Electronic Supplementary Material

Consideration of the bioavailability of metal/metalloid species in freshwaters: experiences regarding the implementation of biotic ligand model-based approaches in risk assessment frameworks

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Publications which consider the bioavailability of metals/metalloids species in the aquatic environment

Table S1: BLMs for studying chronic and acute metal toxicity - literature evaluation (period ca. 2000 - 2013).
WQC - water quality criteria; DOC – dissolved organic carbon; DOM – dissolved organic matter

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute expo-sure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Ag nano-particles	*Ceriodaphnia dubia* (freshwater zooplankton)	A	Ca^{2+}, Na^+	DOC	BLM predictions based on the dissolved fraction in nano-silver suspensions were comparable to observed toxicity; application of BLM for hypothesis testing, use of available model	Kennedy et al. (2012)
Ag nano-particles	*Nitrifying bacteria*	A		SO_4^{2-}, S^{2-}, Cl^-, PO_4^{3-}, EDTA	S^- was the only ligand to effectively reduce nanosilver toxicity. BLM was successful in predicting Ag^+ toxicity BUT it was not	Choi et al. (2009)

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					accurate for Ag nanoparticles in wastewater.	
Ag	*Ceriodaphnia dubia* (freshwater zooplankton)	A		DOM	BLM-calculated toxicity could be improved by incorporating specific chemical constituents of DOM.	Kolts et al. (2008)
Ag	*Pseudokirchneriella subcapitata* and *Chlamydomonas reinhardtii* (freshwater algae)	A		Cl^-	BLM able to predict growth inhibition based on the metal intracellular quota in relation to Cl^-, indicating that Ag toxicity was due to cell accumulation rather than surface interaction.	Lee et al. (2005)
Ag	*Oncorhynchus mykiss* (rainbow trout)	A	Ca^{2+}, Na^+, Mg^{2+}	Cl^-	Evidence to support using BLM to predict Ag toxicity; application of BLM for hypothesis testing, use of available model	Morgan and Wood (2004)
Ag	*Oncorhynchus mykiss* (rainbow trout)	A			BLM together with interaction of water chemistry on the physiological condition of the organisms were incorporated into a model to predict survival time for rainbow trout when exposure to Ag.	Paquin et al (2002)
Ag	*Oncorhynchus mykiss* (rainbow trout), Cambarus diogenes (crayfish), Daphnia magna	A	Na^+, K^+		Na^+ uptake rate should be incorporated in BLM to improve its predictability. In the absence of Na^+ uptake rate, body mass may be used as a substitute.	Bianchini et al (2002)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute expo-sure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Ag	*Oncorhynchus mykiss* gill epithelial cells	A	Na^+, K^+, Ca^{2+}	Transepithelia resistance, transepithelial potential, DOC, Cl^-, pH	With the exception of pH response, the *in vitro* BLM behaved qualitatively and quantitatively similar to in vivo BLM; epithelial gill cells may provide a cost-effective alternative.	Zhou et al (2005)
Ag	*Chlamydomonas reinhardtii, Pseudokirchneriella subcapitata*	A		thiosulfate	BLM was used to assess the uptake and toxicity of Ag in the presence of inorganic ligand and thiosulfate. Results suggest that the $Ag(S_2O_3)^-$ complex remains at least partially intact in the intracellular environment, limiting the internal bioavailability of Ag.	Hiriart-Baer et al. (2006)
Ag	*Daphnia magna*	C	Na^+		The key mechanism involved in chronic Ag toxicity is similar to acute toxicity; Na^+ uptake inhibition is the best endpoint; possibility to extend the acute version of BLM to predict chronic toxicity.	Bianchini and Wood (2002)
Ag	*Daphnia magna*	A+C		S^{2-}, water hardness	Both reactive S^{2-} and water hardness must be taken into account in the development of chronic BLM for Ag.	Bianchini and Wood (2008)
Ag	*Daphnia magna*	A	Na^+, K^+		Mechanism of Ag toxicity in *D. magna* was similar to freshwater fish. BLM for rainbow trout achieves the correct sensitivity for daphnids by reducing the saturation of toxic sites needed to cause toxicity.	Bianchini and Wood (2003)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute expo-sure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Ag	*Daphnia magna, D. pulex, Gammarus pulex*	A	Na^+, K^+, Ca^{2+}	Cl^-, organic thiols, thiosulfate	The derived daphnid BLM did not accurately predict *G. pulex* toxicity and had limited success when applied to waters containing organic thiols or thiosulfate.	Bury et al (2002)
Ag	*Acartia tonsa* (copepod)	A	Na^+, K^+, Mg^{2+}, Ca^{2+}	Presence and absence of food; salinities; Cl^-, $SO4^{2-}$, DOC	Acute Ag toxicity was salinity dependent (decreased as salinity increased); dietary intake affected the toxicity. Future BLM needs to incorporate both salinity and food for estuarine and marine conditions for *A. tonsa*.	Pedroso et al. (2007)
Ag	*Penaeus duorarum* (shrimp), *Aplysia californica* (sea hare), *Diadema antillarum* (sea urchin)	A	Na^+, K^+, Ca^{2+}, Mg^{2+}	Cl^-	Ag toxicity did not affect osmotic or ionoregulation at the hemolymph level in marine organisms; toxicity affected water and ion regulation in cellular level in different tissues. BLM for seawater should consider other ligands in addition to gills	Bianchini et al. (2005)
Ag, Cd	*Chlamydomonas reinhardtii, Pseudokirchneriella subcapitata*	A		Cl^-, NO^{3-}, SO_4^{2-}, $S_2O_3^{2-}$	Genreally, BLM performed crediably except in the presence of alanine or thiosulfate and where the metal-sensitive site is present on the outer surface of the target organism	Campbell et al (2002)
Ag, Cu				S^{2-}	The papers argued that S^{2-} species should be accounted for	Bell et al. (2002), Bianchini and Bowles (2002)

Metal(s)/ Metal-loid(s)	Test organism(s)	Chronic/ acute exposure (C/A)	Cations	Other ligands / factors	Notes	Reference
Ag, Cd, Cu, Zn	Marine fish, molluscs and Daphnids	A	Ca^{2+}, Na^{+}		BLM and bioaccumulation kinetics aremerged into a common mechanistic framework for Metal uptake in aquatic organisms, a new aproach is proposed to combine effect of metal chemodynamics, ligand affinity and species characteristics	Veltman et al. (2010)
As	*Corbicula fluminea* (freshwater clam)	A	Ca^{2+}, Na^{+}		Application of BLM and damage assessment model to examine ecophysiological response of *C. Fluminea:* higher As binding in gill biotic ligand at 50% mortality level gives a lower capacity to accumulate bioavailable As	Chen and Liao (2010)
As	*Oreochromis mossambicus (*tilapia*)*				Application of BLM and damage assessment model to develop a toxicokinetic model for As bioavailability	Tsai et al. (2009)
As	*Oreochromis mossambicus* (tilapia)	A			A BLM-based approach to predict both acute and chronic effects of As concentration on tilapia	Chen et al (2009)
Cd	*Chlamydomonas reinhardtii*	C	Fe^{3+}, Mn^{2+}, Ca^{2+}, Zn^{2+}, Co^{2+}	Nitrilotriacetic acid	BLM predicted increase of Ca^{2+} offered protection of Cd toxicity; essential trace metal concentrations may strongly affect the uptake and toxicity of Cd in *C. reinhardtii*; study recommends improvement of Cd BLM	Lavoie et al. (2012a)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute expo-sure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Cd	*Daphnia pulex*	A	Na^+, Mg^{2+}, Ca^{2+}, K^+, H^+	DOC,Cl^-	HydroQual BLM v. 2.2.3 applied to predict acute Cd toxicity; a modified BLM specific for *D. Pulex* was developed to take into account of the moderating effect of Ca and Mg and DOC	Clifford and McGeer (2010)
Cd	*Photobacterium phosphoreum*	A	Ca^{2+}, Mg^{2+}, K^+	pH, complexants (EDTA, commercial DOM, homemade DOMs)	Cd toxicity was enhanced at larger K^+ concentration; a toxicity alleviation by H^+ was observed over the tested pH range of 5.0-9.0; additions of complexants reduced Cd bioavailability; all factors were finally incorporated into a specific BLM for *P. phosphoreum*	Qu et al. (2013)
Cd	*Perca flavescens* (yellow perch), *Oncorhynchus mykiss* (rainbow trout)	A	Ca^{2+}		The acute Cd BLM could not be extended from rainbow trout to yellow perch by adjustments of LA50 values. Ca^{2+} and Cd pre-exposure also affected Cd and Ca bonding in fish gills. Future refinement of the acute Cd BLM was recommended	Niyogi et al. (2004)
Cd	*Oncorhynchus mykiss* (rainbow trout)	A	Ca^{2+}, Mg^{2+}, Na^+,	pH, alkalinity, DOC	A BLM was developed to predict toxicity of Cd in rainbow trout with good accuracy except for high alkalinity and pH	Niyogi et al (2008)
Cd	*Oncorhynchus mykiss* (rainbow trout)	C		Dietary route of exposure	The route of Cd exposure (dietary or water-borne) affected the internal Cd accumulation and branchial Cd uptake. Furture BLM should consider the route of Cd exposure	Szebedinszky et al (2001)

