Advancements in effect-based water quality assessment

de Baat, M.L.

APPENDIX

&

REFERENCES

1. Crutzen, P. J. Geology of mankind. *Nature* **2002**, *415* (6867), 23–23.
2. Waters, C. N.; Zalasiewicz, J.; Summerhayes, C.; Barnosky, A. D.; Poirier, C.; Ga uszka, A.; Cearreta, A.; Edgeworth, M.; Ellis, E. C.; Ellis, M.; et al. The Anthropocene is functionally and stratigraphically distinct from the Holocene. *Science* **2016**, *351* (6269), aad2622.
3. Bernhardt, E. S.; Rosi, E. J.; Gessner, M. O. Synthetic chemicals as agents of global change. *Front. Ecol. Environ.* **2017**, *15* (2), 84–90.
4. Chemical Abstract Service https://www.cas.org/.
5. Wang, Z.; Walker, G. W.; Muir, D. C. G.; Nagatani-Yoshida, K. Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories. *Environ. Sci. Technol.* **2020**, *54* (5), 2575–2584.
6. Posthuma, L.; de Zwart, D.; Dyer, S. D. Chemical mixtures affect freshwater species assemblages: from problems to solutions. *Curr. Opin. Environ. Sci. Heal.* **2019**, *11*, 78–89.
7. Vörösmarty, C. J.; McIntyre, P. B.; Gessner, M. O.; Dudgeon, D.; Prusevich, A.; Green, P.; Glidden, S.; Bunn, S. E.; Sullivan, C. A.; Liermann, C. R.; et al. Global threats to human water security and river biodiversity. *Nature* **2010**, *467* (7315), 555–561.
8. Hites, R. A. Statistical approach for assessing the stockholm convention's effectiveness: great lakes atmospheric data. *Environ. Sci. Technol.* **2019**, *53* (15), 8585–8590.
9. Escher, B. I.; Stapleton, H. M.; Schymanski, E. L. Tracking complex mixtures of chemicals in our changing environment. *Science* **2020**, *367* (6476), 388–392.
10. Neale, P. A.; Munz, N. A.; Aït-Aïssa, S.; Altenburger, R.; Brion, F.; Busch, W.; Escher, B. I.; Hilscherová, K.; Kienle, C.; Novák, J.; et al. Integrating chemical analysis and bioanalysis to evaluate the contribution of wastewater effluent on the micropollutant burden in small streams. *Sci. Total Environ.* **2017**, *576*, 785–795.
11. Blackwell, B. R.; Ankley, G. T.; Bradley, P. M.; Houck, K. A.; Makarov, S. S.; Medvedev, A. V.; Swintek, J.; Villeneuve, D. L. Potential Toxicity of Complex Mixtures in Surface Waters from a Nationwide Survey of United States Streams: Identifying in Vitro Bioactivities and Causative Chemicals. *Environ. Sci. Technol.* **2019**, *53* (2), 973–983.
12. Tousova, Z.; Oswald, P.; Slobodnik, J.; Blaha, L.; Muz, M.; Hu, M.; Brack, W.; Krauss, M.; Di Paolo, C.; Tarcai, Z.; et al. European demonstration program on the effect-based and chemical identification and monitoring of organic pollutants in European surface waters. *Sci. Total Environ.* **2017**, *601–602*, 1849–1868.
13. Roll, I. B.; Halden, R. U. Critical review of factors governing data quality of integrative samplers employed in environmental water monitoring. *Water Res.* **2016**, *94*, 200–207.
14. van der Oost, R.; Sileno, G.; Janse, T.; Nguyen, M. T.; Besselink, H.; Brouwer, A. SIMONI (Smart Integrated Monitoring) as a novel bioanalytical strategy for water quality assessment: Part II-field feasibility survey. *Environ. Toxicol. Chem.* **2017**, *36* (9), 2400–2416.
15. Hamers, T.; Legradi, J.; Zwart, N.; Smedes, F.; de Weert, J.; van den Brandhof, E.-J.; van de Meent, D.; de Zwart, D. Time-Integrative Passive sampling combined with TOxicity Profiling (TIPTOP): an effect-based strategy for cost-effective chemical water quality assessment. *Environ. Toxicol. Pharmacol.* **2018**, *64*, 48–59.
16. Liscio, C.; Abdul-Sada, A.; Al-Salhi, R.; Ramsey, M. H.; Hill, E. M. Methodology for profiling anti-androgen mixtures in river water using multiple passive samplers and bioassay-directed analyses. *Water Res.* **2014**, *57*, 258–269.
17. Escher, B.; Leusch, F. *Bioanalytical Tools in Water Quality Assessment*; IWA Publishing: London, 2011; Vol. 10.
18. Zabiegała, B.; Kot-Wasik, A.; Urbanowicz, M.; Namieśnik, J. Passive sampling as a tool for obtaining reliable analytical information in environmental quality monitoring. *Anal. Bioanal. Chem.* **2010**, *396* (1), 273–296.
19. Vrana, B.; Allan, I. J.; Greenwood, R.; Mills, G. A.; Dominiak, E.; Svensson, K.; Knutsson, J.; Morrison, G. Passive sampling techniques for monitoring pollutants in water. *TrAC Trends Anal. Chem.* **2005**, *24* (10), 845–868.

20. Jahnke, A.; Mayer, P.; Schäfer, S.; Witt, G.; Haase, N.; Escher, B. I. Strategies for Transferring Mixtures of Organic Contaminants from Aquatic Environments into Bioassays. *Environ. Sci. Technol.* **2016**, *50* (11), 5424–5431.
21. van der Oost, R.; Sileno, G.; Suárez-Muñoz, M.; Nguyen, M. T.; Besselink, H.; Brouwer, A. SIMONI (Smart integrated monitoring) as a novel bioanalytical strategy for water quality assessment: Part I–model design and effect-based trigger values. *Environ. Toxicol. Chem.* **2017**, *36* (9), 2385–2399.
22. Ankley, G. T.; Bennett, R. S.; Erickson, R. J.; Hoff, D. J.; Hornung, M. W.; Johnson, R. D.; Mount, D. R.; Nichols, J. W.; Russom, C. L.; Schmieder, P. K.; et al. Adverse outcome pathways: A conceptual framework to support ecotoxicology research and risk assessment. *Environ. Toxicol. Chem.* **2010**, *29* (3), 730–741.
23. Brack, W.; Ait-Aissa, S.; Burgess, R. M.; Busch, W.; Creusot, N.; Di Paolo, C.; Escher, B. I.; Mark Hewitt, L.; Hilscherova, K.; Hollender, J.; et al. Effect-directed analysis supporting monitoring of aquatic environments — An in-depth overview. *Sci. Total Environ.* **2016**, *544*, 1073–1118.
24. Escher, B. I.; Allinson, M.; Altenburger, R.; Bain, P. A.; Balaguer, P.; Busch, W.; Crago, J.; Denslow, N. D.; Dopp, E.; Hilscherova, K.; et al. Benchmarking organic micropollutants in wastewater, recycled water and drinking water with in vitro bioassays. *Environ. Sci. Technol.* **2014**, *48* (3), 1940–1956.
25. Neale, P. A.; Altenburger, R.; Aït-Aïssa, S.; Brion, F.; Busch, W.; de Aragão Umbuzeiro, G.; Denison, M. S.; Du Pasquier, D.; Hilscherová, K.; Hollert, H.; et al. Development of a bioanalytical test battery for water quality monitoring: Fingerprinting identified micropollutants and their contribution to effects in surface water. *Water Res.* **2017**, *123*, 734–750.
26. Burton, G. A. Assessing sediment toxicity: Past, present, and future. *Environ. Toxicol. Chem.* **2013**, *32* (7), 1438–1440.
27. Borja, A.; Valencia, V.; Franco, J.; Muxika, I.; Bald, J.; Belzunce, M. .; Solaun, O. The water framework directive: water alone, or in association with sediment and biota, in determining quality standards? *Mar. Pollut. Bull.* **2004**, *49* (1–2), 8–11.
28. Li, H.; Zhang, J.; You, J. Diagnosis of complex mixture toxicity in sediments: Application of toxicity identification evaluation (TIE) and effect-directed analysis (EDA). *Environ. Pollut.* **2018**, *237*, 944–954.
29. Burgess, R. M.; Ho, K. T.; Brack, W.; Lamoree, M. Effects-directed analysis (EDA) and toxicity identification evaluation (TIE): Complementary but different approaches for diagnosing causes of environmental toxicity. *Environ. Toxicol. Chem.* **2013**, *32* (9), 1935–1945.
30. Escher, B. I.; Aït-Aïssa, S.; Behnisch, P. A.; Brack, W.; Brion, F.; Brouwer, A.; Buchinger, S.; Crawford, S. E.; Du Pasquier, D.; Hamers, T.; et al. Effect-based trigger values for in vitro and in vivo bioassays performed on surface water extracts supporting the environmental quality standards (EQS) of the European Water Framework Directive. *Sci. Total Environ.* **2018**, *628–629*, 748–765.
31. Tang, J. Y. M.; McCarty, S.; Glenn, E.; Neale, P. A.; Warne, M. S. J.; Escher, B. I. Mixture effects of organic micropollutants present in water: Towards the development of effect-based water quality trigger values for baseline toxicity. *Water Res.* **2013**, *47* (10), 3300–3314.
32. Brion, F.; De Gussem, V.; Buchinger, S.; Hollert, H.; Carere, M.; Porcher, J. M.; Piccini, B.; Féray, C.; Dulio, V.; Könemann, S.; et al. Monitoring estrogenic activities of waste and surface waters using a novel in vivo zebrafish embryonic (EASZY) assay: Comparison with in vitro cell-based assays and determination of effect-based trigger values. *Environ. Int.* **2019**, *130*, 104896.
33. Hollender, J.; Schymanski, E. L.; Singer, H. P.; Ferguson, P. L. Nontarget Screening with High Resolution Mass Spectrometry in the Environment: Ready to Go? *Environ. Sci. Technol.* **2017**, *51* (20), 11505–11512.
34. Albergamo, V.; Schollée, J. E.; Schymanski, E. L.; Helmus, R.; Timmer, H.; Hollender, J.; De Voogt, P. Nontarget screening reveals time trends of polar micropollutants in a riverbank filtration system. *Environ. Sci. Technol.* **2019**, *53* (13), 7584–7594.
35. Wernersson, A. S.; Carere, M.; Maggi, C.; Tusil, P.; Soldan, P.; James, A.; Sanchez, W.; Dulio, V.; Broeg, K.; Reifferscheid, G.; et al. The European technical report on aquatic effect-based monitoring tools under the water framework directive. *Environ. Sci. Eur.* **2015**, *27* (1), 1–11.
36. European Commission. *Directives of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy*; 2013; Vol. 2013.

