Quantitative Structure-Activity Relationships for soil Ecotoxicity

Giesen, D.

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Summary

Pollution with organic compounds is a global problem, threatening ecosystem structure and function. In order the assess and evaluate the potential risk of industrial compounds to soil organisms and communities statistical toxicity models such as quantitative structure activity relationships (QSARs) provide an effective alternative to exhaustive toxicity tests. QSARs use physical-chemical properties of a series of compounds and correlate them with defined toxicological endpoint concentrations in the environment, such as EC_{50} for the reduction of reproduction of soil invertebrates. Standardized toxicity tests, in particular for *Folsomia candida*, belonging to one of the most sensitive taxa to soil contamination, are the base for QSARs. Traditionally, the n-octanol-water partition coefficient ($logK_{ow}$) was found to be a good descriptor for hydrophobic organic compounds, to assess toxicity and classify compounds, as their main mode of action is the disruption of cell membranes and potential interaction with membrane integrated complexes. The freely dissolved concentration in the soil for ECx values is correlated with the lipophilicity of the compounds.

In chapter two, 28d standard toxicity tests with *F. candida* were performed and QSARs developed to determine the EC_{10} and EC_{50} for the effect of nine chlorobenzenes on the reproduction *F. candida*, in natural standard soil LUFA2.2 and OECD artificial soil. For both endpoints, two individual QSAR regression models were obtained, based on different sorption behaviour of the compounds towards the soil organic matter. Estimated free soil interstitial water concentrations for both endpoints were measured with solid-phase microextraction (SPME) in LUFA2.2 soil in order to validate estimated concentrations. However, measured concentrations, though QSAR were developed for it, did not confirm estimated concentrations, indicating the need for exact determination of soil sorption coefficients and further investigation of additional processes.

In chapter three, aniline and 5 chlorinated anilines were used in a similar way to develop QSARs in LUFA2.2 and OECD soil for effects on *F. candida*. For both endpoints and soil regression models showed correlations with their $logK_{ow}$. After SPME measurements for the dichloroaniline, trichloroaniline, tetrachloroaniline and pentachloroaniline, estimated concentrations were only confirmed for the two highest chlorinated

congeners. The losses of bioavailability for dichloroaniline were so extensive that QSARs for measured concentrations were not developed.

Toxicity models for environmental risk assessment of organic compounds use mostly initial nominal concentrations. Yet, the freely dissolved fraction of hydrophobic compounds undergoes dynamic processes, such as biodegradation, sorption and volatilisation. Chapter four addresses this problem by measuring EC_{10} and EC_{50} values for eight chlorobenzenes and four chloroanilines, for *F. candida* at 0, 14 and 28 days, covering the total duration of a standardized toxicity test. Lower chlorinated compounds showed significant losses over time, while compounds with higher chloride substitution and $logK_{ow}$ were stable in the soil interstitial water. QSARs were calculated for the geometric mean concentration, as a measure of the average effective concentration over time, for the set of chlorobenzenes. Conversely, for the chloroanilines, QSARs were not developed due to substantial losses of dichloroaniline, while concentrations of tetra- and pentachloroaniline were stabile over the 28-day test period.

The $logK_{ow}$ as descriptor for the lipophilicity of a compound and the $logK_{oc}$ for the sorption towards organic carbon were often used to explain differences in the toxicity of compounds and interstitial water concentrations in test soils. In order to optimize QSARs for the subset of chlorobenzenes (non-polar narcosis) and chloroanilines (polar narcosis), liposome-water partition coefficients ($logK_{lipw}$) as alternative to the $logK_{ow}$ and soil-specific $logK_{oc}$ values were determined for the organic matter of LUFA2.2 and OECD soil and a model based on measured concentrations was developed in chapter five. SPME measurements revealed substantial differences in freely dissolved compound concentrations, only explainable by the varying water concentrations in the soil. In chapter five, a unified QSAR for two soils and both compound sets was accomplished after concentrations in the water were corrected for the water volume of both soils.