Metal(s)/ Metalloid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Cd, Mn	*Chlamydomonas reinhardtii*	A	Ca^{2+}	pH	Mn and Cd biological internalisation was of first order but maximum transport flux contradicts the BLM (decreased when pH decreased), suggesting non-competitive inhibition of metal uptake by H^+; therefore, the current BLM did not reflect effect of H^+ on Mn and Cd by algae	Francois et al. (2007)
Cd, Pb		A	Ca^{2+}		BLM-based approach to predict Cd/Pb mixture toxicity from the single metal toxicity data	Jho et al. (2011)
Cd+Pb	*Oncorhynchus mykiss* (rainbow trout)	A	Ca^{2+}, H^+, Na^+	NOM	Cd and Pb mixture caused a reduction in metal-gill binding but exacerbated ionic disturbances in soft and moderately acidic waters; the BLM for fish should be re-evaluated in water containing metal mixtures	Birceanu et al. (2008)
Cd, Zn	*Chlamydomonas reinhardtii*	C + A			BLM developed to incorporate the effects of both chemical speciation and physiological regulation of Cd transport system	Lavoie et al. (2012b)
Cd, Zn	*Microcystis aeruginosa*	A + C		EDTA, NTA	Intracellular Cd or Zn was more effective in explaining acute and chronic metal toxicity; BLM may be used to predict Cd or Zn toxivity in *M. aeruginosa*	Zeng et al (2009)

Metal(s)/ Metalloid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Cd, Cu, Pb and Zn			Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}	pH, DOC, SO_4^{2-}	The choice of model (WHAM VI, NICA-Donnan and SHM) that defines metal/organic-matter interactions had little effect on predicted dissolved Cd or Zn speciation and Cd/ or Zn/biotic-ligand concentrations; but the choice influenced the predicted dissolved Cu and Pb speciation and Cu/ or Pb/biotic-ligand concentrations	Balistrieri and Blank (2008)
Cu	*Lampsilis siliquoidea* (freshwater mussels)	C	Na^{+}, K^{+}	-	The US EPA BLM-derived chronic WQC and the hardness-derived WQC both underprotect juvenile *L. siliquoidea*; no further application of BLM approach	Jorge et al. (2013)
Cu	*Lampsilis siliquoidea, Lampsilis fasciola*	A		DOC (8 natural waters)	DOC offered significant protection to mussel larve to Cu toxicity; need to be considered in the BLM	Gillis et al. (2010)
Cu	*Scenedesmus subspicatus* (freshwater alga)	A		EDTA, fulvic acid	Both EDTA and fulvic acid reduced Cu toxicity; Cu toxicity was related to a biotic ligand at algal cell wall. The results suggested BML could be extended to predict the influence of Cu on growth inhibition of alga	Ma et al. (2003)
Cu	*Daphnia magna*	C	-	-	Dietary exposure of Cu it did not affect the predictive capacity of the BLM	De Schamphelaere and Janssen (2004a)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute expo-sure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Cu		A	H^+	Ratio Cu/DOM; binding constants	Compared with the speciation modelVisual MINTEQ; BLM was found to overestimate Cu^{2+} at lower total Cu concentration but underestimate Cu^{2+} at high total concentration	Craven et al. (2012)
Cu	*Daphnia magna*	A	Ca^{2+}, $Mg^{2+,}$ Na^+, K^+, H^+		Results suggested co-toxicity of $CuOH^+$ rather than H^+ competition; a BLM was developed to predict acute Cu toxicity as a function of these water characteristics including $CuOH^+$	De Schamphelaere and Janssen (2002)
Cu	*Daphnia magna*	C	Ca^{2+}, Mg^{2+}, Na^+, H^+	DOC, DOM	A specific absorption coefficient as a DOM quality indicator was incorporated into a BLM to increase accuracy for predicting Cu toxicity	Al-Reasi at al. (2012)
Cu	*Daphnia magna*	A/C	Ca^{2+}, Mg^{2+}, Na^+, H^+		Usage of acute Cu BLM to predict chronic Cu toxicity to *D. magna;* BLM modified by adjusting the accumulation associated with 50% of an effect value	Villavicencio et al. (2011)
Cu	*Daphnia magna*	C	Ca^{2+}, Na^+, H^+	H^+, DOM, water hardness, DOC	All investigated parameters affected the BLM outcome and should be adjusted on base of the study data to improve accuracy of the model	Ryan et al. (2009)
Cu	*Daphnia magna, D. pulex and D. obtuse*	A	Ca^{2+}, Na^+, H^+	DOC	Use of acute Cu BLM with different parameter sets to predict toxicity to daphnids in a range of natural waters in Chile; BLM can be applied to most low-DOC waters; for high-DOC waters, US EPA criteria were overprotective	Villavicencio et al. 2005

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Cu	*Daphnia magna, Mytilus edulis*	A/C			Application of existing Cu BLM to estimate the potential magnitudes and variabilities of bioavailable Cu in fresh surface water from different regions of the world	Van Genderen et al (2008).
Cu	*Hyalella azteca*	A	Ca^{2+},Mg^{2+}, Na^{+}, K^{+}	pH	The developed BLM can be applied to fish and *Daphnia* (with different coefficients)	Borgmann et al. (2005)
Cu	*Oncorhynchus mykiss* (rainbow trout), *O. tshawytscha* (Chinook salmon), *O. kisutch* (coho salmon) and *Pimephale spromelas* (fathered minnows)	A + C			A Cu-olfactory BLM was parameterized by changing the sensitivity parameter in the ionoregulatory-based BLM; US EPA BLM-based WQC for Cu protects against neuro-physiological impairment of these fish but the hardness-based criteria underprotects them	Meyer and Adams (2010)
Cu	Fish	A + C			Considerations for development of a Cu BLM for marine/estuarinewaters; for marine fish intestine should be considered as biotic ligand;the osmotic gradient should also be consideredfor BLM calculations	De Polo and Scrimshaw (2012)
Cu	*Oncorhynchus mykiss* (rainbow trout)	A + C	Ca^{2+}, Mg^{2+}, H^{+}	Soft water	BLM did not adequately predict Cu toxicity to trout in soft water	Ng et al. (2010)
Cu	*Oncorhynchus mykiss* (rainbow trout)	A	Ca^{2+}, Na^{+}, Mg^{2+}, K^{+}	NOM (3 different sources and quality)	BLM consistently underestimated Cu-gill binding; the data suggested variability in toxicity was due to direction actions of NOM on gills which were quality dependent	Gheorghiu et al. (2010)

