In Silico Classification of Industrial Chemicals Associated with Acute Aquatic Toxic Action Utilising Molecular Initiating Events

- Appendices -

Maria Sapounidou

A thesis submitted in partial fulfillment of the requirements of
Liverpool John Moores University for the degree of Doctor of Philosophy

This research programme was carried out in collaboration with the Safety and Environmental Assurance Centre, Unilever Research, Colworth House, Sharnbrook, Bedfordshire, UK.

September 2019

Appendices

Appendix 1: Acute Toxicity Database

All acute toxicity datasets used in this studyand included in the Acute Toxicity Database (see Chapter 2) are available on the USB stick attached to this thesis (AcuteToxicityDB.accdb)

Appendix 2: MIE literature

The MIE training set in SMILES is available on the USB stick attached to this thesis (Tab MIE training set, MIE Appendix.xlsx).

Table 1. Detailed description of MIE literature

#	MIE target	MIE	Xenobiotic	Acute effect	Adapted Bradford Hill considerations	Taxonomic Applicability	References
1.	endoplasmic reticulum calcium ATPase	Inhibition - Calcium mobilization	Atrazine Bifenthrin Chlorpyrifos Diazinon Dichlorobenzene Methoxychlor Methylfarnesoate Nonylphenol Parathion Permethrin Phenanthrene Pyriproxyfen Toluene Toxaphene Trichloroethylene β-estradiol λ-cyhalothrin	Narcosis	1.2, 2, 3.2, 4.1, 5	*Daphnia magna* Teleost Fish Green Algae	[1; 2]
	Cell membrane	Disruption of membrane integrity	1,1,1 -trichloroethane 1,1,2,2-tetrachloroethane 1,2,3-trichloropropane 1,2,3,4-tetrachlorobenzene 1,2,3,5 -tetrachlorobenzene 1,2,3-trichlorobenzene	Narcosis	1.2, 2, 3.1, 3.2, 4.1, 5	*Pimephales promelas* *Oncorhynchus mykiss* *Poecilia reticulata* *Danio rerio* *Lepomis macrochirus*	[3; 4; 5; 6; 7]

		1,2,4,5 -tetrachlorobenzene				
		1,2,4-trichlorobenzene				
		1,2-dichlorobenzene				
		1,2-dichloroethane				
		1,2-dichloropropane				
		1,2-ethanediol				
		1,3,5 -trichlorobenzene				
		1,3-dichlorobenzene				
		1,3-dichloropropane				
		1,4-dichlorobenzene				
		1,1,2-trichloroethane				
		1,1-dichloroethane				
		1-chlorobutane				
		1-octanol				
		2-(2-butoxyethoxy)ethanol				
		2,3,4,5-tetrachloroaniline				
		2,3,4-trichloroaniline				
		2,3-dichloronitrobenzene				
		2,3-dimethylnitrobenzene				
		2,4,5 -trichloroaniline				
		2,4,5-trichlorotoluene				
		2,4-dichloroaniline				
		2,4-dichloronitrobenzene				
		2,4-dichlorophenol				
		2,4-dichlorotoluene				
		2,5 -dichloronitrobenzene				
		2,5-dichloroaniline				
		2-isopropoxyethanol				
		2-butoxyethanol				
		2-chloro-6-nitrotoluene				
		2-chloroaniline				
		2-chloronitrobenzene				
		2-chlorophenol				
		2-ethoxyethanol				
		2-ethyl-1-hexanol				
		2-ethylaniline				
		2-methoxyethanol				
		2-methyl-2-propanol				

		2-methylaniline 2-nitroaniline 2-nitrotoluene 2-propanol 3,4-dichloroaniline 3,4-dichlorotoluene 3,4-dimethylnitrobenzene 3,5 -dichloroaniline 3,5 -dichloronitrobenzene 3,5 -dichlorophenol 3-chloroaniline 3-chloronitrobenzene 3-chlorophenol 3-chlorotoluene 3-ethylaniline 3-methylaniline 3-nitroaniline 3-nitrotoluene 3-pentanol 4-bromophenyl 3-pyridyl ketone 4-chloro-2-nitrotoluene 4-chloroaniline 4-chloronitrobenzene 4-chlorotoluene 4-ethylaniline 4-hexyloxyaniline 4-methylaniline 4-nitroaniline 4-nitrotoluene Acetone Aniline Benzene Dichloromethane Diethylene glycol Diethylether Dimethylaminoterephthalate Ethanol m-bromobenzamide			