37. Altenburger, R.; Ait-Aissa, S.; Antczak, P.; Backhaus, T.; Barceló, D.; Seiler, T.-B.; Brion, F.; Busch, W.; Chipman, K.; de Alda, M. L.; et al. Future water quality monitoring — Adapting tools to deal with mixtures of pollutants in water resource management. *Sci. Total Environ.* **2015**, *512*, 540–551.
38. Fliedner, A.; Lohmann, N.; Rüdel, H.; Teubner, D.; Wellmitz, J.; Koschorreck, J. Current levels and trends of selected EU Water Framework Directive priority substances in freshwater fish from the German environmental specimen bank. *Environ. Pollut.* **2016**, *216*, 866–876.
39. Busch, W.; Schmidt, S.; Kühne, R.; Schulze, T.; Krauss, M.; Altenburger, R. Micropollutants in European rivers: A mode of action survey to support the development of effect-based tools for water monitoring. *Environ. Toxicol. Chem.* **2016**, *35* (8), 1887–1899.
40. Schriks, M.; Heringa, M. B.; van der Kooi, M. M. E.; de Voogt, P.; van Wezel, A. P. Toxicological relevance of emerging contaminants for drinking water quality. *Water Res.* **2010**, *44* (2), 461–476.
41. Schwarzenbach, R. P.; Escher, B. I.; Fenner, K.; Hofstetter, T. B.; Johnson, C. A.; von Gunten, U.; Wehrli, B. The challenge of micropollutants in aquatic systems. *Science* **2006**, *313* (5790), 1072–1077.
42. Neale, P. A.; Ait-Aissa, S.; Brack, W.; Creusot, N.; Denison, M. S.; Deutschmann, B.; Hilscherová, K.; Hollert, H.; Krauss, M.; Novák, J.; et al. Linking in Vitro Effects and Detected Organic Micropollutants in Surface Water Using Mixture-Toxicity Modeling. *Environ. Sci. Technol.* **2015**, *49* (24), 14614–14624.
43. Daughton, C. G. "Emerging" chemicals as pollutants in the environment: A 21st century perspective. *Renew. Resour. J.* **2005**, *23* (December 2005), 6–23.
44. Leusch, F. D. L.; Khan, S. J.; Laingam, S.; Prochazka, E.; Froscio, S.; Trinh, T.; Chapman, H. F.; Humpage, A. Assessment of the application of bioanalytical tools as surrogate measure of chemical contaminants in recycled water. *Water Res.* **2014**, *49*, 300–315.
45. Brack, W.; Dulio, V.; Ågerstrand, M.; Allan, I.; Altenburger, R.; Brinkmann, M.; Bunke, D.; Burgess, R. M.; Cousins, I.; Escher, B. I.; et al. Towards the review of the European Union Water Framework Directive: Recommendations for more efficient assessment and management of chemical contamination in European surface water resources. *Sci. Total Environ.* **2017**, *576*, 720–737.
46. Di Paolo, C.; Ottermanns, R.; Keiter, S.; Ait-Aissa, S.; Bluhm, K.; Brack, W.; Breitholtz, M.; Buchinger, S.; Carere, M.; Chalon, C.; et al. Bioassay battery interlaboratory investigation of emerging contaminants in spiked water extracts – Towards the implementation of bioanalytical monitoring tools in water quality assessment and monitoring. *Water Res.* **2016**, *104*, 473–484.
47. Jia, A.; Escher, B. I.; Leusch, F. D. L.; Tang, J. Y. M.; Prochazka, E.; Dong, B.; Snyder, E. M.; Snyder, S. A. In vitro bioassays to evaluate complex chemical mixtures in recycled water. *Water Res.* **2015**, *80*, 1–11.
48. Novák, J.; Vrana, B.; Rusina, T.; Okonski, K.; Grabic, R.; Neale, P. A.; Escher, B. I.; Macová, M.; Ait-Aissa, S.; Creusot, N.; et al. Effect-based monitoring of the Danube River using mobile passive sampling. *Sci. Total Environ.* **2018**, *636*, 1608–1619.
49. Jones, L.; Ronan, J.; McHugh, B.; McGovern, E.; Regan, F. Emerging priority substances in the aquatic environment: a role for passive sampling in supporting WFD monitoring and compliance. *Anal. Methods* **2015**, *7* (19), 7976–7984.
50. Booij, K.; Smedes, F. An improved method for estimating in situ sampling rates of nonpolar passive samplers. *Environ. Sci. Technol.* **2010**, *44* (17), 6789–6794.
51. Harman, C.; Allan, I. J.; Bäuerlein, P. S. The Challenge of Exposure Correction for Polar Passive Samplers—The PRC and the POCIS. *Environ. Sci. Technol.* **2011**, *45* (21), 9120–9121.
52. Harman, C.; Allan, I. J.; Vermeirssen, E. L. M. Calibration and use of the polar organic chemical integrative sampler-a critical review. *Environ. Toxicol. Chem.* **2012**, *31* (12), 2724–2738.
53. OECD Environmental Health and Safety. OECD 202: Daphnia sp., Acute Immobilisation Test. In *OECD Guidelines for Testing of Chemicals*; 2004.
54. OECD Environmental Health and Safety. OECD 201: Freshwater Alga and Cyanobacteria, Growth Inhibition Test. In *OECD Guidelines for Testing of Chemicals*; 2006.
55. Peterson, H. G.; Nyholm, N.; Ruecker, N. Algal microplate toxicity test suitable for heavy metals. In *Small-Scale Freshwater Toxicity Investigations: Volume 1 - Toxicity Test Methods*; Springer-Verlag: Berlin/Heidelberg, 2005; pp 243–270.

56. Hamers, T.; Kamstra, J. H.; Sonneveld, E.; Murk, A. J.; Kester, M. H. A.; Andersson, P. L.; Legler, J.; Brouwer, A. In Vitro Profiling of the Endocrine-Disrupting Potency of Brominated Flame Retardants. *Toxicol. Sci.* **2006**, *92* (1), 157–173.
57. Murk, A. J.; Legler, J.; Denison, M. S.; Giesy, J. P.; van de Guchte, C.; Brouwer, A. Chemical-Activated Luciferase Gene Expression (CALUX): A Novel in Vitro Bioassay for Ah Receptor Active Compounds in Sediments and Pore Water. *Fundam. Appl. Toxicol.* **1996**, *33* (1), 149–160.
58. Sonneveld, E.; Jansen, H. J.; Riteco, J. A. C.; Brouwer, A.; van der Burg, B. Development of Androgen- and Estrogen-Responsive Bioassays, Members of a Panel of Human Cell Line-Based Highly Selective Steroid-Responsive Bioassays. *Toxicol. Sci.* **2004**, *83* (1), 136–148.
59. Van Der Linden, S. C.; Heringa, M. B.; Man, H. Y.; Sonneveld, E.; Puijker, L. M.; Brouwer, A.; Van Der Burg, B. Detection of multiple hormonal activities in wastewater effluents and surface water, using a panel of steroid receptor CALUX bioassays. *Environ. Sci. Technol.* **2008**, *42* (15), 5814–5820.
60. Pikkemaat, M. G.; Dijk, S. O. v; Schouten, J.; Rapallini, M.; van Egmond, H. J. A new microbial screening method for the detection of antimicrobial residues in slaughter animals: The Nouws antibiotic test (NAT-screening). *Food Control* **2008**, *19* (8), 781–789.
61. Ter Braak, C. J. F. *CANOCO—A FORTRAN program for canonical community ordination by [partial] [detrended][canonical] correspondence analysis, principal component analysis and redundancy analysis (version 2.1)*; 1988.
62. Ter Braak, C. J. F. *Update notes: CANOCO version 3.1.*; Agricultural Mathematics Group, Wageningen., 1990.
63. Verdonschot, P. F. M.; Ter Braak, C. J. F. An experimental manipulation of oligochaete communities in mesocosms treated with chlorpyrifos or nutrient additions: multivariate analyses with Monte Carlo permutation tests. *Hydrobiologia* **1994**, *278* (1–3), 251–266.
64. Manoli, E.; Samara, C. Polycyclic aromatic hydrocarbons in natural waters: Sources, occurrence and analysis. *TrAC - Trends Anal. Chem.* **1999**, *18* (6), 417–428.
65. Kulkarni, P. S.; Crespo, J. G.; Afonso, C. A. M. Dioxins sources and current remediation technologies - A review. *Environ. Int.* **2008**, *34* (1), 139–153.
66. Pieterse, B.; Felzel, E.; Winter, R.; Van Der Burg, B.; Brouwer, A. PAH-CALUX, an optimized bioassay for AhR-mediated hazard identification of polycyclic aromatic hydrocarbons (PAHs) as individual compounds and in complex mixtures. *Environ. Sci. Technol.* **2013**, *47* (20), 11651–11659.
67. Van der Linden, S. C.; von Bergh, A. R. M.; van Vught-Lussenburg, B. M. A.; Jonker, L. R. A.; Teunis, M.; Krul, C. A. M.; van der Burg, B. Development of a panel of high-throughput reporter-gene assays to detect genotoxicity and oxidative stress. *Mutat. Res. - Genet. Toxicol. Environ. Mutagen.* **2014**, *760*, 23–32.
68. Maltby, L. Studying Stress: The Importance of Organism-Level Responses. *Ecol. Appl.* **1999**, *9* (2), 431.
69. Booij, P.; Sjollema, S. B.; van der Geest, H. G.; Leonards, P. E. G.; Lamoree, M. H.; de Voogt, W. P.; Admiraal, W.; Laane, R. W. P. M.; Vethaak, A. D. Toxic pressure of herbicides on microalgae in Dutch estuarine and coastal waters. *J. Sea Res.* **2015**, *102*, 48–56.
70. Schreiner, V. C.; Szöcs, E.; Bhowmik, A. K.; Vijver, M. G.; Schäfer, R. B. Pesticide mixtures in streams of several European countries and the USA. *Sci. Total Environ.* **2016**, *573*, 680–689.
71. Sjollema, S. B.; Martínezgarcía, G.; Van Der Geest, H. G.; Kraak, M. H. S.; Booij, P.; Vethaak, A. D.; Admiraal, W. Hazard and risk of herbicides for marine microalgae. *Environ. Pollut.* **2014**, *187*, 106–111.
72. de Baat, M. L.; Bas, D. A.; van Beusekom, S. A. M.; Droge, S. T. J.; van der Meer, F.; de Vries, M.; Verdonschot, P. F. M.; Kraak, M. H. S. Nationwide screening of surface water toxicity to algae. *Sci. Total Environ.* **2018**, *645*, 780–787.
73. Brettschneider, D. J.; Misovic, A.; Schulte-Oehlmann, U.; Oetken, M.; Oehlmann, J. Detection of chemically induced ecotoxicological effects in rivers of the Nidda catchment (Hessen, Germany) and development of an ecotoxicological, Water Framework Directive–compliant assessment system. *Environ. Sci. Eur.* **2019**, *31* (1), 7.
74. Schriks, M.; Van Leerdam, J. A.; Van Der Linden, S. C.; Van Der Burg, B.; Van Wezel, A. P.; De Voogt, P. High-resolution mass spectrometric identification and quantification of glucocorticoid compounds in various wastewaters in the Netherlands. *Environ. Sci. Technol.* **2010**, *44* (12), 4766–4774.