Metal(s)/ Metalloid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Cu	*Pimephales promelas* (fathead minnows)	A			BLM was combined with a one-compartment uptake-depuration model to predict the acute toxicity of continuous and pulse exposure of Cu to fathead minnows	Meyer et al. (2007)
Cu	*Perca flavescens* (yellow perch), *Oncorhynchus mykiss* (rainbow trout)	A			The BLM could not be extended from rainbow trout to yellow perch; future refinement of the acute Cu BLM for each species was recommended	Pyle and Wood (2008)
Cu	*Pimephales promelas* (fathead minnows), Daphnia	A	Ca^{2+}	NOM, water hardness	A Cu BLM was developed to calculate LC50 which compared well with published data	Santore et al. (2001)
Cu	*Cnesterodon decemmaculatus* (ten-spotted live-bearing fish)	A	Na^{+}, Ca^{2+}, Mg^{2+}	SO_4^{2-}, Cl^{-}	A higher protective effect of Ca, Mg, Na, sulfate and chloride is expected during the dry season; across-fish-species extrapolation of BLM was feasible	Casares et al. (2012)
Cu	*Fundulus heteroclitus* (killifish)	A+C		Salinity	The gills accumulated more Cu at lower salinities but the intestine accumulated more at higher salinities; seawater BLM should consider potential target tissues in addition to gills	Blanchard and Grosell (2005)
Cu	*Acartiatonsa* (copepods)	A		Presence and absence of food and salinity	High salinity (30 parts per thousand, ppt) reduced Cu toxicity; availability of food exerted an important positive impact in protection against Cu toxicity; future BLM needs to incorporate both salinity and food for	Leaes Pinho and Bianchini (2010)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
					Cu toxicity in estuarine and marine waters; *A. tonsa*seems seems to be a suitable model species for saltwater BLM	
Cu	*Acartia tonsa* (euryhaline copepod)	A		DOM	Both salinity (30 ppt) and DOM should be taken into account in the development of an estuarine version of the BLM	Rodrigues Monteiro et al. (2013)
Cu	*Lemna aequinoctialis*	A	Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}	Cl^{-}, SO_4^{2-}, pH DOM	The BLM approach can be used to accurately predict short-term metal toxicity to *L. aequinoctialis* as a function of water quality characteristics	Shoji (2008)
Cu	*Ceriodaphnia dubia*	C	Ca^{2+}, Na^{+}	pH, natural organic matter (NOM)	BLM developed and validated to predict Cu toxicity to *C. dubia* includes the effect of pH and NOM complexation	Schwartz and Vigneault (2007)
Cu		C	Mg^{2+}, Ca^{2+}, Na^{+}, K^{+}	Alkalinity, SO_4^{2-}, Cl^{-}	Simplification of the input requirements of the Cu BLM is proposed by estimating the concentrations of the major ions	Peters et al. (2011a)
Cu	Cladoceran species (4 different families and 11 different genera)	A		Acidity, water chemistry and water types	Bioavailability is more important thaninter-community difference in determining the variability of Cu toxicity across different aquatic systems. BLM was a generally valuable tool but more work was required for acidic surface water	Bossuyt et al. (2004)

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Cu	Cladoceran	A	Na^+		Increased Na (up to 4mM) protected against Cu toxicity; results suggested processes other than Cu-Na competition at a single biotic ligand site was involved in Cu utoxicity. The data could be used to refine the BLM	De Schamphelaere et al. (2007)
Cu	*Ceriodaphnia dubia*,*Daphnia pulex* and *Pimephales promelas*	A	Ca^{2+}, Mg^{2+}, Na^+, H^+	Very hard surface water; DOC	BLM suitable to determine Cu toxicity in hard surface water; BLM generates appropriate criteria compared to the hardness-based equation or water-effect ratio approach	Van Genderen et al. (2007)
Cu	*Mytilus* sp.	C	Mg^{2+}, Ca^{2+}, Na^+, K^+, $^-$	Cl^-, SO_4^{2-}	BLM suitable to predict Cu toxicity in marine and estuarine environment	Arnold et al. (2005)
Cu	*Villosa iris (*unionid mussel*), Ceriodaphnia dubia, Lamsilis siliquidea*	A+C		DOC	Cu AWQC might not adequately protect the mussel from acute and chronic Cu exposure and cladoceran from chronic exposure	Wang et al (2011); Wang et al. (2009)
Cu	*Corbicula fluminea* (freshwater clam)	A			Cu binds to clam gills; Cu-BLM for – *Corbicula*can be used to describe Cu toxicity	Liao et al. (2007a)
Cu	*Corbicula fluminea*		Na^+		A mechanistic model (flux-biological response) based on BLM and Michaelis-Menten kinetics to link between valve closure behaviour and Na transport in response to waterborne Cu; a possible basis for a new biomonitoring tool	Liao et al. (2007b)

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Cu	*Callinectes sapidus* (blue crab) cell line				Results support that Cu toxicity was driven by Cu accumulation in the biotic ligand (gill cells); these cells can be used as a model to develop an in vitro BLM for marine condition	Paganini and Bianchini (2009)
Cu				NOM, wastewater organic matter, S2-	Experimental Cu complexation was compared to WHAM (VI); WHAM did not reflect the Cu binding with wastewater organic matter, possibly due to the presence of nonhumic macromolecules. Future BLM should also consider alternative ligands to humic acid	Sarathy and Allen (2005).
Cu, Al				DOM, Al^{3+}	Using WHAM VI to determine the effect of DOM and Al^{3+} on Cu activity; DOM quality was an important variable and should be included in WHAM VI and BLM	Chappaz and Curtis (2013)
Cu, Cd	*Lemna paucicostata* (duck weed)	A			Toxic Unit (TU) was derived using BLM, can estimate combined toxicity of Cu and Cd	Hatano and Shoji (2008)
Cu, Ni	*Pimephales promelas (fathead minnows)*	A		Water hardness	BLM predicts acute Cu toxicity than free-ion activity for Ni or Cu in fathead minnows	Meyer et al. (1999)
Cu, Pb	*Chlamydomonas reinhardtii*	A			At high concentration (>1mM), Cu inhibits Pb transport; at low concentration, Cu had a synergistic effect on Pb uptake which confounded the BLM; bioaccumulation appeared to be much more dynamic than assumed in the equilibrium models	Chen et al. (2010)

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Cu, Zn	*Chlorella* sp. (freshwater alga)	A	Ca^{2+}	pH	Results support the use of BLM; metal binding sites on cell surface may be a candidate as biotic ligand for a chronic BLM with microalgae	Wilde et al. (2006)
Cu, Cd, Co	*Lemna paucicostata*, *Daphnia magna*, *Oncorhynchus mykiss* (rainbow trout)	A		Exposure time	A BLM incorporating time dependency of toxicity was developed to predict toxicity of Cu, Cd and Co	Hatano and Shoji (2010)
Cu, Cd, Zn	*Oncorhynchus mykiss* (rainbow trout)	C/A			A meta-analysis of literature data of the toxicity these metals on rainbow trout using a modified BLM (incorporating proportion of non-metal binding ligand)	Kamo and Nagai (2008)
Cu, Cd, Zn	*Oncorhynchus mykiss* (rainbow trout)	C/A	Na^+, Ca^{2+}, Mg^{2+}, H^+	OH^-, Cl^-, CO_3^{2-} DOM	A meta analysis of literature data showing impact of chronic acclimation to waterborne factors, dietary composition on gill metal-binding characteristics; a more integrative approach was recommended	Niyogi and Wood (2003)
Cu, Ni, Zn		C		DOC, DOC and pH, or DOC, pH and Mg^{2+}, Ca^{2+} or Na^+	BLM simplified to linear equations with an acceptable level of accuracy, requiring a maximum of three measured water chemistry parameters	Verschoor et al. (2012b)