		Monochlorobenzene m-Xylene Nitroarom atics 4 Nitrobenzene -Xylene p-(tert-butyl) benzamide Pentachloroethane Pentachlorobenzene Phenol Phenyl-4-aminosalicylate p-Xylene Tetrachloroethene Tetrachloromethane Toluene Trichloroethene Trichloromethane Triethylene glycol Tripropargylamine				
DNA	Alkylation	Diethyl nitrosamine Diethyl sulfate Dimethyl nitrosamine Dimethyl sulfate Ethyl methanesulfonate Ethyl nitrosourea Ethyl-N'-nitro-N-nitrosoguanidine Isopropyl methanesulfonate Methyl methanesulfonate Methyl-I-N'-nitro-N- Nitroguanidine coumarins epoxides halogenated alkenes quinones thiophenes –SN2	Reactivity	1.2, 2, 3.2, 4.1, 4.2, 5	Eukaryota	[8; 9; 10]
DNA	DNA adduct formation	*Oxidated metabolites of:* Benzo[a]pyrene Beta-naphthoflavone 3-methylcholanthrene	Reactivity	1, 2, 3.1, 3.2, 4.1, 5	Teleost Fish	[11; 9]

			7,8-diole B[a]P Dibenzo[a,l]pyrene polycyclic aromatic hydrocarbons (PAHs) with so called 'bay region' polycyclic aromatic hydrocarbons (PAHs) with so called 'fjord regions'				
	DNA, protein, lipids (liver)	ROS formation	*Electron reduced metabolites of:* 4-nitroquinoline 1-oxide, Aflatoxin B1 Nitrofurantoin Phenanthrenequinone *Oxidated metabolites of:* Acetaminophen tetrachlorobiphenyls	Reactivity	1, 2, 3.1, 3.2, 4.1, 5	Teleost Fish	[9; 12; 13; 14]
	DNA, proteins	Alkylation	quinones	Reactivity	1, 2, 3.1, 3.3, 4.1, 5	*Oncorhynchus mykiss* Eukaryota	[15; 9]
	DNA, protein, lipids	ROS reactivity mediated by episulfonium ion	*Activated metabolites of:* 1,2- dibromoethane small halogenated alkanes	Reactivity	1, 2, 3, 4, 5	*Ictalurus punctatus* Teleost Fish	[9; 10; 16; 17]
	DNA, protein, lipids	ROS reactivity mediated by nitrenium	*Activated metabolites of:* 2-aminofluorene Aniline Chloroaniline Nitrofurantoin Sulfadimethoxine arylamines quinolones	Reactivity	1, 2, 3, 4, 5	*Oncorhynchus mykiss* *Oryzias latipes* Teleost Fish	[18; 19; 9; 20; 21]
	DNA, protein, lipids	Redox cycle activity	Azoxystrobin Juglone quinones	Reactivity	1, 2, 3, 4, 5	Eukaryota	[15; 9; 22]
	DNA, protein, lipids	Redox cycle	Procyanin	Reactivity	1, 2, 3, 4, 5	*Pseudomona*	[23; 9]

	activity				*aeruginosa* Eukaryota	
DNA, protein, lipids	Fenton-chemistry-like generation of hydroxyl radical	Pyochelin	Reactivity	1, 2, 3.2, 4.2, 4.3, 5	*Pseudomonas aeruginosa* Eukaryota	[23; 9]
DNA, protein, lipids (liver)	ROS reactivity mediated by superoxide anion and peroxide	*Oxidated metabolites of:* Ethanol	Reactivity	1, 2, 3, 4, 5	Teleost Fish	[24; 9]
DNA, proteins, lipids (chloroplast; lung)	Redox cycle activity	Diquat Paraquat bipyridyl-based herbicides	Reactivity	1, 2, 3, 4, 5	Aquatic plants Teleost Fish	[9; 25; 26]
DNA, proteins	Michael addition	acid imides phenolic metabolites polarized alkenes and related nitrogen chemicals polarized alkynes quinones	Reactivity	1, 2, 3, 4, 5	Teleost Fish *Tetrahymena pyriformis* *Daphnia magna*	[9; 10; 16]
Aryl hydrocarbon receptor	Covalent binding leading to activation	2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) 3-Methylcholanthrene Benzidine Dibenzo-p-dioxin Dichlorodiphenyldichloroethylene Hexachlorobenzene Hexachlorobenzene Nonylphenol halogenated aromatic hydrocarbons indoles polychlorinated biphenyls polychlorinated dibenzofurans, polycyclic aromatic hydrocarbons (PAHs)	Specific Toxicity	1, 2, 3, 4, 5	*Danio rerio* *Oncorhynchus mykiss* *Salmo salar* *Xenopus laevis* *Microgadus tomcod*	[27; 8; 28; 9]