75. Hernando, M.; Mezcua, M.; Fernández-Alba, A.; Barceló, D. Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments. *Talanta* **2006**, *69* (2), 334–342.
76. Kümmerer, K. Antibiotics in the aquatic environment - A review - Part I. *Chemosphere* **2009**, *75* (4), 417–434.
77. Zhou, S.; Di Paolo, C.; Wu, X.; Shao, Y.; Seiler, T.-B.; Hollert, H. Optimization of screening-level risk assessment and priority selection of emerging pollutants – The case of pharmaceuticals in European surface waters. *Environ. Int.* **2019**, *128*, 1–10.
78. Virolainen, N.; Karp, M. Biosensors, antibiotics and food. In *Bioluminescence: Fundamentals and Applications in Biotechnology*; Springer, Berlin, Heidelberg, 2014; Vol. 2, pp 153–185.
79. Altenburger, R.; Brack, W.; Burgess, R. M.; Busch, W.; Escher, B. I.; Focks, A.; Mark Hewitt, L.; Jacobsen, B. N.; de Alda, M. L.; Ait-Aissa, S.; et al. Future water quality monitoring: improving the balance between exposure and toxicity assessments of real-world pollutant mixtures. *Environ. Sci. Eur.* **2019**, *31* (1), 12.
80. Armitage, P. D.; Bowes, M. J.; Vincent, H. M. Long-term changes in macroinvertebrate communities of a heavy metal polluted stream: The river Nent (Cumbria, UK) after 28 years. *River Res. Appl.* **2007**, *23* (9), 997–1015.
81. Sin, S. N.; Chua, H.; Lo, W.; Ng, L. M. Assessment of heavy metal cations in sediments of Shing Mun River, Hong Kong. *Environ. Int.* **2001**, *26* (5–6), 297–301.
82. Roig, N.; Nadal, M.; Sierra, J.; Ginebreda, A.; Schuhmacher, M.; Domingo, J. L. Novel approach for assessing heavy metal pollution and ecotoxicological status of rivers by means of passive sampling methods. *Environ. Int.* **2011**, *37* (4), 671–677.
83. Petrie, B.; Barden, R.; Kasprzyk-Hordern, B. A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring. *Water Res.* **2015**, *72*, 3–27.
84. Hogenboom, A. C.; van Leerdam, J. A.; de Voogt, P. Accurate mass screening and identification of emerging contaminants in environmental samples by liquid chromatography–hybrid linear ion trap Orbitrap mass spectrometry. *J. Chromatogr. A* **2009**, *1216* (3), 510–519.
85. Reemtsma, T.; Berger, U.; Arp, H. P. H.; Gallard, H.; Knepper, T. P.; Neumann, M.; Quintana, J. B.; Voogt, P. de. Mind the Gap: Persistent and Mobile Organic Compounds - Water Contaminants That Slip Through. *Environ. Sci. Technol.* **2016**, *50* (19), 10308–10315.
86. Doyle, E.; Biales, A.; Focazio, M.; Griffin, D.; Loftin, K.; Wilson, V. Effect-Based Screening Methods for Water Quality Characterization Will Augment Conventional Analyte-by-Analyte Chemical Methods in Research As Well As Regulatory Monitoring. *Environ. Sci. Technol.* **2015**, *49* (24), 13906–13907.
87. Brack, W.; Aissa, S. A.; Backhaus, T.; Dulio, V.; Escher, B. I.; Faust, M.; Hilscherova, K.; Hollender, J.; Hollert, H.; Müller, C.; et al. Effect-based methods are key. The European Collaborative Project SOLUTIONS recommends integrating effect-based methods for diagnosis and monitoring of water quality. *Environ. Sci. Eur.* **2019**, *31* (1), 10.
88. De Baat, M. L.; Kraak, M. H. S.; Van der Oost, R.; De Voogt, P.; Verdonschot, P. F. M. Effect-based nationwide surface water quality assessment to identify ecotoxicological risks. *Water Res.* **2019**, *159*, 434–443.
89. Abbas, A.; Schneider, I.; Bollmann, A.; Funke, J.; Oehlmann, J.; Prasse, C.; Schulte-Oehlmann, U.; Seitz, W.; Ternes, T.; Weber, M.; et al. What you extract is what you see: Optimising the preparation of water and wastewater samples for in vitro bioassays. *Water Res.* **2019**, *152*, 47–60.
90. Endo, S.; Matsuura, Y.; Vermeirssen, E. L. M. M. Mechanistic Model Describing the Uptake of Chemicals by Aquatic Integrative Samplers: Comparison to Data and Implications for Improved Sampler Configurations. *Environ. Sci. Technol.* **2019**, *53* (3), 1482–1489.
91. Bäuerlein, P. S.; Mansell, J. E.; ter Laak, T. L.; de Voogt, P. Sorption Behavior of Charged and Neutral Polar Organic Compounds on Solid Phase Extraction Materials: Which Functional Group Governs Sorption? *Environ. Sci. Technol.* **2012**, *46* (2), 954–961.
92. Alvarez, D. A.; Petty, J. D.; Huckins, J. N.; Jones-Lepp, T. L.; Getting, D. T.; Goddard, J. P.; Manahan, S. E. Development of a passive, in situ, integrative sampler for hydrophilic organic contaminants in aquatic environments. *Environ. Toxicol. Chem.* **2004**, *23* (7), 1640.

93. Huysman, S.; Vanryckeghem, F.; De Paepe, E.; Smedes, F.; Haughey, S. A.; Elliott, C. T.; Demeestere, K.; Vanhaecke, L. Hydrophilic Divinylbenzene for Equilibrium Sorption of Emerging Organic Contaminants in Aquatic Matrices. *Environ. Sci. Technol.* **2019**, *53* (18), 10803–10812.
94. Ahrens, L.; Daneshvar, A.; Lau, A. E.; Kreuger, J. Characterization of five passive sampling devices for monitoring of pesticides in water. *J. Chromatogr. A* **2015**, *1405*, 1–11.
95. Hamers, T.; Smit, M. G. D.; Murk, A. J.; Koeman, J. H. Biological and chemical analysis of the toxic potency of pesticides in rainwater. *Chemosphere* **2001**, *45* (4–5), 609–624.
96. Alygizakis, N. A.; Besselink, H.; Paulus, G. K.; Oswald, P.; Hornstra, L. M.; Oswaldova, M.; Medema, G.; Thomaidis, N. S.; Behnisch, P. A.; Slobodnik, J. Characterization of wastewater effluents in the Danube River Basin with chemical screening, in vitro bioassays and antibiotic resistant genes analysis. *Environ. Int.* **2019**, *127*, 420–429.
97. Lobpreis, T.; Vrana, B.; Dominiak, E.; Dercová, K.; Mills, G. A.; Greenwood, R. Effect of housing geometry on the performance of Chemcatcher™ passive sampler for the monitoring of hydrophobic organic pollutants in water. *Environ. Pollut.* **2008**, *153* (3), 706–710.
98. Endo, S.; Matsuura, Y. Characterizing Sorption and Permeation Properties of Membrane Filters Used for Aquatic Integrative Passive Samplers. *Environ. Sci. Technol.* **2018**, *52* (4), 2118–2125.
99. Vermeirssen, E. L. M.; Dietschweiler, C.; Escher, B. I.; van der Voet, J.; Hollender, J. Transfer Kinetics of Polar Organic Compounds over Polyethersulfone Membranes in the Passive Samplers Pocis and Chemcatcher. *Environ. Sci. Technol.* **2012**, *46* (12), 6759–6766.
100. Vanryckeghem, F.; Huysman, S.; Van Langenhove, H.; Vanhaecke, L.; Demeestere, K. Multi-residue quantification and screening of emerging organic micropollutants in the Belgian Part of the North Sea by use of Speedisk extraction and Q-Orbitrap HRMS. *Mar. Pollut. Bull.* **2019**, *142*, 350–360.
101. Huysman, S.; Van Meulebroek, L.; Vanryckeghem, F.; Van Langenhove, H.; Demeestere, K.; Vanhaecke, L. Development and validation of an ultra-high performance liquid chromatographic high resolution Q-Orbitrap mass spectrometric method for the simultaneous determination of steroidal endocrine disrupting compounds in aquatic matrices. *Anal. Chim. Acta* **2017**, *984*, 140–150.
102. Escher, B. I.; Abagyan, R.; Embry, M.; Klüver, N.; Redman, A. D.; Zarfl, C.; Parkerton, T. F. Recommendations for Improving Methods and Models for Aquatic Hazard Assessment of Ionizable Organic Chemicals. *Environ. Toxicol. Chem.* **2020**, *39* (2), 269–286.
103. Augusto, F.; Hantao, L. W.; Mogollón, N. G. S.; Braga, S. C. G. N. New materials and trends in sorbents for solid-phase extraction. *TrAC Trends Anal. Chem.* **2013**, *43*, 14–23.
104. Li, J.; Li, N.; Ma, M.; Giesy, J.; Wang, Z. In vitro profiling of the endocrine disrupting potency of organochlorine pesticides. *Toxicol. Lett.* **2008**, *183* (1–3), 65–71.
105. Mnif, W.; Hassine, A. I. H.; Bouaziz, A.; Bartegi, A.; Thomas, O.; Roig, B. Effect of Endocrine Disruptor Pesticides: A Review. *Int. J. Environ. Res. Public Health* **2011**, *8* (6), 2265–2303.
106. Kojima, H.; Katsura, E.; Takeuchi, S.; Niiyama, K.; Kobayashi, K. Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro reporter gene assays using Chinese hamster ovary cells. *Environ. Health Perspect.* **2004**, *112* (5), 524–531.
107. Escher, B. I.; Baumer, A.; Bittermann, K.; Henneberger, L.; König, M.; Kühnert, C.; Klüver, N. General baseline toxicity QSAR for nonpolar, polar and ionisable chemicals and their mixtures in the bioluminescence inhibition assay with Aliivibrio fischeri. *Environ. Sci. Process. Impacts* **2017**, *19* (3), 414–428.
108. Tang, J. Y. M.; Busetti, F.; Charrois, J. W. A.; Escher, B. I. Which chemicals drive biological effects in wastewater and recycled water? *Water Res.* **2014**, *60*, 289–299.
109. Altenburger, R.; Scholze, M.; Busch, W.; Escher, B. I.; Jakobs, G.; Krauss, M.; Krüger, J.; Neale, P. A.; Ait-Aissa, S.; Almeida, A. C.; et al. Mixture effects in samples of multiple contaminants – An inter-laboratory study with manifold bioassays. *Environ. Int.* **2018**, *114*, 95–106.
110. Eggen, R. I. L. L.; Hollender, J.; Joss, A.; Schärer, M.; Stamm, C. Reducing the Discharge of Micropollutants in the Aquatic Environment: The Benefits of Upgrading Wastewater Treatment Plants. *Environ. Sci. Technol.* **2014**, *48* (14), 7683–7689.

111. Hicks, K. A.; Fuzzen, M. L. M.; McCann, E. K.; Arlos, M. J.; Bragg, L. M.; Kleywegt, S.; Tetreault, G. R.; McMaster, M. E.; Servos, M. R. Reduction of Intersex in a Wild Fish Population in Response to Major Municipal Wastewater Treatment Plant Upgrades. *Environ. Sci. Technol.* **2017**, *51* (3), 1811–1819.
112. Booij, P.; Vethaak, A. D.; Leonards, P. E. G.; Sjollema, S. B.; Kool, J.; De Voogt, P.; Lamoree, M. H. Identification of photosynthesis inhibitors of pelagic marine algae using 96-well plate microfractionation for enhanced throughput in effect-directed analysis. *Environ. Sci. Technol.* **2014**, *48* (14), 8003–8011.
113. Muller, R.; Schreiber, U.; Escher, B. I.; Quayle, P.; Bengtson Nash, S. M.; Mueller, J. F. Rapid exposure assessment of PSII herbicides in surface water using a novel chlorophyll a fluorescence imaging assay. *Sci. Total Environ.* **2008**, *401* (1–3), 51–59.
114. Ralph, P. J.; Smith, R. A.; Macinnis-Ng, C. M. O.; Seery, C. R. Use of fluorescence-based ecotoxicological bioassays in monitoring toxicants and pollution in aquatic systems: Review. *Toxicol. Environ. Chem.* **2007**, *89* (4), 589–607.
115. Ricart, M.; Guasch, H.; Barceló, D.; Brix, R.; Conceição, M. H.; Geiszinger, A.; Alda, M. J. L. de; López-Doval, J. C.; Muñoz, I.; Postigo, C.; et al. Primary and complex stressors in polluted mediterranean rivers: Pesticide effects on biological communities. *J. Hydrol.* **2010**, *383* (1–2), 52–61.
116. Escher, B. I.; Bramaz, N.; Mueller, J. F.; Quayle, P.; Rutishauser, S.; Vermeirssen, E. L. M. Toxic equivalent concentrations (TEQs) for baseline toxicity and specific modes of action as a tool to improve interpretation of ecotoxicity testing of environmental samples. *J. Environ. Monit.* **2008**, *10* (5), 612.
117. Sjollema, S. B.; van Beusekom, S. A. M.; van der Geest, H. G.; Booij, P.; de Zwart, D.; Vethaak, A. D.; Admiraal, W. Laboratory algal bioassays using PAM fluorometry: Effects of test conditions on the determination of herbicide and field sample toxicity. *Environ. Toxicol. Chem.* **2014**, *33* (5), 1017–1022.
118. DeLorenzo, M. E.; Scott, G. I.; Ross, P. E. Toxicity of pesticides to aquatic microorganisms: A review. *Environ. Toxicol. Chem.* **2001**, *20* (1), 84–98.
119. Wood, R. J.; Mitrovic, S. M.; Lim, R. P.; Kefford, B. J. How benthic diatoms within natural communities respond to eight common herbicides with different modes of action. *Sci. Total Environ.* **2016**, *557–558*, 636–643.
120. Moschet, C.; Wittmer, I.; Simovic, J.; Junghans, M.; Piazzoli, A.; Singer, H.; Stamm, C.; Leu, C.; Hollender, J. How a complete pesticide screening changes the assessment of surface water quality. *Environ. Sci. Technol.* **2014**, *48* (10), 5423–5432.
121. Smit, C. E.; Kalf, D. *Bestrijdingsmiddelen in oppervlaktewater - Vergelijking tussen Nederland en andere Europese landen*; 2014.
122. McCormick, P. V.; Cairns, J. Algae as indicators of environmental change. *J. Appl. Phycol.* **1994**, *6* (5–6), 509–526.
123. Bae, M.-J.; Park, Y.-S. Biological early warning system based on the responses of aquatic organisms to disturbances: A review. *Sci. Total Environ.* **2014**, *466–467*, 635–649.
124. Ma, J.; Wang, S.; Wang, P.; Ma, L.; Chen, X.; Xu, R. Toxicity assessment of 40 herbicides to the green alga Raphidocelis subcapitata. *Ecotoxicol. Environ. Saf.* **2006**, *63* (3), 456–462.
125. Genty, B.; Briantais, J.-M.; Baker, N. R. The relationship between the quantum yield of photosynthetic electron transport and quenching of chlorophyll fluorescence. *Biochim. Biophys. Acta - Gen. Subj.* **1989**, *990* (1), 87–92.
126. Haanstra, L.; Doelman, P.; Oude Voshaar, J. H. The use of sigmoidal dose response curves in soil ecotoxicological research. *Plant Soil* **1985**, *84* (2), 293–297.
127. Couderchet, M.; Bocion, P. F.; Chollet, R.; Seckinger, K.; Böger, P. Biological Activity of Two Stereoisomers of the N-Thienyl Chloroacetamide Herbicide Dimethenamid. *Pestic. Sci.* **1997**, *50* (3), 221–227.
128. Pesticide Action Network, N. A. PAN Pesticides Database - Chemicals http://pesticideinfo.org/ (accessed Apr 12, 2018).
129. Escher, B. I.; Quayle, P.; Muller, R.; Schreiber, U.; Mueller, J. F. Passive sampling of herbicides combined with effect analysis in algae using a novel high-throughput phytotoxicity assay (Maxi-Imaging-PAM). *J. Environ. Monit.* **2006**, *8*, 456–464.

