs, Z. Xu, V. Desai, A. Wallqvist, ToxProfiler: Toxicity-target profiler based on chemical similarity, Computational Toxicology. 18 (2021). <https://doi.org/10.1016/j.comtox.2021.100162>.
- [223] M.P. Seddon, D.A. Cosgrove, M.J. Packer, V.J. Gillet, Alignment-Free Molecular Shape Comparison Using Spectral Geometry: The Framework, Journal of Chemical Information and Modeling. 59 (2019) 98–116. <https://doi.org/10.1021/acs.jcim.8b00676>.
- [224] B. Aas, Thesis MSc (UU/RIVM) - Chemical Similarity Screening With Machine Learning and Active Learning Using Physical Chemical Properties, 2020.
- [225] J. Baars, Thesis MSc (UvA/RIVM) - The effect of added chemical attributes on the classification of graph based molecular datasets, 2020.
- [226] P. Hartog, Thesis MSc (LU/RIVM) - Predicting and Prioritizing Possible Endocrine Disruptors using Machine Learning, 2021.
- [227] C. Rudin, Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead, Nature Machine Intelligence. 1 (2019) 206–215. <https://doi.org/10.1038/s42256-019-0048-x>.
- [228] A.S. Rifaioglu, H. Atas, M.J. Martin, R. Cetin-Atalay, V. Atalay, T. Dogan, Recent applications of deep learning and machine intelligence on in silico drug discovery: Methods, tools and databases, Briefings in Bioinformatics. 20 (2019) 1878–1912. <https://doi.org/10.1093/bib/bby061>.

- Working Group, (2021). <https://echa.europa.eu/petco-working-group> (accessed August 30, 2021).
- [244] CEFIC LRI, ECO42: Fate-Directed Toxicity Testing and Risk Assessment of UVCBs, (2021). <http://cefic-lri.org/projects/eco42-fate-directed-toxicity-testing-and-risk-assessment-of-uvcbs/> (accessed August 30, 2021).
- [245] U.G. Sauer, R.A. Barter, R.A. Becker, E. Benfenati, E. Berggren, B. Hubesch, H.M. Hollnagel, K. Inawaka, A.M. Keene, P. Mayer, K. Plotzke, R. Skoglund, O. Albert, 21st Century Approaches for Evaluating Exposures, Biological Activity, and Risks of Complex Substances: Workshop highlights, *Regulatory Toxicology and Pharmacology*. 111 (2020). <https://doi.org/10.1016/j.yrtph.2020.104583>.
- [246] ECHA - European Chemicals Agency, Perfluoroalkyl chemicals (PFAS), (2021). <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas> (accessed August 30, 2021).
- [247] K. Savolainen, U. Backman, D. Brouwer, B. Fadeel, T. Fernandes, T. Kuhlbusch, R. Landsiedel, I. Lynch, L. Pylkkänen, *Nanosafety in Europe 2015-2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations*, 2013.
- [248] M. Herzler, P. Marx-Stoelting, R. Pirow, C. Riebeling, A. Luch, T. Tralau, T. Schwerdtle, A. Hensel, The “EU chemicals strategy for sustainability” questions regulatory toxicology as we know it: is it all rooted in sound scientific evidence?, *Archives of Toxicology*. 95 (2021) 2589–2601. <https://doi.org/10.1007/s00204-021-03091-3>.
- [249] Safe-by-Design NL, Safe-by-Design, (2021). <https://www.safe-by-design-nl.nl/home+english/default.aspx> (accessed September 14, 2021).
- [250] NWO - Dutch Research Council, Research data management, (2020). <https://www.nwo.nl/en/research-data-management> (accessed August 30, 2021).
- [251] European Commission, Horizon 2020 Online Manual: Data Management, (2020). https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm (accessed August 30, 2021).
- [252] R.J. Kavlock, T. Bahadori, T.S. Barton-Maclaren, M.R. Gwinn, M. Rasenberg, R.S. Thomas, Accelerating the Pace of Chemical Risk Assessment, *Chemical Research in Toxicology*. 31 (2018) 287–290. <https://doi.org/10.1021/acs.chemrestox.7b00339>.