Calmodulin	Covalent binding leading to inhibition	Cyclosporin	Specific Toxicity	1, 2, 3.1, 4.2, 5	*Carassius auratus* *Danio rerio* Teleost Fish	[9; 29]
Androgen Receptor	Binding – Agonistic effect	17-beta-trenbolone 5-alpha-dihydrotestosterone Spironolactone	Specific Toxicity	1, 2, 3.1, 4.2, 5	*Pimephales promelas* *Oryzias latipes*	[30; 8]
Aromatase (CYP19s)	Interference with electron transfer via the cytochrome P450 heme group of the aromatase enzyme	Fadrozole Letrozole Prochloraz	Specific Toxicity	1, 2, 3.1, 4.2, 5	Teleost Fish *Oryzias latipes*	[8; 9; 31]
Cyclooxygenase	Covalent interference leading to inhibition	1-chloro-4-nitrobenzene 3-(Difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]-1H-pyrazole Acetylsalicylic acid Celecoxib Diclofenac sodium Emamectin benzoate Ibuprofen Indomethacin Naproxen Oxytetracycline hydrochloride Tetraconazole	Specific Toxicity	1, 2, 3.1, 4.2, 5	*Carassius auratus* Teleost Fish Crustaceans	[8; 9]
CYP enzymes	Binding leading to decreased activity	Clotrimazole Ketoconazole Miconazole Sulconazole Tioconazole antifungal imidazoles	Specific Toxicity	1, 2, 3, 4, 5	*Dorosoma cepedianum* *Gadus morhua* *Oncorhynchus mykiss* Teleost Fish	[8; 9; 32]
CYP1A	Binding leading to inhibition	2-aminoanthracene Acrylamide	Specific Toxicity	1, 2, 3, 4, 5	*Oncorhynchus mykiss* *Stenotomus chrysops*	[9; 33; 34; 35; 36]

		PCB77			*Ictalurus punctatus*	
Acetylcholinesterase	Reversible binding leading to inhibition	Carbaryl Alanycarb Aldicarb Bendiocarb Benfuracarb Butocarboxim Butoxycarboxim Carbofuran Carbosulfan Ethiofencarb Fenobucarb Formetanate Furathiocarb Isoprocarb Methiocarb Methomyl Metolcarb Oxamyl Pirimicarb Propoxur Thiodicarb Thiofanox Triazamate Trimethacarb XMC Xylylcarb carbamates quaternary ammonium group tertiary ammonium group	Specific Toxicity	1, 2, 3.1, 4.1, 4.2, 4.3, 5	*Oncorhynchus mykiss* Orthologs in Teleost fish, Amphibian, Crustacean species	[37; 38; 39]
Acetylcholinesterase	Irreversible binding leading to inhibition	Acephate Azamethiphos Azinphos-ethyl Azinphos-methyl Cadusafos Chlorethoxyfos Chlorfenvinphos Chlormephos	Specific Toxicity	1, 2, 3.1, 4.1, 4.2, 4.3, 5	*Oncorhynchus mykiss* Orthologs in Teleost fish, Amphibian, Crustacean species	[37; 38; 39]

		Chlorpyrifos Chlorpyrifos-methyl Coumaphos Cyanophos Demeton-S-methyl Diazinon Dichlorvos/ DDVP Dicrotophos Dimethoate Dimethylvinphos Disulfoton EPN Ethion Ethoprophos Famphur Fenamiphos Fenitrothion Fenthion Fosthiazate Heptenophos Imicyafos isocarbophos Isofenphos Isoxathion Malathion Mecarbam Methamidophos Methidathion Mevinphos Monocrotophos Naled Omethoate Oxydemeton-methyl Parathion Parathion-methyl Phenthoate Phorate Phosalone				

			Phosmet Phosphamidon Phoxim Pirimiphos-methyl Profenofos Propetamphos Prothiofos Pyraclofos Pyridaphenthion Quinalphos Sulfotep Tebupirimfos Temephos Terbufos Tetrachlorvinphos Thiometon Triazophos Trichlorfon Vamidothion				
	Nicotinic acetylcholine receptor	competitive agonist	Acetamiprid Clothianidin Dinotefuran Flupyradifurone Imidacloprid Nitenpyram Sulfoxaflor Thiacloprid Thiamethoxam nicotine Triflumezopyrim	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Daphnia magna,* *Daphnia pulex,* *Danio rerio,* *Lepisosteus oculatus,* *Xenopus tropicalis,* Teleost fish Crustaceans	[37; 40; 41; 42; 38]
	Nicotinic acetylcholine receptor	allosteric agonist	Spinosad Spinetoram	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Daphnia magna,* *Daphnia pulex*	[37; 40; 41; 38]
	Nicotinic acetylcholine receptor	Antagonist leading to inhibitory neurotoxicity	Bensultap Cartap Thiocyclam Thiosultrap-sodium nereistoxin analogues	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Daphnia magna,* *Daphnia pulex,* *Danio rerio,* *Lepisosteus oculatus,* *Xenopus tropicalis,*	[37; 40; 41; 38]