130. Snel, J. F. H.; Vos, J. H.; Gylstra, R.; Brock, T. C. M. Inhibition of photosystem II (PSII) electron transport as a convenient endpoint to assess stress of the herbicide linuron on freshwater plants. *Aquat. Ecol.* **1998**, *32* (2), 113–123.
131. Van Den Brink, P. J.; Hartgers, E. M.; Fettweis, U.; Crum, S. J. H.; Van Donk, E.; Brock, T. C. M. Sensitivity of macrophyte-dominated freshwater microcosms to chronic levels of the herbicide linuron. *Ecotoxicol. Environ. Saf.* **1997**, *38* (1), 13–24.
132. Hermosin, M. C.; Calderon, M. J.; Real, M.; Cornejo, J. Impact of herbicides used in olive groves on waters of the Guadalquivir river basin (southern Spain). *Agric. Ecosyst. Environ.* **2013**, *164*, 229–243.
133. Herrero-Hernández, E.; Rodríguez-Cruz, M. S.; Pose-Juan, E.; Sánchez-González, S.; Andrades, M. S.; Sánchez-Martín, M. J. Seasonal distribution of herbicide and insecticide residues in the water resources of the vineyard region of La Rioja (Spain). *Sci. Total Environ.* **2017**, *609*, 161–171.
134. Konstantinou, I. K.; Hela, D. G.; Albanis, T. A. The status of pesticide pollution in surface waters (rivers and lakes) of Greece. Part I. Review on occurrence and levels. *Environ. Pollut.* **2006**, *141* (3), 555–570.
135. Verro, R.; Finizio, A.; Otto, S.; Vighi, M. Predicting pesticide environmental risk in intensive agricultural areas. II: Screening level risk assessment of complex mixtures in surface waters. *Environ. Sci. Technol.* **2009**, *43* (2), 530–537.
136. Larras, F.; Montuelle, B.; Rimet, F.; Chèvre, N.; Bouchez, A. Seasonal shift in the sensitivity of a natural benthic microalgal community to a herbicide mixture: Impact on the protective level of thresholds derived from species sensitivity distributions. *Ecotoxicology* **2014**, *23* (6), 1109–1123.
137. Shi, Y.; Burns, M.; Ritchie, R. J.; Crossan, A.; Kennedy, I. R. Probabilistic risk assessment of diuron and prometryn in the Gwydir River catchment, Australia, with the input of a novel bioassay based on algal growth. *Ecotoxicol. Environ. Saf.* **2014**, *106*, 213–219.
138. Könemann, S.; Kase, R.; Simon, E.; Swart, K.; Buchinger, S.; Schlüsener, M.; Hollert, H.; Escher, B. I.; Werner, I.; Aït-Aïssa, S.; et al. Effect-based and chemical analytical methods to monitor estrogens under the European Water Framework Directive. *TrAC Trends Anal. Chem.* **2018**, *102*, 225–235.
139. Covich, A. P.; Palmer, M. A.; Crowl, T. A. The Role of Benthic Invertebrate Species in Freshwater Ecosystems. *Bioscience* **1999**, *49* (2), 119.
140. Massei, R.; Hollert, H.; Krauss, M.; von Tümpling, W.; Weidauer, C.; Haglund, P.; Küster, E.; Gallampois, C.; Tysklind, M.; Brack, W. Toxicity and neurotoxicity profiling of contaminated sediments from Gulf of Bothnia (Sweden): a multi-endpoint assay with Zebrafish embryos. *Environ. Sci. Eur.* **2019**, *31* (8), 1–12.
141. den Besten, P. J.; de Deckere, E.; Babut, M. P.; Power, B.; DelValls, T. A.; Zago, C.; Oen, A. M. P.; Heise, S. Biological effects-based sediment quality in ecological risk assessment for European Waters. *J. Soils Sediments* **2003**, *3* (3), 144–162.
142. Li, H.; Yi, X.; Cheng, F.; Tong, Y.; Mehler, W. T.; You, J. Identifying Organic Toxicants in Sediment Using Effect-Directed Analysis: A Combination of Bioaccessibility-Based Extraction and High-Throughput Midge Toxicity Testing. *Environ. Sci. Technol.* **2019**, *53* (2), 996–1003.
143. Jonker, M. T. O.; Van Der Heijden, S. A.; Adelman, D.; Apell, J. N.; Burgess, R. M.; Choi, Y.; Fernandez, L. A.; Flavetta, G. M.; Ghosh, U.; Gschwend, P. M.; et al. Advancing the Use of Passive Sampling in Risk Assessment and Management of Sediments Contaminated with Hydrophobic Organic Chemicals: Results of an International Ex Situ Passive Sampling Interlaboratory Comparison. *Environ. Sci. Technol.* **2018**, *52* (6), 3574–3582.
144. de Deckere, E.; de Cooman, W.; Leloup, V.; Meire, P.; Schmitt, C.; von der Ohe, P. C. Development of sediment quality guidelines for freshwater ecosystems. *J. Soils Sediments* **2011**, *11* (3), 504–517.
145. Li, Y.; Chen, C.-E. L.; Chen, W.; Chen, J.; Cai, X.; Jones, K. C.; Zhang, H. Development of a Passive Sampling Technique for Measuring Pesticides in Waters and Soils. *J. Agric. Food Chem.* **2019**, *67* (22), 6397–6406.
146. Mayer, P.; Parkerton, T. F.; Adams, R. G.; Cargill, J. G.; Gan, J.; Gouin, T.; Gschwend, P. M.; Hawthorne, S. B.; Helm, P.; Witt, G.; et al. Passive sampling methods for contaminated sediments: Scientific rationale supporting use of freely dissolved concentrations. *Integr. Environ. Assess. Manag.* **2014**, *10* (2), 197–209.

147. Droge, S. T. J.; Postma, J. F.; Hermens, J. L. M. Sediment toxicity of a rapidly biodegrading nonionic surfactant: Comparing the equilibrium partitioning approach with measurements in pore water. *Environ. Sci. Technol.* **2008**, *42* (11), 4215–4221.
148. Peijnenburg, W. J.; Teasdale, P. R.; Reible, D.; Mondon, J.; Bennett, W. W.; Campbell, P. G. Passive sampling methods for contaminated sediments: State of the science for metals. *Integr. Environ. Assess. Manag.* **2014**, *10* (2), 179–196.
149. Simpson, S. L.; Batley, G. E. Disturbances to metal partitioning during toxicity testing of iron(II)-rich estuarine pore waters and whole sediments. *Environ. Toxicol. Chem.* **2003**, *22* (2), 424–432.
150. Anderson, B. S.; Hunt, J. W.; Phillips, B. M.; Fairey, R.; Puckett, H. M.; Stephenson, M.; Taberski, K.; Newman, J.; Tjeerdema, R. S. Influence of sample manipulation on contaminant flux and toxicity at the sediment-water interface. *Mar. Environ. Res.* **2001**, *51* (3), 191–211.
151. Castro, B. B.; Guilhermino, L.; Ribeiro, R. In situ bioassay chambers and procedures for assessment of sediment toxicity with Chironomus riparius. *Environ. Pollut.* **2003**, *125* (3), 325–335.
152. Eriksson Wiklund, A.-K.; Dag Broman, B. S. Toxicity evaluation by using intact sediments and sediment extracts. *Mar. Pollut. Bull.* **2005**, *50* (6), 660–667.
153. Costello, D. M.; Harrison, A. M.; Hammerschmidt, C. R.; Mendonca, R. M.; Burton, G. A. Hitting reset on sediment toxicity: Sediment homogenization alters the toxicity of metal-amended sediments. *Environ. Toxicol. Chem.* **2019**, *38* (9), 1995–2007.
154. Hruska, K. A.; Dubé, M. G. Using artificial streams to assess the effects of metal-mining effluent on the life cycle of the freshwater midge (Chironomus tentans) in situ. *Environ. Toxicol. Chem.* **2004**, *23* (11), 2709–2718.
155. Paumen, M. L.; Borgman, E.; Kraak, M. H. S.; van Gestel, C. A. M.; Admiraal, W. Life cycle responses of the midge Chironomus riparius to polycyclic aromatic compound exposure. *Environ. Pollut.* **2008**, *152* (1), 225–232.
156. Beasley, G.; Kneale, P. Reviewing the impact of metals and PAHs on macroinvertebrates in urban watercourses. *Prog. Phys. Geogr.* **2002**, *26* (2), 236–270.
157. Arp, H. P. H.; Azzolina, N. A.; Cornelissen, G.; Hawthorne, S. B. Predicting pore water EPA-34 PAH concentrations and toxicity in pyrogenic-impacted sediments using pyrene content. *Environ. Sci. Technol.* **2011**, *45* (12), 5139–5146.
158. Loos, R.; Carvalho, R.; António, D. C.; Comero, S.; Locoro, G.; Tavazzi, S.; Paracchini, B.; Ghiani, M.; Lettieri, T.; Blaha, L.; et al. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. *Water Res.* **2013**, *47* (17), 6475–6487.
159. Götz, C. W.; Stamm, C.; Fenner, K.; Singer, H.; Schärer, M.; Hollender, J. Targeting aquatic microcontaminants for monitoring: exposure categorization and application to the Swiss situation. *Env. Sci Pollut Res* **2010**, *17*, 341–354.
160. Venkatesan, A. K.; Halden, R. U. Wastewater Treatment Plants as Chemical Observatories to Forecast Ecological and Human Health Risks of Manmade Chemicals. *Sci. Rep.* **2015**, *4* (1), 3731.
161. Schwientek, M.; Guillet, G.; Rügner, H.; Kuch, B.; Grathwohl, P. A high-precision sampling scheme to assess persistence and transport characteristics of micropollutants in rivers. *Sci. Total Environ.* **2016**, *540*, 444–454.
162. Yuan, J.; Van Dyke, M. I.; Huck, P. M. Identification of critical contaminants in wastewater effluent for managed aquifer recharge. *Chemosphere* **2017**, *172*, 294–301.
163. Leslie, H. A.; ter Laak, T. L.; Busser, F. J. M.; Kraak, M. H. S.; Hermens, J. L. M. Bioconcentration of Organic Chemicals: Is a Solid-Phase Microextraction Fiber a Good Surrogate for Biota? *Environ. Sci. Technol.* **2002**, *36* (24), 5399–5404.
164. Blackwell, B. R.; Ankley, G. T.; Corsi, S. R.; Decicco, L. A.; Houck, K. A.; Judson, R. S.; Li, S.; Martin, M. T.; Murphy, E.; Schroeder, A. L.; et al. An “EAR” on Environmental Surveillance and Monitoring: A Case Study on the Use of Exposure–Activity Ratios (EARs) to Prioritize Sites, Chemicals, and Bioactivities of Concern in Great Lakes Waters. *Environ. Sci. Technol.* **2017**, *51* (15), 8713–8724.
165. De Zwart, D.; Posthuma, L. Complex mixture toxicity for single and multiple species: Proposed methodologies. *Environ. Toxicol. Chem.* **2005**, *24* (10), 2665–2676.