In chapter six, a microarray study was used to generate a gene-response profile of *F. candida* after 2-day exposure to concentrations corresponding with predetermined EC_{50}s concentration of aniline and five chloroanilines for potential proton chain inhibition, 1,2,3,4-tetrachlorobenenze as control group for non-polar narcosis acting compounds. Based on the specific response of classifier gene clusters, tetrachloroaniline was identified as uncoupler, while lower chlorinated

anilines showed no significant differences in their molecular response in comparison to inert compounds. Pentachloroaniline showed trends towards similar reaction of tetrachloroaniline, but remained in the cluster of non-polar compounds.

This thesis describes the validation and optimization process of QSARs for soil toxicity tests. It shows that reliable QSARs do not only have to take the structures and properties of a given compound into account, but also characteristics of the matrices used for testing. Furthermore, it demonstrates that the classification of the mode of action can ultimately only be determined by analysing physiological and molecular responses of the organisms. Finally, none of these studies can solely explain toxicity or risk, however, their integration builds a stronghold for future research and evaluation processes.

Samenvatting

Verontreiniging met organische chemicaliën is een wereldwijd probleem, dat de structuur en het functioneren van ecosystemen bedreigt. Voor het bepalen van het mogelijke risico van industriële chemicaliën voor organismen en levensgemeenschappen in de bodem vormen statistische modellen, zoals kwantitatieve structuur-werkingsrelaties (QSARs), een mogelijk alternatief voor de tijdrovende toxiciteitstesten. QSARs maken gebruik van fysisch-chemische eigenschappen van een reeks verwante stoffen en relateren deze aan een gedefinieerde toxicologische effectconcentratie in het milieu, zoals een EC_{50} voor het effect op de reproductie van bodemevertebraten. Gegevens verkregen uit gestandaardiseerde toxiciteitstesten, zoals die met de springstaart *Folsomia candida*, één van de meest gevoelige taxa voor bodemverontreiniging, vormen derhalve de basis voor QSARs. De n-octanol-water verdelingscoëfficiënt ($logK_{ow}$) wordt traditioneel beschouwd als een goede parameter om van de toxiciteit van hydrofobe organische chemicaliën te voorspellen en stoffen te classificeren op basis van hun giftigheid. Dit is gebaseerd op het feit dat de werking van dergelijke stoffen, niet-polaire narcose die tot stand komt door verstoring van celmembranen en mogelijke interactie met membraangeïntegreerde complexen, vooral wordt gestuurd door hun lipofiliteit. Voor deze stoffen blijkt de EC_{50}, uitgedrukt op basis van de vrij opgeloste concentratie van deze stoffen in het bodemvocht (poriewater), goed te correleren met hun lipofiliteit ofwel vetoplosbaarheid waarvoor de $logK_{ow}$ een maat is. Deze vrij opgeloste concentratie in het poriewater wordt daarom verondersteld indicatief te zijn voor de biologische beschikbaarheid van deze stoffen.

In hoofdstuk 2 van dit proefschrift zijn QSARs ontwikkeld voor de toxiciteit van negen chloorbenzenen voor *F. candida*. De QSARs gebruiken de EC_{10} en EC_{50} voor het effect op de reproductie van *F. candida* na 28 dagen blootstelling in standaard toxiciteitstesten in een natuurlijke standaardbodem LUFA2.2 en in OECD kunstgrond. Voor beide eindpunten werden twee aparte QSAR regressie modellen verkregen, omdat de stoffen in verschillende mate bonden bleken te worden aan de organische stof in de twee testgronden. Om de geschatte vrij opgeloste concentraties waarop de QSAR was gebaseerd te valideren, werden ze ook gemeten met behulp van zogenaamde vaste fase micro extractie (solid-phase microextraction: SPME).