					Teleost fish Crustaceans	
Voltage gated sodium channel	Modulator leading to deactivation	Acrinathrin Allethrin Bifenthrin Bioallethrin Bioallethrin S-cyclopentenyl Bioresmethrin Cycloprothrin Cyfluthrin Cyhalothrin Cypermethrin Cyphenothrin [(1R)-trans-isomers] Deltamethrin Empenthrin [(EZ)- (1R)- isomers] Esfenvalerate Etofenprox Fenpropathrin Fenvalerate Flucythrinate Flumethrin Halfenprox Kadethrin Phenothrin [(1R)-trans- isomer] Prallethrin Resmethrin Silafluofen Tefluthrin Tetramethrin Tetramethrin [(1R)- isomers] Tralomethrin Transfluthrin alpha-Cypermethrin beta-Cyfluthrin beta-Cypermethrin d-cis-trans Allethrin d-trans Allethrin	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Danio rerio,* *Xenopus tropicalis,* Teleost fish Crustaceans	[37; 43; 44; 45; 46; 38]

			gamma-Cyhalothrin lambda-Cyhalothrin tau-Fluvalinate theta-Cypermethrin zeta-Cypermethrin DDT Methoxychlor type I pyrethrins type II pyrethrins				
	Voltage gated sodium channel	Binding during the slow inactivated state of the channel leading to deactivation	indoxacarb metaflumizone	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Danio rerio, Xenopus tropicalis, Daphnia magna, Daphnia pulex* Teleost fish	[37; 44; 47; 38; 48]
	GABA-gated chloride channel	Non-competitive antagonism leading to channel deactivation	endosulfan chlordane fipronil ethiprole	Specific Toxicity			[49; 42]
	Glutamate-gated chloride channel	Activation	Abamectin Emamectin benzoate Lepimectin Milbemectin avemectins milbemycins macrocyclic lactones	Specific Toxicity	1, 2, 3.1,3.2, 4.1, 4.3, 5	*Xenopus tropicalis, C. elegans, Daphnia pulex* Crustaceans	[37; 50; 51]
	Ryanodine and ryanodine-like receptors	Binding leading to cytosolic Ca2+ transients	Chlorantraniliprole Cyantraniliprole Flubendiamide	Specific Toxicity	1, 2, 3.1,3.2, 4.1, 4.3, 5	*Daphnia pulex* *C. elegans,* *Danio rerio, Esox Lucius, Gadus morhua, Poecilia formosa*	[37; 52; 38; 53]
	Photosystem II, triazine site	Binding leading to inhibition	Ametryne Amicarbazone Atrazine	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Chlamodomonas reinhardtii, Chlorella pyrenoidosa, P.*	[54; 37; 55; 56; 57]

		Bromacil Cyanazine Desmedipham Desmetryne Dimethametryne Hexazinone Lenacil Metamitron Metribuzin Phenmedipham Prometon Prometryne Propazine Pyrazon Simazine Simetryne Terbacil Terbumeton Terbuthylazine Terbutryne Trietazine			*subcapitata,* Green algae, Cyanobacteria	
Photosystem II, nitrile site	Binding leading to inhibition	Bentazon Bromofenoxim Bromoxynil Ioxynil Pyridate Pyrudafol	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Chlamodomonas reinhardtii, Chlorella pyrenoidosa, P. subcapitata,* Green algae, Cyanobacteria	[54; 37; 55; 56; 57]
Photosystem II, urea site	Binding leading to inhibition	Chlorobromuron Chlorotoluron Chloroxuron Dimefuron Diuron Ethidimuron Fenuron Fluometuron Isoproturon Isouron Linuron	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Chlamodomonas reinhardtii, Chlorella pyrenoidosa, P. subcapitata,* Green algae, Cyanobacteria	[54; 37; 55; 56; 57]

		Methabenzthiazuron Metobromuron Metoxuron Monolinuron Neburon Pentanochlor Propanil Siduron Tebuthiuron				
Photosystem I	Redox interference leading to electron diversion	Diquat Paraquat	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	Green Algae	[58; 37; 56; 59; 26]
Protoporphyrinogen IX oxidase	Inhibiting interference leading to decrease in activity	Acifluorfen-Na Azafenidin Benzfendizone Bifenox Butafenacil Carfentrazone-ethyl Chlomethoxyfen Cinidon-ethyl Fluazolate Flufenpyr-ethyl Flumiclorac-pentyl Flumioxazin Fluoroglycofen-ethyl Fluthiacet-methyl Fomesafen Halosafen Lactofen Oxadiargyl Oxadiazon Oxyfluorfen Pentoxazone Profluazol Pyraclonil Pyraflufen-ethyl	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.3, 5	*Chlamydomonas reinhardtii, Scenedesmus acutus,* Green algae, Cyanobacteria	[37; 60; 61; 62; 38; 63]