166. Sprague, J. B. Measurement of pollutant toxicity to fish-III. Sublethal effects and “safe” concentrations. *Water Res.* **1971**, *5* (6), 245–266.
167. Chaloner, D. T.; Wotton, R. S. Substratum preferences by larvae of three species of midge (Diptera: Chironomidae). *Hydrobiologia* **1996**, *339* (1–3), 93–99.
168. Marinković, M.; Verweij, R. A.; Nummerdor, G. A.; Jonker, M. J.; Kraak, M. H. S.; Admiraal, W. Life cycle responses of the midge Chironomus riparius to compounds with different modes of action. *Environ. Sci. Technol.* **2011**, *45* (4), 1645–1651.
169. OECD. *OECD Guideline 218 (Sediment-Water Chironomid Toxicity Test Using Spiked Sediment)*; 2004.
170. Bettinelli, M.; Baroni, U.; Pastorelli, N. Microwave oven sample dissolution for the analysis of environmental and biological materials. *Anal. Chim. Acta* **1989**, *225* (C), 159–174.
171. SEDIAS (SEDIment ASsistent), https://www.helpdeskwater.nl/secundaire-navigatie/english/sediment/guidance-document/ (accessed Aug 26, 2019).
172. Van Der Heijden, S. A.; Jonker, M. T. O. PAH bioavailability in field sediments: Comparing different methods for predicting in situ bioaccumulation. *Environ. Sci. Technol.* **2009**, *43* (10), 3757–3763.
173. Paschke, A.; Popp, P. Solid-phase microextraction fibre-water distribution constants of more hydrophobic organic compounds and their correlations with octanol-water partition coefficients. *J. Chromatogr. A* **2003**, *999* (1–2), 35–42.
174. Endo, S.; Droge, S. T. J.; Goss, K. U. Polyparameter linear free energy models for polyacrylate fiber-water partition coefficients to evaluate the efficiency of solid-phase microextraction. *Anal. Chem.* **2011**, *83* (4), 1394–1400.
175. Vogt, C.; Nowak, C.; Diogo, J. B.; Oetken, M.; Schwenk, K.; Oehlmann, J. Multi-generation studies with Chironomus riparius - Effects of low tributyltin concentrations on life history parameters and genetic diversity. *Chemosphere* **2007**, *67* (11), 2192–2200.
176. De Cicco, L. A.; Corsi, S. R.; Villeneuve, D. L.; Blackwell, B.; Ankley, G. T. ToxEval: Evaluation of Measured Concentration Data Using the ToxCast High-Throughput Screening Database or a User-Defined Set of Concentration Benchmarks, R package version 1.0.0, 2018 http://usgs-r.github.io/toxEval/index.html (accessed Sep 3, 2019).
177. U.S. EPA. iCSS ToxCast Dashboard, https://comptox.epa.gov/dashboard/ (accessed Sep 3, 2019).
178. Posthuma, L.; van Gils, J.; Zijp, M. C.; van de Meent, D.; de Zwart, D. Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12 386 chemicals. *Environ. Toxicol. Chem.* **2019**, *38* (4), 703–711.
179. Lindim, C.; de Zwart, D.; Cousins, I. T.; Kutsarova, S.; Kühne, R.; Schüürmann, G. Exposure and ecotoxicological risk assessment of mixtures of top prescribed pharmaceuticals in Swedish freshwaters. *Chemosphere* **2019**, *220*, 344–352.
180. Bundschuh, M.; Goedkoop, W.; Kreuger, J. Evaluation of pesticide monitoring strategies in agricultural streams based on the toxic-unit concept - Experiences from long-term measurements. *Sci. Total Environ.* **2014**, *484* (1), 84–91.
181. Wilson, R. S. Monitoring organic enrichment of rivers using chironomid pupal exuvial assemblages. *Netherlands J. Aquat. Ecol.* **1992**, *26* (2–4), 521–525.
182. Calle-Martínez, D.; Casas, J. J. Chironomid species, stream classification, and water-quality assessment: the case of 2 Iberian Mediterranean mountain regions. *J. North Am. Benthol. Soc.* **2006**, *25* (2), 465–476.
183. Simpson, S.; Batley, G. *Sediment quality assessment: a practical guide.*; CSIRO Publishing, 2016.
184. Sibley, P. K.; Ankley, G. T.; Benoit, D. A. Factors Affecting Reproduction And The Importance Of Adult Size On Reproductive Output Of The Midge Chironomus Tentans. *Environ. Toxicol. Chem.* **2001**, *20* (6), 1296.
185. De Lange, H. J.; De Haas, E. M.; Maas, H.; Peeters, E. T. H. M. Contaminated sediments and bioassay responses of three macroinvertebrates, the midge larva Chironomus riparius, the water louse Asellus aquaticus and the mayfly nymph Ephoron virgo. *Chemosphere* **2005**, *61* (11), 1700–1709.

186. Tuikka, A. I.; Schmitt, C.; Höss, S.; Bandow, N.; von der Ohe, P. C.; de Zwart, D.; de Deckere, E.; Streck, G.; Mothes, S.; van Hattum, B.; et al. Toxicity assessment of sediments from three European river basins using a sediment contact test battery. *Ecotoxicol. Environ. Saf.* **2011**, *74* (1), 123–131.
187. Van Den Berg, S. J. P. P.; Baveco, H.; Butler, E.; De Laender, F.; Focks, A.; Franco, A.; Rendal, C.; Van Den Brink, P. J. Modeling the Sensitivity of Aquatic Macroinvertebrates to Chemicals Using Traits. *Environ. Sci. Technol.* **2019**, *53* (10), 6025–6034.
188. Monteiro, H. R.; Pestana, J. L. T.; Novais, S. C.; Soares, A. M. V. M.; Lemos, M. F. L. Toxicity of the insecticides spinosad and indoxacarb to the non-target aquatic midge Chironomus riparius. *Sci. Total Environ.* **2019**, *666*, 1283–1291.
189. Planelló, R.; Servia, M. J.; Gómez-Sande, P.; Herrero, Ó.; Cobo, F.; Morcillo, G. Transcriptional responses, metabolic activity and mouthpart deformities in natural populations of chironomus riparius larvae exposed to environmental pollutants. *Environ. Toxicol.* **2013**, *30* (4), 383–395.
190. Zhang, H.; Davison, W. Use of diffusive gradients in thin-films for studies of chemical speciation and bioavailability. *Environ. Chem.* **2015**, *12* (2), 85.
191. Birch, H.; Gouliarmou, V.; Lützhoft, H. C. H.; Mikkelsen, P. S.; Mayer, P. Passive dosing to determine the speciation of hydrophobic organic chemicals in aqueous samples. *Anal. Chem.* **2010**, *82* (3), 1142–1146.
192. EPA. *Summary of the Clean Water Act §502.7*; 2019; pp 1–2.
193. Bopp, S. K.; Barouki, R.; Brack, W.; Dalla Costa, S.; Dorne, J. L. C. M.; Drakvik, P. E.; Faust, M.; Karjalainen, T. K.; Kephalopoulos, S.; van Klaveren, J.; et al. Current EU research activities on combined exposure to multiple chemicals. *Environ. Int.* **2018**, *120*, 544–562.
194. Booij, K.; Smedes, F.; Van Weerlee, E. M. Spiking of performance reference compounds in low density polyethylene and silicone passive water samplers. *Chemosphere* **2002**, *46* (8), 1157–1161.
195. Panther, J. G.; Bennett, W. W.; Welsh, D. T.; Teasdale, P. R. Simultaneous measurement of trace metal and oxyanion concentrations in water using diffusive gradients in thin films with a chelex-metsorb mixed binding layer. *Anal. Chem.* **2014**, *86* (1), 427–434.
196. Allan, I. J.; Knutsson, J.; Guigues, N.; Mills, G. A.; Fouillac, A. M.; Greenwood, R. Evaluation of the Chemcatcher and DGT passive samplers for monitoring metals with highly fluctuating water concentrations. *J. Environ. Monit.* **2007**, *9* (7), 672–681.
197. Davison, W.; Zhang, H. Progress in understanding the use of diffusive gradients in thin films (DGT) back to basics. *Environ. Chem.* **2012**, *9* (1), 1–13.
198. Vonk, J. A.; Kraak, M. H. S. Herbicide Exposure and Toxicity to Aquatic Primary Producers. *Rev. Environ. Contam. Toxicol.* Under Review.
199. Riegraf, C.; Reifferscheid, G.; Becker, B.; Belkin, S.; Hollert, H.; Feiler, U.; Buchinger, S. Detection and Quantification of Photosystem II Inhibitors Using the Freshwater Alga Desmodesmus subspicatus in Combination with High-Performance Thin-Layer Chromatography. *Environ. Sci. Technol.* **2019**, *53* (22), 13458–13467.
200. Munz, N. A.; Burdon, F. J.; de Zwart, D.; Junghans, M.; Melo, L.; Reyes, M.; Schönenberger, U.; Singer, H. P.; Spycher, B.; Hollender, J.; et al. Pesticides drive risk of micropollutants in wastewater-impacted streams during low flow conditions. *Water Res.* **2017**, *110*, 366–377.
201. Malaj, E.; von der Ohe, P. C.; Grote, M.; Kühne, R.; Mondy, C. P.; Usseglio-Polatera, P.; Brack, W.; Schäfer, R. B. Organic chemicals jeopardize the health of freshwater ecosystems on the continental scale. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111* (26), 9549–9554.
202. Paulus, G. K.; Hornstra, L. M.; Alygizakis, N.; Slobodnik, J.; Thomaidis, N.; Medema, G. The impact of on-site hospital wastewater treatment on the downstream communal wastewater system in terms of antibiotics and antibiotic resistance genes. *Int. J. Hyg. Environ. Health* **2019**, *222* (4), 635–644.
203. Jonkers, T. J. H.; Steenhuis, M.; Schalkwijk, L.; Luirink, J.; Bald, D.; Houtman, C. J.; Kool, J.; Lamoree, M. H.; Hamers, T. Development of a High-Throughput Bioassay for Screening of Antibiotics in Aquatic Environmental Samples. *Environ. Sci. Technol.* Under Review.