Dit is gedaan in LUFA2.2 grond, bij concentraties corresponderend met beide toxicologische effectconcentraties. De gemeten concentraties in het poriewater konden de geschatte waarden niet bevestigen, hetgeen aantoont dat het belangrijk is de sorptie van deze stoffen nauwkeurig te meten en het achterliggende mechanisme nader te onderzoeken.
In hoofdstuk 3 zijn op dezelfde wijze drie anilines and vijf gechloreerde anilines getest om QSARs te ontwikkeling voor hun toxiciteit voor *F. candida* in de LUFA2.2 en OECD gronden. Voor beide toxicologische eindpunten werden in beide gronden goede correlaties gevonden met de $\log K_{ow}$. SPME metingen voor dichlooraniline, trichlooraniline, tetrachlooraniline en pentachlooraniline bevestigden echter alleen voor de twee hoogst gechloreerde congeneren de geschatte vrij opgeloste concentraties in het poriewater. De afname in de biobeschikbare concentraties van dichlooraniline was zo groot dat voor de chlooranilines geen QSARs konden ontwikkeld op basis van de gemeten concentraties.
Toxiciteitmodellen voor de schatting van het milieurisico organische chemicaliën worden meestal gebaseerd op de aan het begin van de test toegevoegde concentratie. De vrij opgeloste concentratie in het poriewater is echter onderhevig aan dynamische processen, zoals afbraak, sorptie en verdamping. Hoofdstuk 4 probeert dit probleem te benaderen door EC_{10} en EC_{50} waarden voor de toxiciteit van acht chloorbenzenen en vier chlooranilines voor *F. candida* te relateren aan vrij opgeloste concentraties in het poriewater die gemeten zijn na 0, 14 en 28 dagen. De lager gechloreerde verbindingen vertoonden een significant verlies in de tijd, terwijl de concentraties in het poriewater stabiel waren voor de stoffen met een hoge mate van chlorering en hoge $\log K_{ow}$. Voor de chloorbenzenen konden QSARs worden onwikkeld op basis van het geometrisch gemiddelde van de concentraties gemeten op de drie tijdstippen, hetgeen correspondeert met de gemiddelde effectieve concentratie over de 28 dagen durende test. Voor de chlooranilines was dit echter niet mogelijk door het grote verlies van vooral dichlooraniline; de concentraties van tetra- en pentachlooraniline bleven wel stabiel gedurende 28 dagen.
Verschillen in de toxiciteit van stoffen en in de vrij opgeloste concentraties in het poriewater kunnen vaak verklaard worden door gebruik te maken van de $\log K_{ow}$ als maat voor de lipofiliteit van een stof en $\log K_{oc}$ als maat voor de binding aan organisch koolstof. In hoofdstuk 5 is geprobeerd de

ontwikkelde QSARs te optimaliseren voor de chloorbenzenen, die werken volgens het principe van niet-polaire narcose, en de chlooranilines die werken volgens polaire narcose. Daartoe zijn liposoom-water verdelingscoëfficiënten ($logK_{lipw}$) gemeten als een alternatief voor de $logK_{ow}$ terwijl bodemspecifieke $logK_{oc}$ waarden zijn bepaald voor de binding van deze stoffen aan de organische stof in de LUFA2.2 en OECD gronden. Vervolgens is een model ontwikkeld gebaseerd op gemeten concentraties. De SPME metingen lieten een flink verschil zien in de vrij opgeloste concentraties in het poriewater van de twee testgronden, dat alleen verklaard kon worden door het verschil in watergehalte. In hoofdstuk 5 is een uniforme QSAR voor de twee gronden en beide series chemicaliën ontwikkeld door de concentraties in het poriewater te corrigeren voor het watergehalte van de gronden.