		Sulfentrazone Thidiazimin				
Phytoene desaturase	Interference leading to disruption of carotenoid synthesis	Beflubutamid Diflufenican Fluridone Flurochloridone Flurtamone Norflurazon Picolinafen	Specific Toxicity	1, 2, 3.1, 3.2, 4.3, 5	Green algae	[37; 64; 56; 65; 38]
Lycopene cyclase	Interference leading to disruption of carotenoid synthesis	Amitrole	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.3, 5	Green algae	[37; 66; 64; 56; 65; 38]
4-hydroxyphenyl pyruvate di-oxygenase	Binding leading to disruption of carotenoid synthesis	Benzobicyclon Benzofenap Isoxachlortole Isoxaflutole Mesotrione Pyrazolynate Pyrazoxyfen Sulcotrione	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.3, 5	Green algae	[37; 67]
EPSP (enolpyruvylshikimate 3-phosphate) synthase	Binding leading to amino acid biosynthesis disruption	Glyphosate Sulfosate	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.3, 5	Green algae	[37; 68; 69]
Acetolactate synthase ALS (acetohydroxy-acid synthase AHAS)	Binding leading to amino acid biosynthesis inhibition	Amidosulfuron Azimsulfuron Bensulfuron-methyl Bispyribac-Na Chlorimuron-ethyl Chlorsulfuron Cinosulfuron Cloransulam-methyl Cyclosulfamuron Diclosulam Ethametsulfuron-methyl Ethoxysulfuron	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	Green algae, Red algae, Brown algae	[37; 70; 68; 71; 72; 69]

		Flazasulfuron Florasulam Flucarbazone-Na Flumetsulam Flupyrsulfuron-methyl-Na Foramsulfuron Halosulfuron-methyl Imazamethabenz-methyl Imazamox Imazapic Imazapyr Imazaquin Imazethapyr Imazosulfuron Iodosulfuron Mesosulfuron Metosulam Metsulfuron-methyl Nicosulfuron Oxasulfuron Penoxsulam Primisulfuron-methyl Propoxycarbazone-Na Prosulfuron Pyrazosulfuron-ethyl Pyribenzoxim Pyriftalid Pyriminobac-methyl Pyrithiobac-Na Rimsulfuron Sulfometuron-methyl Sulfosulfuron Thifensulfuron-methyl Triasulfuron Tribenuron-methyl Trifloxysulfuron Triflusulfuron-methyl Tritosulfuron			

Glutamine synthase	Inhibitory interaction leading to inhibition of amino acid synthesis	Bialaphos Glufosinate-ammonium	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	Algal species, *Ctenopharyngodon idellus*	[37; 73; 74; 38]
Microtubule	Interaction with multiple sites leading to disruption of microtubule assembly and cell division	Amiprophos-methyl Benfluralin Butamiphos Butralin Chlorthal-dimethyl (DCPA) Dinitramine Dithiopyr Ethalfluralin Oryzalin Pendimethalin Propyzamide Tebutam Thiazopyr Trifluralin	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 5	*Lithobates clamitans, Oncorhynchus mykiss,* Daphnia sp., Algae	[37; 75; 76; 77; 38]
Microtubule	Interaction with multiple sites leading to disruption microtubule assembly and mitosis	Barban Chlorpropham Propham	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Thamnocephalus platyurus, Brachionu calyciflorus, Pseudokirchneriella subcapitata,* Algae	[37; 78; 79; 38]
DHP synthase	Inhibition of enzyme and blocking the conversion of 4-aminobenzoic acid to 7,8 - dihydropteroate	Asulam	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	Teleost fish, Green algae	[80; 37; 81; 38]
Acetyl-CoA carboxylase	Binding leading to inhibition of fatty acid	Alloxydim Butroxydim Clethodim	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Danio rerio, Xenopus laevis, Discoglossus scovazzi,* Teleost fish,	[37; 82; 83; 84; 38]

	synthesis	Clodinafop-propargyl Cycloxydim Cyhalofop-butyl Diclofop-methyl Fenoxaprop-P-ethyl Fluazifop-P-butyl Haloxyfop-R-methyl Pinoxaden Profoxydim Propaquizafop Quizalofop-P-ethyl Sethoxydim Spirodiclofen Spiromesifen Spirotetramat Tepraloxydin Tralkoxydim			Green algae (except the class of Prasinophyceae), Red algae	
Fatty acid synthesis	Interaction with components of the cycle (not acetyl-CoA carboxylase) leading to inhibition	Benfuresate Bensulide Benthiocarb Butyrate Cycloate Dalapon Dimepiperate EPTC Esprocarb Ethofumesate Flupropanate Molinate Orbencarb Pebulate Prosulfocarb TCA Tiocarbazil Triallate Vernolate	Specific Toxicity	1.2, 2, 3.1, 4.1, 5	*Ictalurus punctatus, Morona saxatilis, Thalassiosira pseudonana,* Green algae	[85; 86; 37; 87; 88; 89]
VLCFA (very long chain fatty acid)	Interaction with components of	Acetochlor Alachlor	Specific Toxicity	1.2, 2, 3.1, 4.1, 5	*Cyprinus carpio, Perca fluviatilis*	[37; 90; 91; 92]

synthesis	the process leading inhibition and disruption of cell division	Anilofos Butachlor Cafenstrole Dimethachlor Dimethanamid Diphenamid Fentrazamide Flufenacet Mefenacet Metazachlor Metolachlor Naproanilide Napropamide Pethoxamid Piperophos Pretilachlor Propachlor Propisochlor Thenylchlor				
Cellulose synthase	Interaction leading to cell wall (cellulose) synthesis inhibition	Chlorthiamid Dichlobenil Flupoxam Isoxaben Quinclorac	Specific Toxicity	1.2, 2, 3.1, 4.1, 4.3, 5	Green algae	[37; 93; 94]