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Cu, Ni, Zn					BLM was used to calculate average toxicity in a new method for calculating comparative toxicity of Cu, Ni and Zn in fresh water for Life Cycle Impact Analysis	Gandhi et al. (2010)
Cu, Ni, Zn	*Daphnia magna* *Gammarus roeseli*	C	Ca^{2+}, Mg^{2+}, H^+	DOC	Relations between bioaccumulation and fractional occupancy of the Biotic Ligand were investigated for two aquatic species under ambient field conditions	Verschoor et al. (2012a)
Hg	*Oncorhynchus mykiss* (rainbow trout)		Ca^{2+}, K^+	Cl^-, EDTA, NTA, ethylenediamine, cysteine, NOM	The study examined physiologically regulated Hg uptake from passive up take by rainbow trout; Hg has high $K_{Hg\text{-}gill}$ which suggests it was a suitable candidate for creating a BLM for inorganic Hg and fish	Klinck et al. (2005)
Mn	Fish, invertebrates and algae	C	Ca^{2+}, Mg^{2+}, H^+	DOC	Ca protects fish and invertebrates, Mg also protects invertebrates, and H^+ algae; DOC had very little effect on toxicity of Mn^{2+}	Peters et al. (2011b)
Ni	*Lymnaea stagnalis* (snail), *Chironomus tentans* and *Brachionus calyciflorus* (rotifer);*Lemna minor*	C	Ca^{2+}, Mg^{2+}, H^+	DOC	BLM for *Daphnia magna, Ceriodaphnia dubia* was used to predict Ni toxicity to invertebrates; BLM for *Pseudokirchneriella subcapitata* and *Hordeum vulgare* to predict Ni toxicity to *L. minor*	Schlekat et al. (2010)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Ni	*Chironomus riparius, Lymnaea stagnalis, Lumbriculus variegatus and Daphnia pulex*	A	Ca^{2+}		Bioaccumulation and acute toxicity was tested; water hardness was protective against acute Ni toxicity; higher water hardness significantly reduced Ni bioaccumulation	Leonard and Wood (2013)
Ni	*Pseudokirchnerielia subcapitata*	A	Ca^{2+} Mg^{2+}	Water hardness	Mg and not Ca protected the alga against Ni toxicity; log K(Mg-BL) was identical for soft and hard waters; it was suggested that a single bioavailability model could be used to predict Ni toxicity in both soft and hard surface waters	Deleebeeck et al. (2009a, 2009b)
Ni	*Chlamydomonas reinhardtii*	A	H^+, Mg^{2+}, Ca^{2+}, Al^{3+}, Cu^{2+}, Zn^{2+}		Ni internalisation fluxes were linked to H^+, Mg^{2+}, Al^{3+}, Cu^{2+} and Zn^{2+}; results will contribute towards improving predictability of BLM on the stability constants of these metals	Worms and Wilkinson (2007).
Ni	*Lemna minor L.*		Ca^{2+}, Mg^{2+}, Na^+, K^+	SO_4^{2-}, Cl^-, NO_3^-	Total dissolved Ni concentration and free Ni ion activity was determined and Ni accumulation kinetics was explored; major cations did not inhibit Ni accumulation via competitive inhibition as expected by the BLM	Gopalapillai et al. 2013
Ni	*Daphnia pulex*	A	Ca^{2+}, Mg^{2+}, Na^+, K^+, H^+	Natural organic matter, Cl^-	A BLM was developed for *D. pulex* in soft water to predict Ni toxicity over a wide range; Na, K and Cl did not influence the toxicity response	Kozlova et al. (2009)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute expo-sure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Ni	*Daphnia magna*	A		Sediments	Addition of humate attenuated Ni toxicity; organic ligands and suspended solids should be incorporated into BLM	Cloran et al. (2010)
Ni	*Daphnia magna*	A	Ca^{2+}. Mg^{2+}, Na^{+}	pH	A modified BLM (exclude log K(Na-BL), include log K(Mg-BL) and log K(Ca-BL) offered better prediction of Ni toxicity; the effect of pH required further research	Deleebeeck et al. (2008)
Ni	*Daphnia magna*	C	Ca^{2+}, Mg^{2+}	pH, DOC	DOC protected *D. magna* against chronic Ni toxicity; BLM was optimised to correct the overestimation in natural waters	Deleebeeck et al. (2008)
Ni	*Pimephales promelas*(fathead minnows)	A	Ca^{2+}, H^{+}	pH, NOM	Ni toxicity was inversely related to water hardness; the effect of pH was confounded by hardness and the presence of NOM; the BLM was not accurate at the extreme ends of pH; it may need to consider $NiCO_3$ to be bioavailable to improve its accuracy	Hoang et al. (2004)
Ni	*Oncorhynchus mykiss* (rainbow trout)	C	Ca^{2+}, Mg^{2+}	pH	The developed BLM was promising but need to take into account of the effect of pH and the mechanisms to modified Ni toxicity by Ca^{2+}, Mg^{2+} and pH need to be further explored	Deleebeeck et al. (2007)

Metal(s)/ Metalloid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Pb	*Pimephales promelas* (fathead minnows), *Ceriodaphnia dubia* (daphnids)	A	Ca^{2+}	Water hardness, DOC (humic acid), alkalinity ($NaHCO_3$)	Ca^{2+} protected acute Pb toxicity to *P. promelas* but not to *C. dubia*; DOC and alkalinity offered stronger protection to *P. promelas.* Cross-species BLM was not recommended for *P. promelas* and *C. dubia*	Mager et al. (2011a)
Pb	*Ceriodaphnia dubia* (cladoceran), *Lymnaea stagnalis* (snail) and *Philodina rapida* (rotifer)	C	Ca^{2+}, H^+	DOC and total CO_2	Analysed using multi-linear regression analysis; cross-species modelling of invertebrate chronic Pb toxicity using *C. dubia* seems inappropriate	Esbaugh et al. (2012)
Pb	*Ceriodaphnia dubia*	C		Water hardness, DOM, NOM, DOC (humic acid), pH, alkalinity ($NaHCO_3$)	Hardness did not protect against chronic Pb toxicity; HA and increased alkalinity offered protection but low pH increased the toxicity. A chronic Pb BLM as an alternative approach to hardness-based regulation was recommended	Mager et al (2011b)
Pb	*Pimephales promelas* (fathead minnows)	C		Water hardness, DOC (humic acid)	Only DOC offered protection again Pb accumulation and changes of mRNA expression. Data helped to develop a new chronic Pb BLM for future environmental monitoring and regulatory strategies	Mager et al. (2008).
Sc	*Chlamydomonas reinhardtii*	A	H^+	pH	BLM can be used to predict trivalent ion (e.g. Sc) at pH below 6.5 but not above due to transmembrane transport of undissociated Sc hydroxo-complexes	Cremazy et al. (2013)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Tl	*Chlorella sp., Synechococcus leopoliensis, Brachionus calyciflorus*	A	K^+, Na^+, Mg^{2+}, Ca^{2+}	Trace metals (Cu, Co, Mo, Mn, Fe and Zn)	BLM successfully predicted the competitive interaction between Tl^+ and K^+; similar amount of K also suppressed toxicity to *S. leopoliensis* and *B. calyciflorus*; absence of trace metals increases Tl uptake and decreased the effect of K^+. K^+ should be considered in predicting biogeochemical fate of Tl in the aquatic environment	Hassler et al. (2007)
Zn	*Fundulus heteroclitus* and *Kryptolebias marmoratus* (killifish)	A	Ca^{2+}	Salinity (estuarine and marine systems)	Zn toxicity decreases as salinity increases	Bielmyer et al. (2012)
Zn		A + C	Ca^{2+}, Mg^{2+}, Na^+, H^+		Proposal of a unified BLM that can predict both acute and chronic toxicity over a range of Zn bioavailabilities	DeForest and Van Genderen (2012)
Zn	*Lymnaea stagnalis* (snail), *Brachionus calyciflorus* (rotifer)	C	Ca^{2+}, H^+	DOC	Chronic Zn model developedfor *Daphnia magna*was used to predict bioavailability of Zn in the mollusc *L. stagnalis* and the rotifer *B. calyciflorus*	De Schamphelaere and Janssen (2010)
Zn	*Oncorhynchus mykiss* (rainbow trout), *Pimephales promelas (fathead minnows), Daphnia magna*	A	Na^+. Mg^{2+}, Ca^{2+},	OH^-, Cl^-, pH, water hardness	Development and application of a Zn BLM; the BLM described well the Zn complexation and Zn-H^+ competition	Santore et al. (2002).

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Zn	*Daphnia pulex*	A	Ca^{2+}, Na^{+}, Mg^{2+}, K^{+}, H^{+}	DOC, soft water	Zn BLM was modified to predict acute Zn toxicity on *D. pulex* in soft water; increasing concentrations of DOC or Ca^{2+} (and Mg^{2+} to a lesser degree) had a protective effect	Clifford and McGeer (2009)
Zn	*Daphnia magna*	C	Ca^{2+}, Na^{+}, Mg^{2+},H^{+}		BLM developed to predict chronic Zn toxicity for *D. magna*	Heijerick et al. (2005)
Zn	*Daphnia magna*	A/C			Application of existing Zn BLM to estimate the potential magnitudes and variability of bioavailable Zn in fresh surface water from different regions of the world	Van Genderen et al (2009).
Zn	*Daphnia magna*	A	Ca^{2+}, Na^{+}, Mg^{2+}, K^{+}, H^{+}	Water hardness, DOC	K^{+} and H^{+} did not significantly affect Zn toxicity; BLM developed and validated using 17 media and various pH, water hardness and DOC	Heijerick et al. (2002b)
Zn	*Oncorhynchus mykiss*	C	Ca^{2+}, Na^{+}, Mg^{2+}, H^{+}		The developed BLM predicts chronic effect concentrations with an error of less than a factor of 2 in most cases	De Schamphelaere and Janssen (2004b)
Zn	*Pimephales promelas (fathead minnows)*	A	Ca^{2+}, Mg^{2+}, Na^{+}	DOM, DOC, Cl-	BLM over predicted Zn toxicity in water containing <1 mg DOC/L; the current composite-species BLM for Zn for fathead minnows should be modified	Bringolf et al. (2006)

Metal(s)/ Metal-loid(s)	**Test organism(s)**	**Chronic/ acute exposure (C/A)**	**Cations**	**Other ligands / factors**	**Notes**	**Reference**
Zn	*Pseudokirchneriella subcapitata*	A	Ca^{2+}, Na^{+}, Mg^{2+},H^{+}		BLM can be used to predict Zn toxicity in the green alga but need to take into consideration pH and effects of test medium	Heijerick et al (2002a)
U	*Ceratophyllum demersum* (freshwater macrophyte)	A	Ca^{2+}, Mg^{2+}		U toxicity is hardness dependent; this finding should be used in guidelines in absence of a U specific BLM	Markich (2013)
U	*Chlamydomonas reinhardtii*	A	Ca^{2+}	CO_3^{2-}, PO_4^{3-}, OH^-, NOM, EDTA	No evidence for the transport of intact UO_2^{2+} complexes. BLM was used to correlate the free UO_2^{2+} ion concentration and U uptake	Fortin et al (2004)

References for Table S1:

Al-Reasi, HA; Smith, DS; Wood, CM (2012) Evaluating the ameliorative effect of natural dissolved organic matter (DOM) quality on copper toxicity to *Daphnia magna*: improving the BLM. Ecotoxicology, 21, 524-37. 10.1007/s10646-011-0813-z.

