1	BAC	KGRO	UND AND MOTIVATION 1
	1.1	Measu	rement and prediction of biological effects 2
		1.1.1	Predicting biological effects from chemical moni-
			toring 2
		1.1.2	Measuring biological effects 2
	1.2		oxicogenomics 3
			Transcriptomics 5
		1.2.2	-
			cogenomics 6
	1.3	Vision	: Ecotoxicogenomics as non-target bioassay 6
	1.4		and objectives 6
		1.4.1	Molecular profiles for effect categories and adver-
			sity - Which genes are responding?
		1.4.2	Concentration- and time dependence - How do
			the genes respond? 10
		1.4.3	Combination effects 11
2	MET	ra-ana	ALYSIS OF TRANSCRIPTOME DATA 19
	2.1	Introd	uction 19
	2.2	Metho	ods 21
		2.2.1	Data import, quality control, normalization and
			cleaning 23
		2.2.2	Grouping of contrasts 23
		2.2.3	Analysis 26
2.3 Results 26			
			Heterogeneous exposure settings 27
		2.3.2	Association of experimental factors 28
		2.3.3	. , ,
			tween studies 29
		2.3.4	Effect size analysis – common trends of gene reg-
			ulation 30
		2.3.5	Meta-genes for experimental subgroups 32
	2.4	Discus	
		Conclu	
3			ENOMIC LANDSCAPES - CONCENTRATION AND
			ENDENT RESPONSES IN THE TOXICOGENOMIC
		VERSE	
		Introd	
	3.2		imental setup 54
			Model compound selection 56
	9.0	3.2.2	• •
	3.3		analysis pipeline 58
		3.3.1	Import, quality control and normalization 59

		3.3.2	Time normalization 60	
		3.3.3	Self-organizing maps 60	
		3.3.4	Regression models for time and concentration de-	
			pendent toxicogenomic response 62	
		3.3.5	Selecting significantly affected toxnodes 65	
	3.4	Result	s 66	
		3.4.1	Data overview 66	
		3.4.2	The toxicogenomic universe 67	
		3.4.3	Visual inspection of molecular toxicodynamic maps	69
		3.4.4	Quantitative description of toxnode levels by re-	
			gression models 74	
		3.4.5	Summary of toxicogenomic landscapes of model	
			substances 77	
		3.4.6	Toxnodes specifically affected by cyclooxygenase	
			(COX)-inhibitors 82	
		3.4.7	Assessing regulation of affected toxnodes in the	
			toxicogenomic universe 83	
	3.5	Discus	ssion 88	
		3.5.1	"Self-organization" of toxicogenomic knowledge 88	
		3.5.2	Regression models to describe toxnode behav-	
			ior 89	
		3.5.3	Time and concentration dependent transcriptomics	90
		3.5.4	Detection of a mode of action in the ZFE tran-	
			scriptome 90	
4	TOX	CICOGE	ENOMIC MIXTURE EFFECTS 99	
	4.1	Introd	uction 99	
		4.1.1	Application of toxicogenomics in environmental	
			monitoring 100	
		4.1.2	Mixture toxicology 101	
	4.2	Metho	ods 103	
		4.2.1		
			Effect addition in toxicogenomics 104	
			Concentration addition in toxicogenomics 105	
		4.2.4	•	
			Confidence interval for predictions 107	
		4.2.6	Mixture design 108	
	4.3	Result		
		4.3.1	Toxnodes affected by mixture exposure (mixture	
			effects) 110	
		4.3.2	Identification and predictability of combination	
			effects on transcriptome level 110	
		4.3.3	Prediction of qualitative toxicogenomic mixture	
			landscape – which toxnodes are affected? 116	
		4.3.4	Prediction of quantitative toxicogenomic mixture	
			landscapes – how are the toxnodes affected? 118	
		4.3.5	Deviations from predictions 120	

	4.4	Discussion 124				
		4.4.1 Experimental design, model and prediction uncertainties 130				
		4.4.2 Recovery of effect profiles in toxicogenomic mix-				
		ture landscapes – qualitative combination effects 131				
		4.4.3 Occurrence of quantitative combination effects 132				
		4.4.4 Predictability of combination effects 132				
		4.4.5 Predictability of whole toxicogenomic mixture land-				
		scape 133				
	4.5	Conclusion 134				
5	CON	CLUSIONS AND FUTURE PERSPECTIVES 139				
An	pend	ix				
A	SUPPLEMENTAL INFORMATION CHAPTER 2 151					
••	A.1					
	A.2	Annotation 151				
	А.З	Retrieval of genesets for functional annotation 152				
	<b>A.4</b>	Supplemental figures 153				
В	0 101					
	в.1	Exposure 181				
	в.2	RNA extraction and isolation 181				
		Measurement of transcript abundance (ta) 182				
		Removal of batch effect 182				
	в.5	Parameter boundaries 182				
		Supplemental figures 186				
	в.7	Supplemental tables 189				
$\mathbf{C}$		UPPLEMENTAL INFORMATION CHAPTER 4 193				
	C.1	Biphasic concentration addition 193				
	C.2	Supplemental Figures 194				