14a-demethylase (CYP51)	Binding indicative of coordination between the triazole N-4 and the haem Fe^{3+} leading to inhibition of the 14a-demethylation during ergosterol biosynthesis	Azaconazole Bitertanol Bromuconazole Cyproconazole Difenoconazole Diniconazole Epoxiconazole Etaconazole Fenarimol Fenbuconazole Fluquinconazole Flusilazole Flutriafol Hexaconazole Imazalil Imibenconazole Ipconazole Metconazole Myclobutanil Nuarimol Oxpoconazole Pefurazoate Penconazole Prochloraz Propiconazole Prothioconazole Pyrifenox Pyrisoxazole Simeconazole Tebuconazole Tetraconazole Triadimefon Triadimenol Triflumizole Triforine Triticonazole	Specific Toxicity	1.1, 1.2, 2, 3.1,3.2, 4.1, 4.2, 4.3, 5	*Danio rerio, Xenopus tropicalis,* Teleost fish, Green algae (Chlamydomonadales)	[37; 95; 96; 97; 98]
squalene epoxidase	Hydrogen bonding leading	Naftitine Pyributicarb	Specific Toxicity	1.1, 1.2, 2, 3.1, 4.1, 4.3, 5	*Amphimedon queenslandica, Danio*	[37; 99; 96; 100; 38]

	to inhibition of ergosterol and cholesterol biosynthetic pathways (terbinafine site: hydroxyl group of Tyr90)	Terbinafine			*rerio, Daphnia pulex, Oryzias latipes, Trichoplax adhaerens,*	
RNA polymerase I	Interaction leading to disruption of nucleic acid biosynthesis	Benalaxyl Benalaxyl-M Furalaxyl Metalaxyl Metalaxyl-M Ofurace Oxadixyl	Specific Toxicity	1.1, 1.2, 2, 3.1, 4.1, 4.3, 5	*Tetrahymena thermophile, Thalassiosira pseudonana*	[37; 101; 56; 102; 96; 103; 38]
DNA topoisomerase type II	Disruptive interaction leading to nucleic acid biosynthesis inhibition	Oxolinic acid	Specific Toxicity	1.1, 1.2, 2, 3.1, 3.2, 4.1, 4.3, 5	Crustacean	[37; 104; 38; 105]
Protein biosynthesis	Disruptive interaction leading to inhibition of protein synthesis	Blasticidin-S Kasugamycin Streptomycin Oxytetracycline	Specific Toxicity	1.2, 2, 3.1, 4.1, 4.3, 5	Green algae	[37; 106; 107]
β-tubulin assembly in mitosis	Disruptive interaction leading to mitosis and cell division inhibition	Benomyl Carbendazim Diethofencarb Ethaboxam Fuberidazole Thiabendazole Thiophanate Thiophanate-methyl Zoxamide	Specific Toxicity	1.1, 1.2, 2, 3.1, 3.2, 4.2, 4.3, 5	Crustacean, Green algae	[108; 37; 109; 110; 111; 112]
sterol 24-C-methyltransferase	Binding leading to inhibition of	Edifenphos Iprobenfos (IBP)	Specific Toxicity	1, 2, 3.1, 4.1, 4.3, 5	Crustaceans (daphnids)	[113; 37; 114; 115; 116; 96;

	phosphatidyl choline synthesis	Isoprothiolane Pyrazophos				117]
NADH oxireductase (mitochondria)	Binding to membrane subunit of the enzyme (coupling site I) leading to inhibition of the mitochondrial respiratory chain	Diflumetorim Rotenone Tolfenpyrad	Specific Toxicity	1, 2, 3.1, 4.1, 4.2, 5	*Daphnia pulex, Paradiaptomus lamellatus* Teleost fish *no effect in Potamonuates sp.	[37; 118; 119; 120; 121]
complex I electron transport (mitochondria)	Interference with electron transport chain leading to inhibition of mitochondrial respiratory chain	Fenpyroximate Pyridaben Pyrimidifen Tebufenpyrad Tolfenpyrad	Specific Toxicity	1, 2, 3.1, 4.1, 4.2, 5		[37; 122]
succinic dehydrogenase (mitochondria)	Interaction with the complex II of the enzyme leading to inhibition of mitochondrial respiratory chain	Benodanil Benzovindiflupyr Bixafen Boscalid Carboxin Cyenopyrafen Cyflumetofen Fenfuram Fluopyram Flutolanil Fluxapyroxad Furametpyr Isofetamid Isopyrazam Mepronil Oxycarboxin Penflufen	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	Teleost fish (*Danio rerio* embryos), invertebrates	[123; 64; 124; 101; 56; 59; 125; 126; 127; 128]