204. Logemann, A.; Schafberg, M.; Brockmeyer, B. Using the HPTLC-bioluminescence bacteria assay for the determination of acute toxicities in marine sediments and its eligibility as a monitoring assessment tool. *Chemosphere* **2019**, *233*, 936–945.
205. Guo, J.; Deng, D.; Wang, Y.; Yu, H.; Shi, W. Extended suspect screening strategy to identify characteristic toxicants in the discharge of a chemical industrial park based on toxicity to Daphnia magna. *Sci. Total Environ.* **2019**, *650*, 10–17.
206. Kümmerer, K.; Dionysiou, D. D.; Olsson, O.; Fatta-Kassinos, D. A path to clean water. *Science* **2018**, *361* (6399), 222–224.
207. Roex, E. W. M.; Van Gestel, C. A. M.; Van Wezel, A. P.; Van Straalen, N. M. Ratios between acute aquatic toxicity and effects on population growth rates in relation to toxicant mode of action. *Environ. Toxicol. Chem.* **2000**, *19* (3), 685–693.
208. Zhang, H.; Davison, W. Performance Characteristics of Diffusion Gradients in Thin Films for the in Situ Measurement of Trace Metals in Aqueous Solution. *Anal. Chem.* **1995**, *67* (19), 3391–3400.
209. Smith, K. E. C.; Oostingh, G. J.; Mayer, P. Passive dosing for producing defined and constant exposure of hydrophobic organic compounds during in vitro toxicity tests. *Chem. Res. Toxicol.* **2010**, *23* (1), 55–65.
210. Hammershøj, R.; Birch, H.; Knudsmark Sjøholm, K.; Mayer, P. Accelerated passive dosing of hydrophobic complex mixtures – controlling level and composition in aquatic tests. *Environ. Sci. Technol.* **2020**, *Manuscript*, acs.est.9b06062.
211. Ensminger, M. P.; Vasquez, M.; Tsai, H. J.; Mohammed, S.; Van Scoy, A.; Goodell, K.; Cho, G.; Goh, K. S. Continuous low-level aquatic monitoring (CLAM) samplers for pesticide contaminant screening in urban runoff: Analytical approach and a field test case. *Chemosphere* **2017**, *184*, 1028–1035.
212. Amato, E. D.; Covaci, A.; Town, R. M.; Hereijgers, J.; Bellekens, B.; Giacometti, V.; Breugelmans, T.; Weyn, M.; Dardenne, F.; Bervoets, L.; et al. A novel active-passive sampling approach for measuring time-averaged concentrations of pollutants in water. *Chemosphere* **2018**, *209*, 363–372.
213. Schulze, T.; Ahel, M.; Ahlheim, J.; Aït-Aïssa, S.; Brion, F.; Di Paolo, C.; Froment, J.; Hidasi, A. O.; Hollender, J.; Hollert, H.; et al. Assessment of a novel device for onsite integrative large-volume solid phase extraction of water samples to enable a comprehensive chemical and effect-based analysis. *Sci. Total Environ.* **2017**, *581–582*, 350–358.
214. Vrana, B.; Rusina, T.; Okonski, K.; Prokeš, R.; Carlsson, P.; Kopp, R.; Smedes, F. Chasing equilibrium passive sampling of hydrophobic organic compounds in water. *Sci. Total Environ.* **2019**, *664*, 424–435.
215. Jeong, Y.; Schäffer, A.; Smith, K. A comparison of equilibrium and kinetic passive sampling for the monitoring of aquatic organic contaminants in German rivers. *Water Res.* **2018**, *145*, 248–258.
216. Jeong, Y.; Schäffer, A.; Smith, K. Equilibrium partitioning of organic compounds to OASIS HLB ® as a function of compound concentration, pH, temperature and salinity. *Chemosphere* **2017**, *174*, 297–305.
217. Leusch, F. D. L.; Neale, P. A.; Hebert, A.; Scheurer, M.; Schriks, M. C. M. Analysis of the sensitivity of in vitro bioassays for androgenic, progestagenic, glucocorticoid, thyroid and estrogenic activity: Suitability for drinking and environmental waters. *Environ. Int.* **2017**, *99*, 120–130.
218. Välitalo, P.; Massei, R.; Heiskanen, I.; Behnisch, P.; Brack, W.; Tindall, A. J.; Du Pasquier, D.; Küster, E.; Mikola, A.; Schulze, T.; et al. Effect-based assessment of toxicity removal during wastewater treatment. *Water Res.* **2017**, *126*, 153–163.
219. Collins, F. S.; Gray, G. M.; Bucher, J. R. Transforming environmental health protection. *Science* **2008**, *319* (5865), 906–907.
220. Johnson, A. C. Is freshwater macroinvertebrate biodiversity being harmed by synthetic chemicals in municipal wastewater? *Curr. Opin. Environ. Sci. Heal.* **2019**, *11*, 8–12.
221. de Voogt, P.; van Hattum, B. Wildlife ecotoxicology: Concerted global efforts required. *Environ. Toxicol. Chem.* **1997**, *16* (9), 1769–1770.
222. Brack, W. Solutions for present and future emerging pollutants in land and water resources management. Policy briefs summarizing scientific project results for decision makers. *Environ. Sci. Eur.* **2019**, *31* (1).

223. Vermeulen, R.; Schymanski, E. L.; Barabási, A.-L.; Miller, G. W. The exposome and health: Where chemistry meets biology. *Science* **2020**, *367* (6476), 392–396.
224. Brack, W.; Hollender, J.; de Alda, M. L.; Müller, C.; Schulze, T.; Schymanski, E.; Slobodnik, J.; Krauss, M. High-resolution mass spectrometry to complement monitoring and track emerging chemicals and pollution trends in European water resources. *Environ. Sci. Eur.* **2019**, *31* (1).

&

APPENDIX

SUMMARY - ADVANCEMENTS IN EFFECT-BASED WATER QUALITY ASSESSMENT

Background and aim

An increasingly wide variety of chemicals is emitted to the aquatic environment, where thousands of substances may be simultaneously present. The resultant complex and varying mixtures of chemicals exert a potential threat to human health and aquatic biodiversity. Current legally-prescribed chemical water quality assessment strategies focus on the chemical analysis of an only limited selection of legacy contaminants and overlook the risks of the complex mixtures of emerging contaminants that nowadays govern chemical water quality. As such, they are unfit for the risk assessment of present-day chemical contamination, and there is a need for future-proof monitoring methods that allow for the impact assessment of the ever-changing complex chemical burden on aquatic ecosystems.

The combination of time integrative sampling methods, known as passive sampling, and methods that employ living cells or organisms (bioanalyses or bioassays), known as effect-based methods, can overcome many of the limitations of traditional chemical water quality assessment methods. Over the past two decades, fundamental steps have been taken in the scientific underpinning of technological innovations for effect-based water quality assessment approaches and the interpretation of the obtained results. Nonetheless, their regular implementation is still in its infancy, and scientific knowledge gaps exist that need to be addressed to unleash the full potential of effect-based methods in chemical water quality assessment. Therefore, the present research aimed to fuel the paradigm shift towards new chemical aquatic environmental quality monitoring methods by providing a scientific basis for the advancement of effect-based water quality assessment. To meet this aim, the state-of-the-art of effect-based tools was explored and applied in five field- and laboratory-based studies.

Field and experimental work

To gain insight into the state-of-science of effect-based surface water quality assessment and its potential for implementation into regular water quality monitoring, the aim of **chapter 2** was to perform an effect-based nationwide water quality assessment to identify ecotoxicological risks in a wide variety of surface waters. To this end, passive sampling of polar and non-polar organic compounds was combined with a battery of *in situ*, *in vivo* and *in vitro* bioassays for 45 surface water locations. The bioassay battery was selected such that it could identify the risks posed by a wide range of chemical pollutants and their transformation products, while simultaneously allowing for targeted identification of groups of compounds that cause specific effects. Bioassay responses were compared to effect-based trigger values to identify potential ecotoxicological risks at the investigated locations. Responses were observed in all bioassays, and trigger values were exceeded in 9 out of the 21 applied assays, allowing for ranking of the investigated locations based on ecotoxicological risks. No relationship between land use and the identification of ecotoxicological risks was observed. Based on the results, considerations regarding future improvements of effect-based monitoring were given, which were addressed in the chapters 3-6. It was concluded that effect-based water quality assessment allowed the prioritization of sites

based on ecotoxicological risks, identified the presence of hazardous compounds regardless of being listed as priority substances and meanwhile could prevent costly chemical analysis at sites with low ecotoxicological risks.

The design of integrative passive samplers can affect the accumulation of compounds and therewith the detected bioassay responses. **Chapter 3** aimed to determine the effects of sampler housing and sorbent type on bioassay responses to polar passive sampler extracts. To this end, four integrative passive sampler configurations, resulting from the combination of polar organic chemical integrative sampler (POCIS) and Speedisk housings with hydrophilic-lipophilic balance and hydrophilic divinylbenzene sorbents, were simultaneously exposed at reference and contaminated surface water locations. To measure the toxicity of the accumulated polar organic compounds, a battery of five bioassays was exposed to the extracts. Extracts from POCIS caused higher bioassay responses in 91% of cases, while extracts from the two sorbents caused equally frequent but different bioassay responses. Hence, the passive sampler design critically affected the toxicity detection of polar organic contaminants, highlighting the importance of active choices in passive sampling for effect-based water quality assessment.

Since algal photosynthesis is a sensitive process that can be applied to identify the presence of hazardous herbicides in surface water, the aim of **chapter 4** was to employ an algal photosynthesis bioassay to assess surface water toxicity to algae and to identify the compounds causing the observed effects. To this end, *Raphidocelis subcapitata* was exposed to surface water samples and after 4.5 h photosynthetic efficiency was determined using PAM fluorometry. In this rapid high throughput bioassay, algal photosynthesis was affected by surface water from only one of 39 locations. Single compounds toxicity confirmation elucidated that the observed effect could be solely attributed to the herbicide linuron, which occurred at 110 times the EQS concentration and which is not included in the WFD priority substances list. In conclusion, applying the algal photosynthesis bioassay enables more efficient and effective assessment of toxicity to primary producers because it: (i) identifies the presence of herbicides that would be overlooked by routine chemical WFD monitoring, and (ii) avoids redundant chemical analyses by focusing only on (non-)target screening in samples with demonstrated effects.

Sediment quality assessment methods that consider the risks caused by the combined action of all sediment-associated contaminants to benthic biota are still underrepresented in water quality assessment strategies. **Chapter 5** aimed to integrate effect-monitoring and chemical profiling of sediment contamination. To this end, 28-day life cycle bioassays with *Chironomus riparius* using intact whole sediment cores from contaminated sites were performed in tandem with explorative chemical profiling of bioavailable concentrations of groups of legacy and emerging sediment contaminants to investigate ecotoxicological risks to benthic biota. All contaminated sediments caused effects on the resilient midge *C. riparius*, stressing that sediment contamination is ubiquitous and potentially harmful to aquatic ecosystems. However, bioassay responses were not in line with any of the calculated toxicity indices, suggesting that toxicity was caused by unmeasured compounds. Hence, this study underlines the relevance of effect-based sediment quality assessment and provides smarter ways to do so.

It was hypothesized that the refined insights and methodological improvements obtained in the previous chapters would contribute to an improved strategy for the assessment of the aggregated risk of all bioavailable micropollutants present in the aquatic environment. **Chapter 6** aimed to advance effect-based water quality assessment by implementing the developed methodological improvements and to gain insight into contamination source-specific bioanalytical responses. To this end, passive sampling of non-polar and polar organic compounds and metals was applied at 14 surface water locations that were characterized by two major anthropogenic contamination sources, agriculture and WWTP effluent, as well as reference sites with an expected low impact from micropollutants. A revised battery of 20 *in vivo* and *in vitro* bioassays was exposed to the passive sampler extracts, and the bioanalytical responses were compared to effect-based trigger values to identify potential ecotoxicological risks. The bioanalytical assessment of the joint risks of metals and (non-)polar organic compounds resulted in the successful identification of pollution source-specific ecotoxicological risk profiles. Cumulative ecotoxicological risks were lowest for reference locations, followed by agriculture locations and the highest for WWTP locations, and were mainly driven by polar organic contaminants. It was concluded that the employed advanced effect-based methods can readily be applied in surface water quality assessment and that the integration of chemical- and effect-based monitoring approaches will foster future-proof water quality assessment strategies on the road to a non-toxic environment.

Recommendations and outlook

This thesis advanced the scientific basis of effect-based chemical water quality assessment by providing methodological and theoretical improvements to this emerging field of research. In the **synthesis** (**chapter 7**), it was postulated that four specific requirements need to be met to achieve the full potential of effect-based water quality assessment.

First, the sampling methods should capture all relevant contaminants from the water. In the present research, this was pursued by i) developing an improved understanding of the characteristics that determine the uptake of contaminants in polar passive samplers, ii) applying a suite of passive samplers to capture organic contaminants from a very wide polarity range, iii) the expansion of the suite of passive samplers to include ecotoxicological risk assessment of metals, and iv) the expansion of the passive sampling strategy to allow the bioavailability-based extraction of sediment-associated contaminants.

Second, the environmental samples should be transferred as representative mixtures at environmentally relevant concentrations to the bioassays. Here, several methods were applied for the approximation of field-relevant passive sampler extract concentrations. This highlighted the limitations of the currently available approaches, and resulted in the recommendation to apply passive dosing to obtain environmentally relevant mixtures and concentrations of both non-polar and polar organic contaminants in bioassays.