Arnold, WR; Santore, RC; Cotsifas, S (2005) Predicting copper toxicity in estuarine and marine waters using the Biotic Ligand Model. Marine Pollution Bulletin, 50, 1634-40. 10.1016/j.marpolbul.2005.06.035.

Balistrieri, LS; Blank, RG (2008) Dissolved and labile concentrations of Cd, Cu, Pb, and Zn in the South Fork Coeur d'Alene River, Idaho: Comparisons among chemical equilibrium models and implications for biotic ligand models. Applied Geochemistry, 23, 3355-3371. 10.1016/j.apgeochem.2008.06.031.

Bell, RA; Ogden, N; Kramer, JR (2002) The biotic ligand model and a cellular approach to class B metal aquatic toxicity. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 175- 188. 10.1016/S1532-0456(02)00109-6.

Bianchini, A; Playle, RC; Wood, CM; Walsh, PJ (2005) Mechanism of acute silver toxicity in marine invertebrates. Aquatic Toxicology, 72, 67-82. 10.1016/j.aquatox.2004.11.012.

Bianchini, A; Wood, CM (2003) Mechanism of acute silver toxicity in Daphnia magna. Environmental Toxicology and Chemistry, 22, 1351-1367. 10.1897/1551-5028(2003)022<1361:MOASTI>2.0.CO;2.

Bianchini, Adatto; Wood, Chris M. (2008) Does sulfide or water hardness protect against chronic silver toxicity in *Daphnia magna*? A critical assessment of the acute-to-chronic toxicity ratio for silver. Ecotoxicology and Environmental Safety, 71, 32-40. 10.1016/j.ecoenv.2008.03.006

Bianchini, A; Wood, CM (2002) Physiological effects of chronic silver exposure in *Daphnia Magana*. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 137-145. 10.1016/S1532-0456(02)00088-1.

Bianchini, A; Bowles, KC (2002) Metal sulfides in oxygenated aquatic systems: implications for the biotic ligand model. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 51-64. 10.1016/S1532-0456(02)00073-X.

Bianchini, A; Grosell, M; Gregory, SM; Wood, CM (2002) Acute silver toxicity in aquatic animals is a function of sodium uptake rate. Environmental Science and Technology, 36-1763-1766. 10.1021/es011028t.

Bielmyer, GK; Bullington, JB; DeCarlo, CA; Chalk, SJ; Smith, K (2012) The Effects of Salinity on Acute Toxicity of Zinc to Two Euryhaline Species of Fish, *Fundulus heteroclitus* and *Kryptolebias marmoratus*. Integrative and Comparative Biology, 52, 753-60. 10.1093/icb/ics045.

Birceanu, O; Chowdhury, MJ; Gillis, PL; McGeer, JC; Wood, CM; Wilkie, MP (2008) Modes of metal toxicity and impaired branchial ionoregulation in rainbow trout exposed to mixtures of Pb and Cd in soft water. Aquatic Toxicology, 89, 222-231. 10.1016/j.aquatox.2008.07.007.

Blanchard, J; Grosell, M (2005) Effects of salinity on copper accumulation in the common killifish (*Fundulus heteroclitus*). Environmental Toxicology and Chemistry, 24, 1403-1413. 10.1897/04-373R.1.

Borgmann, U; Nowierski, M; Dixon, DG (2005) Effect of major ions on the toxicity of copper to *Hyalella azteca* and implications for the biotic ligand model. Aquatic Toxicology, 73, 268-87. 10.1016/j.aquatox.2005.03.017.

Bossuyt, BTA; De Schamphelaere, KAC; Janssen, CR (2004) Using the biotic ligand model for predicting the acute sensitivity of Cladoceran dominated communites to copper in natural surface waters. Environmental Science and Technology, 38, 5030-5037. 10.1021/es049907d.

Bringolf, RB ; Morris, BA; Boese, CJ; Santore, RC; Allen, HE; Meyer, JS (2006). Influence of dissolved organic matter on acute toxicity of zinc to larval fathead minnows (*Pimephales promelas*). Archives of Environmental Contamination and Toxicology, 51, 438-444. 10.1007/s00244-005-0088-6.

Bury, NR; Shaw, J; Glover, C; Flogstrand, C (2002) Derivation of a toxicity-based model to predict how water chemistry influences silver toxicity to invertebrates.Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 259-270. 10.1016/S1532-0456(02)00096-0.

Campbell, PGC; Errecalde, O; Fortin, C; Hiriart-Baer, WR; Vigneault, B (2002) Metal bioavailability to phytoplankton - applicability of the biotic ligand model. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 189-206. 10.1016/S1532-0456(02)00104-7.

Casares, MV; de Cabo, LI; Seoane, RS; Natale, OE; Castro Rios, M; Weigandt, C; de Iorio, AF (2012) Measured Copper Toxicity to Cnesterodon decemmaculatus (Pisces: Poeciliidae) and Predicted by Biotic Ligand Model in Pilcomayo River Water: A Step for a Cross-Fish-Species Extrapolation. Journal of Toxicology, 2012, 849315. 10.1155/2012/849315.

Chappaz A, Curtis PJ (2013) Integrating empirically disoolved organic matter quality for WHAM VI using the DOM optical properties: a case stidu pf Cu-Al-DOM interactioins. Environmental Science and Technology, 47, 2001-2007. 10.1021/es3022045.

Chen, B; Chen, W; Liao, C (2009) A biotic ligand model-based toxicodynamic approach to predict arsenic toxicity to tilapia gills in cultural ponds. Ecotoxicology, 18, 377-383. 10.1007/s10646-008-0292-z.

Chen, W; Liao, C (2010) Dynamic features of ecophysiological response of freshwater clam to arsenic revealed by BLM-based toxicological model. Ecotoxicology, 19, 1074-83. 10.1007/s10646-010-0489-9.

Chen, Zi; Zhu, L; Wilkinson, KJ (2010) Validation of the Biotic Ligand Model in Metal Mixtures: Bioaccumulation of Lead and Copper. Environmental Science and Technology, 44, 3586-3586. 10.1021/es1003457.

Choi, O; Cleuenger, TE; Deng, B; Surampalli, RY; Ross, L; Hu, Z (2009) Role of sulfide and ligand strength in controlling nanosilver toxicity. Water Research, 43, 1879-1886. 10.1016/j.watres.2009.01.029.

Clifford, M; McGeer, JC (2010) Development of a biotic ligand model to predict the acute toxicity of cadmium to *Daphnia pulex*. Aquatic Toxicology, 98, 1-7. 10.1016/j.aquatox.2010.01.001.

Clifford, M; McGeer, JC (2009) Development of a biotic ligand model for the acute toxicity of zinc to *Daphnia pulex* in soft waters. Aquatic Toxicology, 91, 26-32. 10.1016/j.aquatox.2008.09.016.

Craven, AM; Aiken, GR; Ryan, JN (2012). Copper(II) Binding by Dissolved Organic Matter: Importance of the Copper-to-Dissolved Organic Matter Ratio and Implications for the Biotic Ligand Model. Environmental Science and Technology, 46, 9948-55. 10.1021/es301015p.

Cremazy, A; Campbell, PG C; Fortin, C (2013) The Biotic Ligand Model Can Successfully Predict the Uptake of a Trivalent Ion by a Unicellular Alga Below pH 6.50 but not Above: Possible Role of Hydroxo-Species. Environmental Science and Technology, 47, 2408-2415. 10.1021/es3038388.

de Polo, A; Scrimshaw, MD (2012) Challenges for the development of a biotic ligand model predicting copper toxicity in estuaries and seas. Environmental Toxicology and Chemistry, 31, 230-8.   10.1002/etc.1705.

De Schamphelaere, KAC; Janssen, CR (2010) Cross-phylum extrapolation of the *Daphnia magna* chronic biotic ligand model for zinc to the snail *Lymnaea stagnalis* and the rotifer *Brachionus calyciflorus*. Science of the Total Environment, 408, 5414-5422.   10.1016/j.scitotenv.2010.07.043.