In hoofdstuk 6 is een microarray test gebruikt om het genexpressie profiel te bepalen van *F. candida* na 2 dagen blootstelling aan concentraties die overeenkomen met de EC_{50} voor het effect op de reproductie in een 28 dagen standaard test. Hiertoe werden testen uitgevoerd met aniline en 5 chlooranilines als stoffen met een mogelijke remmende werking op de protonen-keten, terwijl 1,2,3,4-tetrachloorbenzeen werd meegenomen als controle voor stoffen die werken volgens het mechanisme van niet- polaire narcose. Gebaseerd op de specifieke response van clusters van zogenaamde 'classifier' genen werd tetrachlooraniline geïdentificeerd als ontkoppelaar terwijl de lager gechloreerde chlooranilines geen significant verschil in genexpressie profiel vertoonden in vergelijking met de inerte referentiestof. De response op pentachlooraniline vertoonde overeenkomsten met die op tetrachlooraniline, maar kon niet onderscheiden worden van dat voor de stoffen met niet-polaire werking.

Dit proefschrift beschrijft de validatie en optimalisatie van QSARs voor toxiciteitstesten met bodemorganismen. Het laat zien dat voor een betrouwbare QSAR niet alleen de structuur en eigenschappen van een chemische stof in beschouwing moeten worden genomen, maar dat ook de eigenschappen van de testmatrix van belang zijn. Daarnaast wordt aangetoond dat een classificatie van stoffen op basis van werkingsmechanisme uiteindelijk alleen maar bepaald kan worden door de fysiologische en moleculairbiologische response van het testorganisme mee te nemen. Geen van deze factoren kan op zichzelf de toxiciteit verklaren,

maar integratie van de verschillende elementen kan leiden tot een solide basis voor verder onderzoek en een betrouwbare evaluatie van nieuwe chemische stoffen.

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Curriculum Vitae

Daniel Giesen was born on the 5th of June 1981 in Duisburg, Germany. In 1986 he announced with the age of 5 that he wanted to study animal science. Starting in 2001 he studied biology at the Ernst Moritz Arndt University Greifswald and graduated 2007. He wrote his *Diplom*-thesis in a cooperation with the Microbial Ecology and the Stichting Bargerveen of the Radboud University Nijmegen and the Biological Field Station Hiddensee of the EMAU Greifswald, about the effects of nitrogen fertilisation on nitrosifying bacteria and archea communities in dry heath-land soils. After his graduation he worked as researcher investigating bio-geochemical sulphide detoxification pathways of marshland vegetations until 2008 when he was given the opportunity to do a PhD study at the Department of Ecology at the VU Free University Amsterdam. He studied and worked about toxic effects of organic pollutants to soil invertebrates with the goal to develop and optimize Quantitative Structure-Activity- Relationships (QSARs).

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Epilogue

They met during a summer rain in the lower countries at the shores of the northern oceans. A wrinkle faced old man dressed in a white lab coat and a younger man with dark rings around his eyes, holding a lab journal like a shield. The loud wind was whipping the sand and mounting the waves when the old man approvingly said:
"You survived the long darkness in the laboratories, climate chambers and never ending corridors. The light of day, the sun's sweet kiss, a long forgotten memory, just a reminiscence of a wonderful dream. The years changed your physiology so you could sustain only on coffee and stale air. You swam through the agonisingly cold waters of frustration, forcing you to repeat tests and experiments over and over again. You fought and conquered all of the main five demons; Self-Doubt, Over-Ambition, Broken Equipment, Deadline and Statistic, in all his forms. Driven like a madman by curiosity and the urge to prove theories. Walking in footsteps of bigger man and women, climbing giant's shoulders just to see an inch further. You became adventurer, teacher, craftsman, author, manager and politician."

"All these for this moment in time in which you can say", the old continued turning towards the ocean and with full breath he yelled, "Finally Doctor!" The words seemed to hang for one moment in the air, resisting the elements.

He nodded to the younger one before he continued, "And with the completion of the PhD thesis, the scientist is inaugurated into the highest halls of academia. Yet there will be no time for rest. It will be the battle for funding from now on. You will be forced to vagabond the planet once more, which bares new demons to fight. From now on you will constantly question findings of others and cautiously await the newcomer who identified the little mistakes in your work."

"I am ready", said the young, flexed his shoulders and grinned. "Bring it on!"