Third, the bioassay battery should represent all toxicity endpoints relevant to aquatic ecosystem health. Criteria that determine the relevance of bioassays for application in effect-based water quality assessment were defined that consider the responsiveness of bioassays, the range of endpoints in a bioassay battery, and the early-warning function of bioassays. The application of these criteria to the bioassays applied in the present work resulted in the exclusion of several bioassays that appeared not fit-for-purpose and their replacement with more relevant and sensitive alternatives.

Last, the defined thresholds for the interpretation of bioassay responses should be indicative of ecotoxicological risks in the environment. Therefore, a novel approach was proposed that switches the point-of-departure of effect-based trigger value derivation from compound concentration-based thresholds to ecological protection goals. Despite existing challenges, the here postulated novel, more ecologically relevant, approach would strongly aid the achievement of the ultimate goal of effect-based trigger values: to protect natural populations of organisms in the aquatic environment.

It is concluded that in an ideal future, chemical water quality monitoring will result in a comprehensive assessment of the 'exposome of the natural aquatic environment', where (semi) continuous simultaneous biological and chemical analyses reveal the chemicals that (jointly) pose a threat to the biotic environment.

SAMENVATTING - PROGRESSIE IN EFFECTGEBASEERDE WATERKWALITEITSBEOORDELING

Achtergrond en doel van het promotieonderzoek

Er wordt een steeds grotere verscheidenheid aan chemicaliën uitgestoten in het aquatisch milieu, waar dientengevolge duizenden stoffen tegelijkertijd aanwezig kunnen zijn. Deze complexe en variërende mengsels van chemische stoffen vormen een potentiële bedreiging voor de menselijke gezondheid en de aquatische biodiversiteit. De huidige wettelijk voorgeschreven chemische waterkwaliteitsbeoordelingsstrategieën richten zich echter alleen op de chemische analyse van een beperkte selectie van bestaande verontreinigingen en zien hiermee de risico's over het hoofd van de complexe mengsels van nieuwe onbekende verontreinigingen die tegenwoordig de chemische waterkwaliteit bepalen. Daardoor zijn traditionele meetmethoden ongeschikt voor de risicobeoordeling van de hedendaagse chemische verontreiniging en is er behoefte aan toekomstbestendige monitoringsmethoden die het mogelijk maken om de effecten van de steeds veranderende complexe chemische belasting op aquatische ecosystemen te bepalen.

De combinatie van tijd-geïntegreerde bemonsteringsmethoden, bekend als passieve bemonstering (passive sampling), en methoden waarbij levende cellen of hele organismen worden gebruikt (bioanalyses en bioassays), bekend als effectgebaseerde methoden, kunnen veel van de beperkingen van de traditionele methoden voor de beoordeling van de chemische waterkwaliteit verhelpen. In de afgelopen twee decennia zijn grote stappen gezet in de fundamentele wetenschappelijke onderbouwing en de technologische innovatie van effectgerichte benaderingen van waterkwaliteitsbeoordeling en in de interpretatie van de verkregen resultaten. Desalniettemin staat de reguliere implementatie hiervan nog in de kinderschoenen en bestaan er lacunes in de wetenschappelijke kennis die moeten worden gevuld om het volledige potentieel van effectgebaseerde methoden bij de beoordeling van chemische waterkwaliteit tot haar recht te laten komen. Daarom was het doel van het huidige onderzoek de paradigma verschuiving naar nieuwe meetmethoden voor chemische waterkwaliteit te stimuleren door een wetenschappelijke basis te bieden voor de vooruitgang van effectgebaseerde waterkwaliteitsbeoordeling. Om dit doel te bereiken werden de meest recente ontwikkelingen in effectgebaseerde methoden onderzocht en toegepast in vijf veld- en laboratoriumstudies.

Experimentele benadering

Om inzicht te krijgen in de stand van de wetenschap betreffende de effectgebaseerde beoordeling van oppervlaktewaterkwaliteit en het potentieel ervan voor implementatie in reguliere waterkwaliteitscontrole, was het doel van **hoofdstuk 2** om een effectgebaseerde landelijke waterkwaliteitsbeoordeling uit te voeren om ecotoxicologische risico's te identificeren in een grote verscheidenheid aan oppervlaktewateren. Daartoe werd passieve bemonstering van hydrofiele en hydrofobe organische stoffen op 45 oppervlaktewaterlocaties gecombineerd met een batterij van veld- en laboratorium-bioassays. De bioassay-batterij werd zo gekozen dat deze de risico's van een breed scala aan verontreinigende stoffen en hun transformatieproducten kon identificeren, terwijl het tegelijkertijd de identificatie mogelijk maakte van groepen van verbindingen die specifieke effecten veroorzaken. Bioassay-responsen werden vergeleken met effect signaalwaarden om potentiële ecotoxicologische risico's op de onderzochte locaties te identificeren. Alle bioassays vertoonden responsen en de effect signaalwaarden werden overschreden in 9 van de 21 toegepaste assays. Hierdoor konden de onderzochte locaties worden gerangschikt op basis van ecotoxicologische risico's. Er werd echter geen verband tussen landgebruik en specifieke ecotoxicologische risico's waargenomen. Op basis van de resultaten werden suggesties voor toekomstige verbeteringen van effectgebaseerde monitoring gegeven, welke vervolgens behandeld werden in de hoofdstukken 3-6. Er werd geconcludeerd dat effectgebaseerde waterkwaliteitsbeoordeling de prioritering van locaties op basis van ecotoxicologische risico's mogelijk maakte, de aanwezigheid van gevaarlijke verbindingen identificeerde, ongeacht hun status als prioritaire stoffen, en tegelijkertijd kostbare chemische analyse kon voorkomen op locaties met lage ecotoxicologische risico's.

Het ontwerp van methoden voor passieve bemonstering (het passive sampler ontwerp) kan de ophoping van stoffen en daarmee de responsen in bioassays beïnvloeden. In **hoofdstuk 3** werden daarom de effecten van de passive sampler behuizing en het sorptiemiddel op bioassay responsen op hydrofiele passive sampler extracten bepaald. Hiertoe werden vier passive sampler configuraties, die het resultaat waren van de combinatie van polaire organische chemische integratieve sampler (POCIS) en Speedisk- behuizingen met hydrofiel-lipofiele balans en hydrofiele divinylbenzeen-sorptiemiddelen, tegelijkertijd blootgesteld op referentie- en verontreinigde oppervlaktewaterlocaties. Om de toxiciteit van de opgehoopte hydrofiele organische stoffen te bepalen, werd een batterij van vijf bioassays aan de extracten blootgesteld. Extracten van POCIS veroorzaakten in 91% van de gevallen hogere bioassay-responsen, terwijl extracten van de twee sorptiemiddelen even frequente, maar verschillende bioassay-responsen veroorzaakten. Het ontwerp van de passive sampler beïnvloedde dus de detectie van toxiciteit van hydrofiele organische verontreinigingen, wat het belang van het maken van actieve keuzes in passieve bemonstering voor een effectgebaseerde waterkwaliteitsbeoordeling benadrukte.

Aangezien fotosynthese een gevoelig proces is dat kan worden toegepast om de aanwezigheid van gevaarlijke herbiciden in oppervlaktewater te identificeren, was het doel van **hoofdstuk 4** om een bioassay voor algenfotosynthese in te zetten om de oppervlaktewatertoxiciteit voor algen te beoordelen en de stoffen te identificeren die de waargenomen effecten veroorzaakten. Hiertoe werd de microalg *Raphidocelis subcapitata* blootgesteld aan oppervlaktewater monsters en werd na 4.5 uur de fotosynthetische efficiëntie bepaald met behulp PAM fluorometrie. In dit snelle bioassay met een hoge monster doorvoercapaciteit werd de fotosynthese van algen beïnvloed door oppervlaktewater van slechts één van de 39 locaties. Toxiciteitstesten met individuele stoffen lieten zien dat het waargenomen effect uitsluitend kon worden toegeschreven aan het herbicide linuron, dat aanwezig was bij een 110 keer hogere concentratie dan de maximaal aanvaardbare concentratie, en dat bovendien niet is opgenomen in de KRW-lijst van prioritaire stoffen. Het toepassen van het algenfotosynthese-bioassay maakte dus een efficiëntere en effectievere beoordeling van de toxiciteit van oppervlaktewater voor primaire producenten mogelijk omdat het: (i) de aanwezigheid van herbiciden identificeert die over het hoofd zouden worden gezien door routinematige chemische KRW monitoring, en (ii) overbodige chemische analyses vermijdt door alleen chemische screening uit te voeren in monsters die daadwerkelijk effecten veroorzaakten.

Kwaliteitsbeoordelingsmethoden voor sedimenten die rekening houden met de risico's die worden veroorzaakt door de gecombineerde werking van alle in het sediment aanwezige verontreinigingen voor organismen die in de waterbodem voorkomen (benthische biota), zijn nog steeds ondervertegenwoordigd in strategieën voor waterkwaliteitsbeoordeling. Het doel van **hoofdstuk 5** was daarom het integreren van effectmetingen en chemische karakteriseringen van sedimentverontreiniging. Daartoe werden 28 dagen durende levenscyclus bioassays met de dansmug *Chironomus riparius* met intacte sedimentkernen van verontreinigde locaties uitgevoerd, in combinatie met exploratieve chemische karakterisering van de biologisch beschikbare concentraties van groepen bekende en nieuwe onbekende sedimentverontreinigingen om zo de ecotoxicologische risico's voor bentische biota te onderzoeken. Alle verontreinigde sedimenten veroorzaakten effecten op de relatief ongevoelige dansmuggen, wat benadrukte dat sedimentverontreiniging alomtegenwoordig is en mogelijk schadelijk is voor aquatische ecosystemen. De bioassay-responsen waren echter niet in overeenstemming met de berekende toxiciteitsindices gebaseerd op aanwezigheid van gemeten stoffen, wat erop wijst dat de toxiciteit werd veroorzaakt door niet-gemeten stoffen. Daarom onderstreepte deze studie de relevantie van effectgebaseerde beoordeling van sedimentkwaliteit en bood deze slimmere manieren om dit te doen.

Er werd verondersteld dat de verfijnde inzichten en methodologische verbeteringen die in de vorige hoofdstukken waren verkregen zouden kunnen bijdragen aan een verbeterde strategie voor de beoordeling van het geaggregeerde risico van alle biologisch beschikbare microverontreinigingen in het aquatisch milieu. **Hoofdstuk 6** beoogde daarom de ontwikkelde methodologische verbeteringen te implementeren in effectgebaseerde waterkwaliteitsbeoordeling en inzicht te krijgen in de bioanalytische reacties op bronspecifieke verontreinigingen. Daartoe werd passieve bemonstering van hydrofobe en hydrofiele organische verbindingen en metalen toegepast op 14 oppervlaktewaterlocaties die werden gekenmerkt door twee belangrijke antropogene verontreinigingsbronnen, landbouw en rioolwaterzuivering (RWZI) effluent, evenals referentielocaties met een verwachte lage impact van microverontreinigingen. Een herziene batterij van 20 bioassays met levende cellen en organismen werd blootgesteld aan de passive sampler-extracten en de bioanalytische responsen werden vergeleken met effect signaalwaarden om potentiële ecotoxicologische risico's te identificeren. De bioanalytische beoordeling van de gezamenlijke risico's van metalen en organische stoffen resulteerde in de succesvolle identificatie van bronspecifieke ecotoxicologische risicoprofielen. De cumulatieve ecotoxicologische risico's waren het laagst voor de referentielocaties, gevolgd door de landbouwlocaties en het hoogst voor de RWZI locaties. Deze risico's werden voornamelijk veroorzaakt door hydrofiele organische verontreinigingen. Er werd geconcludeerd dat de gebruikte geavanceerde effectgebaseerde methoden makkelijk kunnen worden toegepast in de beoordeling van oppervlaktewaterkwaliteit en dat de integratie van chemische en effectgebaseerde monitoring toekomstbestendige waterkwaliteitsbeoordelingsstrategieën mogelijk maakt op de weg naar een niet-giftig milieu.

Discussie en toekomstperspectief

Dit proefschrift heeft de wetenschappelijke basis van effectgebaseerde chemische waterkwaliteitsbeoordeling versterkt door methodologische en theoretische verbeteringen te bieden aan het bestaande onderzoeksgebied. In de **synthese** (**hoofdstuk 7**) werd gepostuleerd dat aan vier specifieke eisen moet worden voldaan om het volledige potentieel van effectgebaseerde waterkwaliteitsbeoordeling te kunnen benutten.

Ten eerste moeten de bemonsteringsmethoden alle relevante verontreinigende stoffen uit het water kunnen opnemen. In het huidige onderzoek werd dit nagestreefd door i) een beter begrip te ontwikkelen van de kenmerken die de opname van verontreinigingen in passive samplers voor hydrofiele stoffen bepalen, ii) verschillende passive samplers tegelijkertijd toe te passen om organische contaminanten met sterk uiteenlopende waterminnendheid op te nemen, iii) de toevoeging van passive samplers om de ecotoxicologische risicobeoordeling van metalen mogelijk te maken, en iv) de uitbreiding van de passieve monsternamestrategie om de extractie van biologisch beschikbare sediment geassocieerde verontreinigingen mogelijk te maken.

Ten tweede moeten de milieumonsters naar de bioassays worden overgebracht als representatieve mengsels bij milieurelevante concentraties. In dit proefschrift werden verschillende methoden toegepast om milieurelevante concentraties te benaderen bij het gebruik van passive sampler extracten in bioassays. Dit benadrukte de beperkingen van de momenteel beschikbare benaderingen, en resulteerde in de aanbeveling om passieve dosering toe te passen om voor het milieu relevante mengsels en concentraties van zowel hydrofobe als hydrofiele organische verontreinigingen in bioassays te verkrijgen.

Ten derde moet een bioassay batterij voorzien in de detectie van alle mogelijke vormen van toxiciteit die relevant zijn voor de gezondheid van aquatische ecosystemen. Daartoe werden criteria gedefinieerd die de relevantie van bioassays voor toepassing in effectgebaseerde waterkwaliteitsbeoordeling bepalen. Deze criteria omvatten de responsiviteit van de bioassays, selectie van eindpunten in een bioassaybatterij en de vroegtijdige diagnosefunctie van bioassays. De toepassing van deze criteria op de bioassays die in het huidige proefschrift zijn toegepast resulteerde in de uitsluiting van verschillende bioassays die niet geschikt bleken voor hun doel en in hun vervanging door relevantere en gevoeliger alternatieven.

Tot slot moeten de gedefinieerde normen voor de interpretatie van bioassay responsen een betrouwbare indicatie van ecotoxicologische risico's in het milieu geven. Daarom werd een nieuwe benadering voorgesteld die de afleiding van effect signaalwaarden verschuift van op stofconcentraties gebaseerde drempels naar ecologische beschermdoelen. Ondanks de bestaande uitdagingen zal de hier gepostuleerde vernieuwde en meer ecologisch relevante aanpak sterk helpen bij het bereiken van het uiteindelijke doel van effect signaalwaarden: het beschermen van natuurlijke populaties van organismen in het aquatisch milieu.

In een ideale toekomst zal de monitoring van de chemische waterkwaliteit leiden tot een alomvattende beoordeling van de 'blootstelling van het natuurlijk aquatisch milieu', waar (semi) continue gelijktijdige biologische en chemische analyses de chemicaliën aan het licht brengen die (gezamenlijk) een bedreiging vormen voor de levende omgeving.

AUTHOR CONTRIBUTIONS

Chapter 1: ML de Baat, MHS Kraak
Drafting the chapter: MLdB and MHSK. Critical revision of the chapter: MHSK. Final approval of the version to be published: all authors.

Chapter 2: ML de Baat, MHS Kraak, R van der Oost, P de Voogt, PFM Verdonschot
Conception of the work: MLdB, MHSK, RvdO and PFMV. Data collection: MLdB. Data analysis and interpretation: MLdB, RvdO and MHSK. Drafting the article: MLdB. Critical revision of the article: MHSK, RvdO, PdV and PFMV. Final approval of the version to be published: all authors.

Chapter 3: ML de Baat, J de Weert, D Giesen, H Beeltje, T Hamers, P de Voogt, MHS Kraak
Conception of the work: MLdB and JdW. Data collection: MLdB, JW and HB. Data analysis and interpretation: MLdB and JdW. Drafting the article: MLdB. Critical revision of the article: JdW, DG, TH, PdV and MHSK. Final approval of the version to be published: all authors.

Chapter 4: ML de Baat, DA Bas, SAM van Beusekom, F van der Meer, M de Vries, PFM Verdonschot, MHS Kraak
Conception of the work: MLdB and MHSK. Data collection: MLdB, DAB, SAMvB, FvdM and MdV. Data analysis and interpretation: MLdB, FvdM and DAB. Drafting the article: MLdB and DAB. Critical revision of the article: SAMvB, PFMV and MHSK. Final approval of the version to be published: all authors.

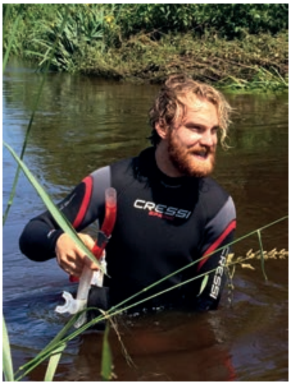
Chapter 5: ML de Baat, N Wieringa, STJ Droge, BG van Hall, F van der Meer, MHS Kraak
Conception of the work: MLdB, NW, STJD and MHSK. Data collection: MLdB, NW, STJD, BGvH and FvdM. Data analysis and interpretation: MLdB, NW, STJD, and BGvH. Drafting the article: MLdB and NW. Critical revision of the article: STJD and MHSK. Final approval of the version to be published: all authors. MLdB and NW contributed equally to this study.

Chapter 6: ML de Baat, R van der Oost, GH van der Lee, N Wieringa, T Hamers, PFM Verdonschot, P de Voogt, MHS Kraak
Conception of the work: MLdB, GHvdL, NW, PFMV and MHSK. Data collection: MLdB, GHvdL and NW. Data analysis and interpretation: MLdB. Drafting the article: MLdB. Critical revision of the article: RvdO, GHvdL, NW, TH, PFMV, PdV and MHSK. Final approval of the version to be published: all authors.

ACKNOWLEDGEMENTS

Pursuing a doctorate is an exciting yet often arduous endeavor. For scientific knowledge, we look to our predecessors, but it is our contemporaries, that offer comfort and guidance, that define our experiences along the way. Not only do I now stand on the shoulders of giants, but, more importantly, throughout this journey, I walked alongside many magnificent friends and colleagues. Without their dedication to me and my project, this book would not be in your hands today. Here, I want to express my sincere gratitude to those who contributed so wholeheartedly to this journey. However, I have come to realize that it would be impossible to mention everyone explicitly, nor will I be able to thank them enough for all they have done. Therefore, I hope to celebrate the finalization of my thesis with each of you personally soon.

CURRICULUM VITAE



Milo Leon de Baat was born on the 4th of February 1989 in Amsterdam, The Netherlands. While pursuing a Bachelor's degree in Biology at the University of Amsterdam (2008-2011), he was introduced to the research field of Aquatic Ecotoxicology under the enthusiastic supervision of Dr. Michiel Kraak. Inspired by several courses on Aquatic Biology, he finalized his undergraduate studies with a thesis on the adaptative mechanisms of non-biting midges to high levels of metal toxicity and solar radiation in high-altitude tropical mountain streams.

After his BSc graduation, he obtained his Open Water SCUBA diving certification in Colombia, which fueled a deeper interest in the underwater world. Growing ever-more passionate about Aquatic Biology and the processes that define life below the surface, he decided to pursue a Master's degree in Limnology and Oceanography at the University of Amsterdam (2012-2014). Jumpstarted by the work he did for his Bachelor's thesis, he initiated his graduate studies with a research project in Peru, where he studied the effects of metal pollution and high altitude on insect species assemblages in the tropical Andes. During his studies, he followed courses on freshwater as well as marine Biology, in tropical and temperate ecosystems. This was followed by his final research project, in which he studied the genetic diversity and toxicity of cyanobacterial mats on the reefs of the Caribbean island of Curaçao.

After his MSc graduation, he went on to further his diving skills and obtained a Rescue Diver certification. This turned out to be a valuable asset when he collaborated as a scientific diver on a research project on the distribution of Queen Conch populations around the Caribbean island of St. Eustatius. It was during this research project that Milo decided that he wanted to pursue a career in which scientific research plays a central role.

At the end of 2015, Milo started his doctoral studies at the Department of Freshwater and Marine Ecology of the University of Amsterdam. The Ph.D. project was supervised by Michiel Kraak, Piet Verdonschot, Ron van der Oost and Pim de Voogt, a supervisory committee with expertise ranging from Aquatic Ecology to Analytical Chemistry. In collaboration with the Dutch water authorities, the project aimed to advance the field of effect-based chemical water quality assessment. This time, the research was conducted in the temperate river delta of The Netherlands. Working in these murky waters came with its own particular set of challenges, but Milo hopes the resulting findings can be transferred to other aquatic ecosystems and contribute to improved chemical water quality assessment around the globe.

LIST OF PUBLICATIONS

De Baat, M. L., Van der Oost, R., Van der Lee, G. H., Wieringa, N., Hamers, T., Verdonschot, P. F. M., De Voogt, P. & Kraak, M. H. S. (2020). Advancements in effect-based surface water quality assessment. *Water Research, 183*, 116017.

De Baat, M. L., Wieringa, N., Droge, S. T., van Hall, B. G., van der Meer, F., & Kraak, M. H. (2019). Smarter Sediment Screening: Effect-Based Quality Assessment, Chemical Profiling, and Risk Identification. *Environmental Science & Technology*, *53*(24), 14479-14488.

De Baat, M. L. & Kraak, M. H. S. (2019). Effect-based water quality assessment. In Van Gestel C. A. M. (Ed.), *Environmental Toxicology, an open online textbook*.

De Baat, M. L., Kraak, M. H. S., Van der Oost, R., De Voogt, P., & Verdonschot, P. F. M. (2019). Effect-based nationwide surface water quality assessment to identify ecotoxicological risks. *Water research*, *159*, 434-443.

De Baat, M. L., Bas, D. A., van Beusekom, S. A. M., Droge, S. T. J., van der Meer, F., de Vries, M., Verdonschot, P. F. M. & Kraak, M. H. S. (2018). Nationwide screening of surface water toxicity to algae. *Science of the Total Environment*, *645*, 780-787.

Verdonschot, P. F. M., Verdonschot, R. C. M., van der Lee, G. H., & **de Baat, M. L.** (2018). Adaptief monitoren: Versterking kennisbasis en verfijning waterbeheer. *Landschap: tijdschrift voor landschapsecologie en milieukunde*, *2018*(1), 58-65.

Van der Meer, T. V., **de Baat, M. L.**, Verdonschot, P. F., & Kraak, M. H. (2017). Benthic invertebrate bioturbation activity determines species specific sensitivity to sediment contamination. *Frontiers in Environmental Science*, *5*, 83.

Loayza-Muro, R. A., **de Baat, M. L.**, Palomino, E. J., Kuperus, P., Kraak, M. H., Admiraal, W., & Breeuwer, J. A. (2014). Metals and altitude drive genetic diversity of chironomids in A ndean streams. *Freshwater Biology*, *59*(1), 56-63.

Loayza-Muro, R. A., Marticorena-Ruiz, J. K., Palomino, E. J., Merritt, C., **De Baat, M. L.**, Van Gemert, M. V., Verweij R. A., Kraak, M. H. S. & Admiraal, W. (2013). Persistence of chironomids in metal polluted Andean high altitude streams: does melanin play a role? *Environmental Science & Technology*, *47*(1), 601-607.

De Baat, M. L., van Gemert, M., Verweij, R. A., Loayza-Muro, R. A., & Kraak, M. H. S. (2012). Combined effects of Cu and UVR on survival and melanin synthesis in Chironomus riparius larvae. In *Proceedings of the Netherlands Entomological Society Meeting* (Vol. 23, pp. 39-48).