		Penthiopyrad Pydiflumetofen Pyflubumide Sedaxane Thifluzamide				
ubiquinol oxidase at Qo site	Reactive interaction targeting complex III site of mitochondrial respiratory chain leading to inhibition	Azoxystrobin Coumoxystrobin Dimoxystrobin Enoxastrobin Famoxadone Fenamidone Fenaminstrobin Flufenoxystrobin Fluoxastrobin Kresoxim-methyl Mandestrobin Metominostrobin Orysastrobin Picoxystrobin Pyraclostrobin Pyrametostrobin Pyraoxystrobin Pyribencarb Triclopyricarb Trifloxystrobin	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 4.3, 5	*Danio rerio, Daphnia magna, Chlorella vulgaris*, Xenopus sp.,	[37; 129; 130; 131; 96]
complex IV, proton gradient (mitochondria)	Uncoupling via disruption of proton gradient within complex IV leading to inhibition of the oxidative phosphorylation	Binapacryl Chlorfenapyr Dinocap DNOC Fluazinam Meptyldinocap Sulfuramid	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 5	Cladocera, Copepoda, Rotifera (crustacean)	[37; 132]
respiration, ATP synthase	inhibition	Azocyclotin Cyhexatin Diafenthiuron	Specific Toxicity	1, 2, 3.1, 3.2, 4.1, 4.2, 5	*Danio rerio, Oryzias latipes*, Teleost fish (early life), Xenopus	[37; 133; 134; 135; 136; 137; 138; 139]

		Fenbutatin oxide Fentin acetate Fentin chloride Fentin hydroxide Propargite Tetradifon			sp. (early life), Cyanobacteria, Green algae	
juvenile hormone	Mimicking effect leading to increased male neonate production	Fenoxycarb Hydroprene Kinoprene Methoprene Pyriproxyfen	Specific Toxicity	1, 2, 3.1, 4.1, 5	*Daphnia magna,* Crustacean	[37; 140]
ecdysone receptor	Agonistic effect leading to premature molting	Chromafenozide Halofenozide Methoxyfenozide Tebufenozide	Specific Toxicity	1, 2, 3.1, 4.3, 5	*Xenopus tropicalis*	[37; 96]
Chitin biosynthesis	Disruption of chitin biosynthesis leading to premature molting	Bistrifluron Bistrifluron Chlorfluazuron Diflubenzuron Etoxazole Flucycloxuron Flufenoxuron Hexaflumuron Lufenuron Novaluron Noviflumuron Teflubenzuron Triflumuron	Specific Toxicity	1, 2, 3.1, 4.1, 5	*Daphnia magna*	[37; 141; 142]

References:

[1] P. Antczak, T.A. White, A. Giri, F. Michelangeli, M.R. Viant, M.T. Cronin, C. Vulpe, F. Falciani, Systems Biology Approach Reveals a Calcium-Dependent Mechanism for Basal Toxicity in Daphnia magna. Environ Sci Technol 49 (2015) 11132-11140.
[2] O. Thastrup, P.J. Cullen, B.K. Drøbak, M.R. Hanley, A.P. Dawson, Thapsigargin, a tumor promoter, discharges intracellular Ca2+ stores by specific inhibition of the endoplasmic reticulum Ca2(+)-ATPase. (1990).
[3] C.M. Ellison, P. Piechota, J.C. Madden, S.J. Enoch, M.T. Cronin, Adverse Outcome Pathway (AOP) Informed Modeling of Aquatic Toxicology: QSARs, Read-Across, and Interspecies Verification of Modes of Action. Environ Sci Technol 50 (2016) 3995-4007.
[4] J.M. McKim, S.P. Bradbury, G.J. Niemi, FISH ACUTE TOXICITY SYNDROMES AND THEIR USE IN THE QSAR APPROACH TO HAZARD ASSESSMENT. Environmental Health Perspectives 71 (1987) 171-186.
[5] M. Nendza, M. Muller, A. Wenzel, Discriminating toxicant classes by mode of action: 4. Baseline and excess toxicity. Sar and Qsar in Environmental Research 25 (2014) 393-405.
[6] D.W. Roberts, J.F. Costello, Mechanisms of action for general and polar narcosis: A difference in dimension. Qsar & Combinatorial Science 22 (2003) 226-233.
[7] H.J.M. Verhaar, C.J. Vanleeuwen, J.L.M. Hermens, CLASSIFYING ENVIRONMENTAL-POLLUTANTS .1. STRUCTURE-ACTIVITY-RELATIONSHIPS FOR PREDICTION OF AQUATIC TOXICITY. Chemosphere 25 (1992) 471-491.
[8] AOP-Wiki, AOP-Wiki, 2018.
[9] R.T. Di Guilo, D.E. Hinton, The Toxicology of Fishes, CRC Press, 2008.
[10] S.J. Enoch, M.T.D. Cronin, A review of the electrophilic reaction chemistry involved in covalent DNA binding. http://dx.doi.org/10.3109/10408444.2010.494175 (2010).
[11] Błaszczyk Ewa, M.-Š. Danuta, Polycyclic aromatic hydrocarbons and PAH-related DNA adducts. (2017).
[12] D.L. Eaton, E.P. Gallagher, Mechanisms of aflatoxin carcinogenesis. Annu Rev Pharmacol Toxicol 34 (1994) 135-172.
[13] B.M. Hasspieler, G.D. Haffner, K. Adeli, Roles of DT diaphorase in the genotoxicity of nitroaromatic compounds in human and fish cell lines. Journal of Toxicology and Environmental Health 52 (1997) 137-148.
[14] W.F. Hodnick, A.C. Sartorelli, Measurement of dicumarol-sensitive NADPH: (menadione-cytochrome c) oxidoreductase activity results in an artifactual assay of DT-diaphorase in cell sonicates. Anal Biochem 252 (1997) 165-168.
[15] J.L. Bolton, M.A. Trush, T.M. Penning, G. Dryhurst, T.J. Monks, Role of quinones in toxicology. Chemical Research in Toxicology 13 (2000) 135-160.
[16] S.J. Enoch, C.M. Ellison, T.W. Schultz, M.T. Cronin, A review of the electrophilic reaction chemistry involved in covalent protein binding relevant to toxicity. Crit Rev Toxicol 41 (2011) 783-802.
[17] W.E. Hawkins, W.W. Walker, M.O. James, C.S. Manning, D.H. Barnes, C.S. Heard, R.M. Overstreet, Carcinogenic effects of 1,2-dibromoethane (ethylene dibromide; EDB) in Japanese medaka (Oryzias latipes). Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis 399 (1998) 221-232.

[18] S.P. Bradbury, J.M. Dady, P.N. Fitzsimmons, M.M. Voit, D.E. Hammermeister, R.J. Erickson, Toxicokinetics and metabolism of aniline and 4-chloroaniline in medaka (*Oryzias latipes*). Toxicology and Applied Pharmacology 118 (1993) 205-214.
[19] W. de Wolf, W. Seinen, J.L. Hermens, N-acetyltransferase activity in rainbow trout liver and in vitro biotransformation of chlorinated anilines and benzenes in fish. Xenobiotica 23 (1993) 1045-1056.
[20] K.M. Kleinow, W.L. Beilfuss, H.H. Jarboe, B.F. Droy, J.J. Lech, Pharmacokinetics, bioavailability, distribution, and metabolism of sulfadimethoxine in the rainbow-trout (*Oncorhynchus mykiss*). Canadian Journal of Fisheries and Aquatic Sciences 49 (1992) 1070-1077.
[21] Z.E. Suntres, P.N. Shek, Nitrofurantoin-induced pulmonary toxicity. In vivo evidence for oxidative stress-mediated mechanisms. Biochem Pharmacol 43 (1992) 1127-1135.
[22] L.T. Dinkova-Kostova, P. Talalay, Persuasive evidence that quinone reductase type 1 (DT diaphorase) protects cells against the toxicity of electrophiles and reactive forms of oxygen. Free Radical Biology and Medicine 29 (2000) 231-240.
[23] B.E. Britigan, T.L. Roeder, G.T. Rasmussen, D.M. Shasby, M.L. McCormick, C.D. Cox, Interaction of the Pseudomonas aeruginosa secretory products pyocyanin and pyochelin generates hydroxyl radical and causes synergistic damage to endothelial cells. Implications for Pseudomonas-associated tissue injury. J Clin Invest 90 (1992) 2187-2196.
[24] A.A. Caro, A.I. Cederbaum, Oxidative stress, toxicology, and pharmacology of CYP2E1. Annual Review of Pharmacology and Toxicology 44 (2004) 27-42.
[25] S.D. Su, S.G. Cong, Y.K. Bi, D.D. Gao, Paraquat promotes the epithelial-mesenchymal transition in alveolar epithelial cells through regulating the Wnt/beta-catenin signal pathway. European Review for Medical and Pharmacological Sciences 22 (2018) 802-809.
[26] W.-T. Tsai, A review on environmental exposure and health risks of herbicide paraquat. Toxicological and Environmental Chemistry 95 (2013) 197-206.
[27] C.C. