Toxicity of active substances to aquatic organisms - examples from aquatics with indication of the most sensitive species

Overview of effects of active substances. The following endpoints from literature studies and the cited assessment reports respectively are freely available. They were submitted and assessed as part of the marketing authorisation application for human medicinal products. (02.2025)

Active substance	Use*	Most sensitive species	Toxicity	Effect concentration	Reference
Analgesics					
Acetylsalicylic acid	VMP, HMP	 Fish	moderate	NOEC = 283 µg/L	Janusinfo.se / Assessment Report Aspirin
Diclofenac	HMP	 Fish; mussels	very high	NOEC = 0.44 µg/L	EU- WFD. Circa (2022)
Ibuprofen	HMP	 Fish	very high	NOEC = 6.88 µg/L	EU- WFD. Circa (2022)
Ketoprofen	HMP, VMP	 Green algae	high	NOEC = 17.8 µg/L	Janusinfo.se / Assessment Report Orudis
Naproxen	HMP	 Water flea	high	NOEC = 32 µg/L	Janusinfo.se / Assessment Report Naprosyn Entero
Paracetamol	HMP, VMP	 Water flea	moderate	NOEC = 100 µg/L	Janusinfo.se / Assessment Report Panocod
Antibiotics					
Amoxicillin (Amoxicillin Penicillin Acid)	VMP, HMP	 Cyanobacteria	very high	NOEC = 0.8 µg/L	Andreozzi et al., 2004
Azithromycin	HMP	 Cyanobacteria	very high	NOEC = 0.019 µg/L	EU- WFD. Circa (2022), Oekotoxzentrum 2015
Clarithromycin	HMP	 Cyanobacteria	very high	E_rC10 = 0.13 µg/L	EU- WFD. Circa (2022), Baumann et al. 2015
Doxycycline	VMP, HMP	 Cyanobacteria	high	NOEC = 22.4 µ/L	Assessment Report Altidox
Erythromycin	VMP, HMP	 Cyanobacteria	very high	E_rC10 = 0.5 µg/L	EU- WFD. Circa (2022)
Oxytetracycline	VMP, HMP	 Cyanobacteria	high	EC50 = 261 µg/L	Assessment Report OXTRA

Sulfadiazine	VMP, HMP		Cyanobacteria	low	NOEC = 2,500 µg/L	Assessment Report Diatrim
Sulfamethoxazole	VMP, HMP		Cyanobacteria	High	NOEC = 59 µg/L	Ferrari et al. 2004
Tetracycline	VMP, HMP	 	Cyanobacteria Green algae	low low	EC50 = 6,200 µg/L EC50 = 3,300 µg/L	González-Pleiter M. et al., 2013
Trimethoprim	VMP, HMP		Cyanobacteria	low	EC50 > 16,700 µg/L	Assessment Report Diatrim
Antidepressants						
Citalopram	HMP		Water flea	moderate	NOEC = 320 µg/L	LANUV 2016
Fluoxetine	HMP		Green algae	very high	NOEC < 0.6 µg/L	Oakes et al. 2010
Oxazepam	HMP		Fish	high	NOEC < 18 µg/L	Brodin et al. 2013
Antiepileptics						
Carbamazepine	HMP		Water flea	very high	NOEC = 2.5 µg/L	Ferrari et al (2004), UQN Dossier
Antiparasitics						
Ivermectin	HMP, VMP		Water flea	very high	48-h-EC50 = 5.7 ng/L = 0.0057 µg/L	Liebig M. et al., 2010
Permethrin	HMP, VMP		Water flea	very high	NOEC = 0.27 ng/L = 0.00027µg/	EU- WFD. Circa (2022)
Endocrine active substances – steroid hormones						
17-Beta Estradiol (E2)	HMP		Fish	very high	NOEC= 0.8 ng/L = 0.00018 µg/L	EU- WFD. Circa (2022)
Dienogest	HMP		Fish	very high	NOEC = 3.51 ng/L = 0.0035 µg/L	Teigeler et al. 2024

Drospirenone	HMP	 Fish	very high	LOEC = 230 ng/L = 0.23 µg/L	Assessment Report Drovelis
Ethinylestradiol (EE2)	HMP	 Fish	very high	NOEC = 0.0016 ng/L = 0.0000016 µg/L	EU- WFD. Circa (2022)
Levonorgestrel	HMP	 Fish	very high	NOEC < 1 ng/L < 0.001 µg/L	Zeilinger et al. 2009
Endocrine active substances – Glucocorticoids					
Beclomethasone	HMP	 Fish	very high	NOEC = 0.13 µg/L	Assessment Report Trimbow
Budesonide	HMP	 Fish	very high	NOEC = 0.032 µg/L	Assessment Report Jorveza
Dexamethasone	HMP, VMP	 Fish	high	NOEC = 10.5 µg/L	Teigeler et al. 2024
Fluticasone furoate	HMP	 Fish	very high	NOEC = 0.29 µg/L	Assessment Report Trelegy Ellipta
Hydrocortisone	HMP	Environmental risk not expected as easily biodegradable.			

HMP– Human Medicinal Product VMP– Veterinary Medicinal Product toxic effect
classification for acute toxicity tests (LC/EC/IC50): < 1 mg/L – very high toxicity; 1-10 mg/L – high toxicity; 10 – 100 mg/L - moderate toxicity; >100 mg/L – low toxicity
classification for chronic toxicity tests (NOEC/EC10): < 10µg/L – very high toxicity; 10 - < 100 µg/L – high toxicity; 100 – 1000 µg/L moderate toxicity; >1000 µg/L – low toxicity

* pharmnet-bund.de (08.2024)

References:

Andreozzi, R.; Caprio, V.; Ciniglia, C.; de Champdoré, M.; Lo Giudice, R.; Marotta, R.; Zuccato E. (2004) Antibiotics in the Environment: Occurrence in Italian STPs, Fate, and Preliminary Assessment on Algal Toxicity of Amoxicillin Environ. Sci. Technol. 2004, 38, 24, 6832–6838. https://pubs.acs.org/doi/10.1021/es049509a

Assessment Report Altidox: Medicines Evaluation Board (2021) Publicly available assessment report for a veterinary medicinal product Altidox 500 mg/g Powder for Use in Drinking Water for Pigs, Chickens and Turkeys (https://db.cbg-meb.nl/pars/v118085.pdf)

Assessment Report DFV Doxivet: Medicines Evaluation Board (2020): Publicly available assessment report for a veterinary medicinal product DFV Doxivet 500mg/ml powder for administration via drinking water for chickens and pigs (https://www.vmd.defra.gov.uk/productinformationdatabase/files/UKPAR_Documents/UKPAR_1983096.PDF)

Assessment Report Drovelis (2021): EMA Assessment report Drovelis Procedure No. EMEA/H/C/005336/0000 (https://www.ema.europa.eu/en/documents/assessment-report/drovelis-epar-public-assessment-report_en.pdf)

Assessment Report Jorveza (2020): EMA Assessment report Jorveza Procedure No. EMEA/H/C/004655/X/0007/G (https://www.ema.europa.eu/en/documents/variation-report/jorveza-004655-x-0007-g-epar-assessment-report-variation_en.pdf)

Assessment Report OXTRA: Health Products Regulatory Authority (2020): Publicly Available Assessment Report for a Veterinary Medicinal Product OXTRA DD 100 mg/ml solution for injection for cattle, sheep, pigs, horses, dogs and cats (https://www.hpra.ie/img/uploaded/swedocuments/Public_AR_VPA10836-010-001_09102020161639.pdf)

Assessment Report Trelegy Ellipta (2018): EMA Assessment report Procedure No. EMEA/H/C/WS1369 (https://www.ema.europa.eu/en/documents/variation-report/trelegy-ellipta-h-c-ws-1369-epar-assessment-report-variation_en.pdf)

Assessment Report Trimbow: EMA (2021) Assessment report Trimbow Procedure No. EMEA/H/C/004257/X/0012 (https://www.ema.europa.eu/en/documents/variation-report/trimbow-h-c-4257-x-0012-epar-assessment-report-extension_en.pdf)

Assessment Report T.S.-sol: Medicines Evaluation Board (2021) Publicly available assessment report for a veterinary medicinal product T.S.-sol 20/100, solution for use in drinking water for pigs and chickens (https://mri.cts-mrp.eu/portal/v1/odata/Document%2856029a7e-002c-ec11-80f8-0050569c593a%29/Download)

Baumann, M., Weiss, K., Maletzki, D., Schüssler, W., Schudoma, D., Kopf, W., & Kühnen, U. (2015). Aquatic toxicity of the macrolide antibiotic clarithromycin and its metabolites. Chemosphere, 120, 192-198. https://doi.org/10.1016/j.chemosphere.2014.05.089

Coors et al., (2017) Joint effects of pharmaceuticals and chemicals regulated under REACH in wastewater treatment plant effluents – Evaluating concepts for a risk assessment by means of experimental scenarios, Umweltbundesamt, UBA Texte | 61/2017. https://doi.org/10.60810/openumwelt-7092

Eguchi, K., Nagase, H., Ozawa, M., Endoh, Y. S., Goto, K., Hirata, K., Miyamoto, K., Yoshimura, H. (2004) Evaluation of antimicrobial agents for veterinary use in the ecotoxicity test using microalgae. Chemosphere, 57(11), 1733-1738. https://doi.org/10.1016/j.chemosphere.2004.07.017

EU- WFD- CIRCA BC: https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/f3f3d157-3099-44a9-8e2e-5ba208ac042c

Fernandez, C.; Alonso, C.; Babin, M. M.; Pro, J.; Carbonell, G.; Tarazona, J. V. (2004) Ecotoxicological assessment of doxycycline in aged pig manure using multispecies soil systems. Sci Total Environ, 323, (1–3), 63–9. https://doi.org/10.1016/j.scitotenv.2003.10.015

Ferrari, B., R. Mons, B. Vollat, B. Fraysse, N. Paxéus, R. Lo Giudice, A. Pollio and J. Garric (2004). Environmental risk assessment of six human pharmaceuticals: are the current environmental risk procedures sufficient for the protection of the aquatic environment. Environmental Toxicology and Chemistry, 23, 1344–1354. https://doi.org/10.1897/03-246

González-Pleiter, M.; Gonzalo, S.; Rodea-Palomares, I.; Leganés, F.; Rosal, R.; Boltes, K.; Marco, E.; Fernández-Piñas, F.(2013) Toxicity of five antibiotics and their mixtures towards photosynthetic aquatic organisms: Implications for environmental risk assessment. Water Research, 47, (6), 2050–2064 https://doi.org/10.1016/j.watres.2013.01.020

Holten Lützhøft, H. C.; Halling-Sørensen, B.; Jørgensen, S. E.(1999) Algal toxicity of antibacterial agents applied in Danish fish farming. Archives of Environmental Contamination and Toxicology, 36, (1), 1–6. https://doi.org/10.1007/s002449900435

Janusinfo.se "Pharmaceuticals and Environment": https://janusinfo.se/beslutsstod/lakemedelochmiljo/pharmaceuticalsandenvironment.4.7b57ecc216251fae47487d9a.html

Kim, Y.; Choi, K.; Jung, J.; Park, S.; Kim, P. G.; Park, J. (2007) Aquatic toxicity of acetaminophen, carbamazepine, cimetidine, diltiazem and six major sulfonamides, and their potential ecological risks in Korea. Environment International, 33, (3), 370–375. https://doi.org/10.1016/j.envint.2006.11.017

LANUV 2016, Anwendung von Stoffpriorisierungsverfahren für Oberflächengewässer Datenrecherche und Einsatz modellierter Daten LANUV-Fachbericht 72 (nrw.de), https://www.lanuv.nrw.de/fileadmin/lanuvpubl/3_fachberichte/Fachbericht 72_web.pdf

Liebig M, Fernandez A A, Blübaum-Gronau E, Boxall A, Brinke M, Carbonell G, Egeler P, …, Duis K (2010): Environmental risk assessment of ivermectin: A case study. Integrated environmental assessment and management, 6 (Suppl. 1): 567–587. https://doi.org/10.1002/ieam.96

Oakes et al. 2010, Environmental risk assessment for the serotonin re-uptake inhibitor fluoxetine: Case study using the European risk assessment framework, Integrated Environmental Assessment and Management 6 Suppl(S1):524-39 https://doi.org/10.1002/ieam.77

Oekotoxzentrum (2015). EQS - Vorschlag des Oekotoxzentrums für: Azithromycin. https://www.oekotoxzentrum.ch/media/lbbddy02/azithromycin-eqs-dossier_stand-2015.pdf

Park, S.; Choi, K. (2008) Hazard assessment of commonly used agricultural antibiotics on aquatic ecosystems. Ecotoxicology 17, 526- 538. https://doi.org/10.1007/s10646-008-0209-x

Teigeler et al. (2024) New-Generation Steroid Hormones, Texte. https://doi.org/10.60810/openumwelt-6129

Zeilinger, J.; Steger-Hartmann, T.; Maser, E.; Goller, S.; Vonk, R.; Lange, R. (2009). "Effects of synthetic gestagens on fish reproduction." Environ Toxicol Chem 28(12): 2663-2670. https://doi.org/10.1897/08-485.1