De Schamphelaere, KAC; Bossuyt, BTA; Janssen, CR (2007) Variability of the protective effect of sodium on the acute toxicity of copper to freshwater cladocerans. Environmental Toxicology and Chemistry, 26, 535-542.   10.1897/06-247R.1.

De Schamphelaere, KAC; Janssen, CR (2004a) Effects of chronic dietary copper exposure on growth and reproduction of *Daphnia magna*. Environmental Toxicology and Chemistry, 23, 2038-2047. 10.1897/03-411.

De Schamphelaere, KAC; Janssen, CR (2004b) Bioavailability and chronic toxicity of zinc to juvenile rainbow trout (*Oncorhynchus mykiss*): Comparison with other fish species and development of a biotic ligand model. Environmental Science and Technology, 38, 6201-9. 10.1021/es049720m.

De Schamphelaere, KAC; Janssen, CR (2002) A biotic ligand model predicting acute copper toxicity for *Daphnia magna*: The effects of calcium, magnesium, sodium, potassium and pH. Environmental Science and Technology, 36, 48-54.   10.1021/es000253s.

DeForest, DK;Van Genderen, EJ (2012) Application of U.S. EPA guidelines in a bioavailability-based assessment of ambient water quality criteria for zinc in freshwater. Environmental Toxicology and Chemistry, 31, 1264-72.   10.1002/etc.1810.

Deleebeeck, NME; De Laender, ; Chepurnov, VA; Vyverman, W; Janssen, CR; De Schamphelaere KA C (2009a) A single bioavailability model can accurately predict Ni toxicity to green microalgae in soft and hard surface waters. Water Research, 43, 1935-1947.   10.1016/j.watres.2009.01.019.

Deleebeeck, NME; De Schamphelaere, KAC; Janssen, CR (2009b) Effects of Mg2+ and H+ on the toxicity of Ni^{2+} to the unicellular green alga *Pseudokirchneriella subcapitata*: Model development and validation with surface waters. Science of the Total Environment, 407, 1901-1914. 10.1016/j.scitotenv.2008.11.052.

Deleebeeck, Nele M. E.; De Schamphelaere, Karel A. C.; Janssen, Colin R. (2008a) A novel method for predicting chronic nickel bioavailability and toxicity to *Daphnia magna* in artificial and natural waters. Environmental Toxicology and Chemistry, 27, 2097-2107. 10.1897/07-579.1.

Deleebeeck, NME.; De Schamphelaere, KAC; Heijerick, DG; Bossuyt, BTA; Janssen, CR (2008b) The acute toxicity of nickel to *Daphnia magna*: Predictive capacity of bioavailability models in artificial and natural waters. Ecotoxicology and Environmental Safety, 70, 67-78.   10.1016/j.ecoenv.2007.05.002.

Deleebeeck, NME; De Schamphelaere, KAC; Janssen, CR (2007) A bioavailability model predicting the toxicity of nickel to rainbow trout (*Oncorhynchus mykiss*) and fathead minnow (*Pimephales promelas*) in synthetic and natural waters. Ecotoxicology and Environmental Safety, 67, 1-13. 10.1016/j.ecoenv.2006.10.001.

Esbaugh, AJ; Brix, KV; Mager, EM; De Schamphelaere, K; Grosell, M (2012) Multi-linear regression analysis, preliminary biotic ligand modeling, and cross species comparison of the effects of water chemistry on chronic lead toxicity in invertebrates. Comparative Biochemistry and Physiology C – Toxicology and Pharmacology, 155, 423-31. 10.1016/j.cbpc.2011.11.005.

Fortin, C; Dutel, L; Garnier-Laplace, J (2004) Uranium complexation and uptake by a green alga in relation to chemical speciation: The importance of the free uranyl ion. Environmental Toxicology and Chemistry, 23, 974-981. 10.1897/03-90.

Francois, L; Fortin C; Campbell PGC (2007) pH modulates transport rates of manganese and cadmium in the green alga *Chlamydomonas reinhardtii* through non-competitive interactions: implicatios for an algal BLM. Aquatic Toxicology, 84, 123-132. 10.1016/j.aquatix.2007.02.019.

Gandhi, N; Diamond, ML;Huijbregts, MAJ ;Guinee, JB; Peijnenburg, WJGM; van de Meent, D (2010) Implications of considering metal bioavailability in estimates of freshwater ecotoxicity: examination of two case studies. INTERNATIONAL JOURNAL OF LIFE CYCLE ASSESSMENT, 16, 774-787. 10.1007/s11367-011-0317-3.

Gheorghiu, C; Smith, D S; Al-Reasi, HA; McGeer, JC; Wilkie, MP (2010) Influence of natural organic matter (NOM) quality on Cu-gill binding in the rainbow trout (*Oncorhynchus mykiss*). Aquatic Toxicology, 97, 343-352. 10.1016/j.aquatox.2010.01.003.

Gillis, PL; McGeer, JC; Mackie, GL; Wilkie, MP; Ackerman, JD (2010) The effect of natural dissolved organic carbon on the acute toxicity of copper to larval freshwater mussels (*Glochidia*). Environmental Toxicology and Chemistry, 29, 2519-2528. 10.1002/etc.299.

Gopalapillai Y; Hale B; Vigneault B (2013). Effect of major cations (Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}) and anions (SO_4^{2-}, Cl- , NO_3^{-}) on Ni accumulation and toxicity in aquatic plant (*Lemna minor* L.): implications For Ni risk assessment.Environmental Toxicology and Chemistry, 32, 810-21. 10.1002/etc.2116.

Hassler, CS; Chafin, RD; Klinger, MB; Twiss, MR (2007) Application of the biotic ligand model to explain potassium interaction with thallium uptake and toxicity to plankton. Environmental Toxicology and Chemistry, 26, 1139-1145. 10.1897/06-315R.1.

Hatano, A; Shoji, R (2010) A new model for predicting time course toxicity of heavy metals based on Biotic Ligand Model (BLM). Comparative biochemistry and physiology C – Toxicology and Pharmacology, 151, 25-32.

Hatano, A; Shoji, R (2008) Toxicity of copper and cadmium in combinations to duckweed analyzed by the biotic ligand model. Environmental Toxicology and Chemistry, 23, 372-378. 10.1002/tox.20348.

Heijerick, DG; De Schamphelaere, KAC; Van Sprang, PA; Janssen, CR (2005) Development of a chronic zinc biotic ligand model for *Daphnia magna*. Ecotoxicology and Environmental Safety, 62, 1-10. 10.1016/j.ecoenv.2005.03.020.

Heijerick, DG; De Schamphelaere, KAC; Janssen, CR (2002a) Biotic ligand model development predicting Zn toxicity to the alga *Pseudokirchneriella subcapitata*: possibilities and limitations. Comparative Biochemistry and Physiology C – Toxicology and Pharmacology, 133, 207-18. 10.1016/S1532-0456(02)00276-4.

Heijerick, DG; De Schamphelaere, KAC; Janssen, CR (2002b) Predicting acute zinc toxicity for *Daphnia magna* as a function of key water chemistry characteristics: Development and validation of a biotic ligand mode. Environmental Toxicology and Chemistry, 21, 1309-1315. 10.1897/1551-5028(2002)021<1309:PAZTFD>2.0.CO;2.

Hiriart-Baer, VP; Fortin, C; Lee, D; Campbell, PG C (2006) Toxicity of silver to two freshwater algae, *Chlamydomonas reinhardtii* and *Pseudokirchneriella subcapitata*, grown under continuous culture conditions: Influence of thiosulphate. Aquatic Toxicology, 78, 136-148. 10.1016/j.aquatox.2006.02.027.

Hoang TC; Tomasso JR; Klaine SJ (2004) Influence of water quality and age on nickel toxicity to fathead minnows (*Pimephales promelas*). Environmental Toxicology and Chemistry, 23, 86-92. 10.1897/03-11.Jho, EunHea; An, Jinsung; Nam, Kyoungphile (2011) Extended biotic ligand model for prediction of mixture toxicity of Cd and Pb using single metal toxicity data. Environmental Toxicology and Chemistry, 7, 1697-1703. 10.1002/etc.556.

Jorge, MB; Loro, VL; Bianchini, A; Wood, CM; Gillis, PL (2013) Mortality, bioaccumulation and physiological responses in juvenile freshwater mussels (*Lampsilissiliq.uoidea*) chronically exposed to copper. Aquatic Toxicology, 126, 137-47. 10.1016/j.aquatox.2012.10.014 . 10.1016/j.aquatox.2012.10.014.

Kamo M; Nagai T (2008). An application of the biotic ligand model to predict the toxic effects of metal mixtures. Environmental Toxicology and Chemistry, 27, 1479-1487. 10.1897/07-425.1.

Kennedy AJ; Chappell, MA; Bednar, AJ; Ryan, AC; Laird, JG; Stanley, JK; Steevens, JA (2012) Impact of organic carbon on the stability and toxicity of fresh and stored silver nanoparticles. Environmental Science and Technology, 46, 10772-80. 10.1021/es302322y.

Klinck J; Dunbar M; Brown S; Nichols J; Winter A; Hughes C; Playle R.C. (2005) Influence of water chemistry and natural organic matter on active and passive uptake of inorganic mercury by gills of rainbow trout (*Oncorhynchus mykiss*). Aquatic Toxicology, 72, 161-175. 10. 6/j.aquatox.2004.11.013.

Kolts, JA; Brooks, ML; Cantrell, BD; Boese, CJ; Bell, RA.; Meyer, JS (2008) Dissolved fraction of standard laboratory cladoceran food alters toxicity of waterborne silver to *Ceriodaphnia dubia*. Environmental Toxicology and Chemistry, 27, 1426-1434. 10.1897/07-326.1.

Kozlova, T; Wood, CM; McGeer, JC (2009) The effect of water chemistry on the acute toxicity of nickel to the cladoceran *Daphnia pulex* and the development of a biotic ligand model. Aquatic Toxicology, 91, 221-8. 10.1016/j.aquatox.2008.11.005.

Lavoie, M; Fortin, C; Campbell, PG C (2012a) Influence of essential elements on cadmium uptake and toxicity in a unicellular green alga: The protective effect of trace zinc and cobalt concentrations. Environmental Toxicology and Chemistry, 31, 1445-52.   10.1002/etc.1855

Lavoie, M; Campbell, PGC; Fortin, C (2012b) Extending the Biotic Ligand Model to Account for Positive and Negative Feedback Interactions between Cadmium and Zinc in a Freshwater Alga. Environmental Science and Technology, 46, 12129-36.   10.1021/es302512r

Leaes Pinho, GL; Bianchini, A (2010) Acute copper toxicity in the euryhaline copepod Acartiatonsa: implications for the development of an estuarine and marine biotic ligand model. Environmental Toxicology and Chemistry, 29, 1834-40.   10.1002/etc.212.

Lee DY; Fortin C; Campbell PGC (2005) Contrasting effects of chloride on the toxicity of silver to two green alage, *Pseudokirchneriella subcapitata* and *Chlamydomonas reinhardtii*. Aquatic Toxicology, 75, 127-135.   10.1016/j.aquatix.2005.06.011.

Leonard EM, Wood CM (2013) Acute toxicity, critical body residues, Michaelis-Menten analysis of bioaccumulation, and ionoregulatory disturbance in response to waterborne nickel in four invertebrates: *Chironomus riparius, Lymnaea stagnalis, Lumbriculus variegatus* and *Daphnia pulex.* CompBiochemPhysiol C ToxicolPharmacol158, 10-21.

Liao, C; Jou, L; Lin, C; Chiang, K; Yeh, C; Chou, Berry Y (2007a) Predicting acute copper toxicity to valve closure behavior in the freshwater clam *Corbicula fluminea* supports the biotic ligand model. Environmental Toxicology, 22, 295-307.   10.1002/tox.20263.

Liao, C; Lin, C; Jou, L; Chiang, KC (2007b) Linking valve closure behaviour and sodium transport mechanism in freshwater clam *Coricula fluminea* in response to copper. ENVIRONMENTAL POLLUTION, 147, 656-667.   10.1016/j.envpol.20056.09.017.

Ma, M; Zhu, WZ; Wang, ZJ; Witkamp, GJ. (2003) Accumulation, assimilation and growth inhibition of copper on freshwater alga (*Scenedesmus subspicatus* 86.81 SAG) in the presence of EDTA and fulvic acid. Aquatic Toxicology, 63, 221-228.   10.1016/S0166-445X(02)00179-0.

Mager, EM; Esbaugh, AJ; Brix, KV; Ryan, AC; Grosell, M (2011a) Influences of water chemistry on the acute toxicity of lead to *Pimephales promelas* and *Ceriodaphnia dubia*.Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 153, 82-90.   10.1016/j.cbpc.2010.09.004.

Mager, EM; Brix, KV; Gerdes, RM; Ryan, AC; Grosell, M (2011b) Effects of water chemistry on the chronic toxicity of lead to the cladoceran, *Ceriodaphnia dubia*. Ecotoxicology and Environmental Safety, 74, 238-243.   10.1016/j.ecoenv.2010.11.005.

Mager, EM;Wintz, H; Vulpe, CD; Brix, KV; Grosell, M (2008) Toxicogenomics of water chemistry influence on chronic lead exposure to the fathead minnow (*Pimephales promelas*). Aquatic Toxicology, 87, 200-209.   10.1016/j.aquatox.2008.02.001.

Markich, SJ (2013) Water hardness reduces the accumulation and toxicity of uranium in a freshwater macrophyte (*Ceratophyllum demersum*). The Science of the Total Environment, 443, 582-9. 10.1016/j.scitotenv.2012.11.038.

Meyer, JS;Adams, WJ (2010) Relationship between biotic ligand model-based water quality criteria and avoidance and olfactory responses to copper by fish. Environmental Toxicology and Chemistry, 29, 2096-2103. 10.1002/etc.254.

Meyer, JS; Boese, CJ; Morris, JM (2007) Use of the biotic ligand model to predict pulse-exposure toxicity of copper to fathead minnows (*Pimephales promelas*). Aquatic Toxicology, 84, 268-278. 10.1016/j.aquatox.2006.12.022.

Meyer JS; Santore RC; Bobbitt JP; Debrey LD; Boese CJ; Paquin PR; Allen HE: Bergman HL; Di Toro DM (1999) Binding of nickel and copper to fish gills predicts toxicity when water hardness varies, but free-ion activity does not. Environmental Science and Technology, 33, 913-916. 10.1021/ES980715q.

Morgan, TP; Wood, CM (2004) A relationship between gill silver accumulation and acute silver toxicity in the freshwater rainbow trout: Support for the acute silver biotic ligand model. Environmental Toxicology and Chemistry, 23, 1261-7. 10.1897/03-181.

Ng, TY; Chowdhury, MJ; Wood, CM (2010) Can the Biotic Ligand Model Predict Cu Toxicity Across a Range of pHs in Softwater-Acclimated Rainbow Trout? Environmental Toxicology and Chemistry, 29, 2096-2103. 10.1021/es101375q.

Niyogi, S; Kent, R; Wood, CM (2008) Effects of water chemistry variables on gill binding and acute toxicity of cadmium in rainbow trout (*Oncorhynchus mykiss*): A biotic ligand model (BLM) approach. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 148, 305-314. 10.1016/j.cbpc.2008.05.015.

Niyogi, S; Couture, P; Pyle, G; McDonald, DG; Wood, CM. (2004) Acute cadmium biotic ligand model characteristics of laboratory-reared and wild yellow perch (*Perca flavescens*) relative to rainbow trout (*Oncorhynchus mykiss*). CANADIAN JOURNAL OF FISHERIES AND AQUATIC SCIENCES, 61, 942-953. 10.1139/F04-044

Niyogi, S; Wood, CM (2003) Effects of chronic waterborne and dietary metal exposures on gill metal-binding: Implications for the Biotic Ligand Model. Human and Ecological Risk Assessment, 9, 813-846. 10.1080/713610011.

Paganini, CL; Bianchini, A (2009) Copper accumulation and toxicity in isolated cells from gills and hepatopancreas of the blue Crab (*Callinectes sapidus*). Environmental Toxicology and Chemistry, 28, 1200-1205.

Paquin, PR; Zoltay, V; Winfield, RP; Wu, KB; Mathew, R; Santore, RC; Di Toro, DM (2002) Extension of the biotic ligand model of acute toxicity to a physiologically-based model of the survival time of rainbow trout (*Oncorhynchus mykiss*) exposed to silver. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 305-343. 10.1016/S1532-0456(02)00105-9.

Pedroso MS; Bersano JG; Bianchini A (2007) Acute silver toxicity in the euryhaline copepod *Acartia tonsa*: influence of salinity and food. Environmental Toxicology and Chemistry, 26, 2158-2165. 10.1897/06-485R.1.

Peters, A; Merrington, G; de Schamphelaere, K; Delbeke, K (2011a) Regulatory consideration of bioavailability for metals: simplification of input parameters for the chronic copper biotic ligand model. Integrated Environmental Assessment and Management, 7, 437-44. 10.1002/ieam.159.

Peters, A; Lofts, S; Merrington, G; Brown, B; Stubblefield, W; Harlow, K (2011b) Development of biotic ligand models for chronic manganese toxicity to fish, invertebrates and algae. Environmental Toxicology and Chemistry, 30, 2407-15. 10.1002/etc.643.

Pyle, G; Wood, C (2008) Radiotracer studies on waterborne copper uptake, distribution, and toxicity in rainbow trout and yellow perch: A comparative analysis. HUMAN AND ECOLOGICAL RISK ASSESSMENT 14, 243-265. 10.1080/10807030801934994

Rodrigues Monteiro, SC; Leaes Pinho, GL; Hoffmann, K; Barcarolli, IF; Bianchini, A (2013) Acute waterborne copper toxicity to the euryhaline copepod Acartia tonsa at different salinities: Influence of natural freshwater and marine dissolved organic matter. Environmental Toxicology and Chemistry, 32, 1412-1419. 10.1002/etc.2197

Qu R; Wang X; Liu Z; Yan Z; Wang Z (2013) Development of a model to predict the effect of water chemistry on the acute toxicity of cadmium to *Photobacterium phosphoreum*. J Hazard Mater. 262C, 288-296

Ryan, AC; Tomasso, JR; Klaine, SJ (2009) Influence of pH, hardness, dissolved organic carbon concentration and dissolved organic matter source on the acute toxicity of copper to *Daphia magna* in soft waters: implications for the biotic ligand model. Environmental Toxicology and Chemistry, 28, 1663-70.

Santore, RC; Mathew, R; Paquin, PR; DiToro, D. (2002) Application of the biotic ligand model to predicting zinc toxicity to rainbow trout, fathead minnow and *Daphnia magna*. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 133, 271-285. 10.1016/S1532-0456(02)00106-0.

Santore, RC; Di Toro, DM; Paquin, PR; Allen, HE; Meyer, JS. (2001) Biotic ligand model of the acute toxicity of metals. 2. Application to acute copper toxicity in freshwater fish and *Daphnia*. Environmental Toxicology and Chemistry, 20, 2397-2402. 10.1897/1551-5028(2001)020<2397:BLMOTA>2.0.CO;2.

Sarathy, V; Allen, HE (2005) Copper complexation by dissolved organic matter from surface water and wastewater effluent. Ecotoxicology and Environmental Safety, 61, 337-344. 10.1016/j.ecoenv.2005.01.006.

Schlekat, CE; Van Genderen, E; De Schamphelaere, KAC; Antunes, PMC; Rogevich, EC; Stubblefield, WA (2010) Cross-species extrapolation of chronic nickel Biotic Ligand Models. Science of the Total Environment, 408, 6148-57. 10.1016/j.scitotenv.2010.09.012.

Schwartz, ML; Vigneault, B (2007) Development and validation of a chronic copper biotic ligand model for Ceriodaphniadubia. Aquatic Toxicology, 84, 247-54. 10.1016/j.aquatox.2007.01.011.

Shoji, R (2008) Effect of dissolved organic matter source on phytotoxicity to *Lemna aequinoctialis*. Aquatic Toxicology, 87, 210-214. 10.1016/j.aquatox.2008.02.005.

Szebedinszky, C; McGeer, JC; McDonald, DG; Wood, CM (2001) Effects of chronic Cd exposure via the diet or water on internal organ-specific distribution and subsequent gill Cd uptake kinetics in juvenile rainbow trout (*Oncorhynchus mykiss*). Environmental Toxicology and Chemistry, 20, 597-607. 10.1897/1551-5028(2001)020<0597:EOCCEV>2.0.CO;2.

Tsai, J;Chen, W; Ju, Y; Liao, C (2009) Bioavailability links mode of action can improve the long-term field risk assessment for tilapia exposed to arsenic. Environment International, 35, 727-736. 10.1016/j.envint.2009.01.014.

Van Genderen, E; Adams, W; Cardwell, R; Volosin, J; Santore, R; Rodriguez, P (2009) An evaluation of the bioavailability and aquatic toxicity attributed to ambient zinc concentrations in fresh surface waters from several parts of the world. Integrated environmental assessment and management, 5, 426-434. 10.1897/IEAM_2008-082.1.

Van Genderen, E; Adams, W; Cardwell, R; van Sprang, P; Arnold, R; Santore, R; Rodriguez, P (2008). An Evaluation of the Bioavailability and Aquatic Toxicity Attributed to Ambient Copper Concentrations in Surface Waters from Several Parts of the World. Integrated Environmental Assessment and Management, 4, 416-424. 10.1897/IEAM_2008-014.1.

Van Genderen, Eric; Gensemer, Robert; Smith, Carrie; Santore, Robert; Ryan, Adam (2007) Evaluation of the Biotic Ligand Model relative to other site-specific criteria derivation methods for copper in surface waters with elevated hardness. Aquatic Toxicology, 84, 279-91. 10.1016/j.aquatox.2007.02.024.

Van Sprang, PA; Verdonck, FAM; Van Assche, F; Regoli, L; De Schamphelaere, KAC (2009) Environmental risk assessment of zinc in European freshwaters: A critical appraisal. Science of the Total Environment, 407, 5373-5391. 10.1016/j.scitotenv.2009.06.029.

Veltman, K; Huijbregts, MAJ; Hendriks, AJ (2010) Integration of Biotic Ligand Models (BLM) and Bioaccumulation Kinetics into a Mechanistic Framework for Metal Uptake in Aquatic Organisms. Environmental Toxicology and Chemistry, Science and Technology, 44, 5022-8. 10.1021/es903697c.

Verschoor, AJ; Hendriks, J; Vink, JPM; De Snoo, G; Vijver, M (2012a). Multimetal accumulation in crustaceans in surface water related to body size and water chemistry. Environmental Toxicology and Chemistry 31, 2269-80.

Verschoor, AJ; Vink, JPM; Vijver, MG (2012b) Simplification of biotic ligand models of Cu, Ni, and Zn by 1-, 2-, and 3-parameter transfer functions. Integrated Environmental Assessment and Management, 8, 738-48. 10.1002/ieam.1298.

Villavicencio, G; Urrestarazu, P; Arbildua, J; Rodriguez, PH. (2011) Application of an acute biotic ligand model to predict chronic copper toxicity to Daphnia magna in natural waters of Chile and reconstituted synthetic water. Environmental Toxicology and Chemistry, 30, 2319-25.   10.1002/etc.629.

Villavicencio, G; Urrestarazu, P; Carvajal, C; De Schamphelaere, KAC; Janssen, CR; Torres, JC ; Rodriguez, PH (2005) Biotic ligand model prediction of copper toxicity to daphnids in a range of natural waters in Chile. Environmental Toxicology and Chemistry, 24, 1287-99.   10.1897/04-095R.1.

Wilde KL; Stauber JL; Markich SJ; Franklin NM; Brown PL (2006). The effect of pH on the uptake and toxicity of copper and zinc in a tropical freshwater alga (Chlorella sp.) Archives of Environmental Contamination and Toxicology, 51, 174-185.   10.1007/s00244-004-0256-0.

Wang, N; Mebane, CA; Kunz, JL; Ingersoll, CG; Brumbaugh, WG; Santore, RC; Gorsuch, JW; Arnold, WR (2011) Indfluence of dissolved organic carbon on toxicity of copper to a unionid mussel (*Villosa iris*) and a Cladoceran (*Ceriodaphnia dubia*) in acute and chronic water exposures. Environmental Toxicology and Chemistry, 30, 2115-2125.   10.1002/etc.596.

Wang, N; Mebane, CA; Kunz, JL; Ingersoll, CG; May, TW; Arnold, WR; Santore, RC; Augspurger, T; Dwyer, FJ; Barnhart, MC (2009) Evaluation of acute copper toxicity to juvenile freshwater mussels (fatmucket *Lampsilis siliquoidea*) in natural and reconstituted waters. Environmental Toxicology and Chemistry, 28, 2367-2377.   10.1897/08-655.S3.

Worms, IAM; Wilkinson, KJ (2007) Ni uptake by a green alga. 2. Validation of equilibrium models for competition effects. Environmental Science and Technology, 41, 4264-4270.   10.1021/es0630341.

Zeng, J; Yang, L; Wang, W (2009) Cadmium and zinc uptake and toxicity in two strains of *Microcystis aeruginosa* predicted by metal free ion activity and intracellular concentration. Aquatic Toxicology, 91, 212-220.   10.1016/j.aquatox.2008.11.004.

Zhou, BS; Nichols, J; Playle, RC; Wood, CM (2005) An *in vitro* biotic ligand model (BLM) for silver binding to cultured gill epithelia of freshwater rainbow trout (*Oncorhynchus mykiss*). Toxicology and Applied Pharmacology, 202, 25-37.   10.1016/j.taap.2004.06.003.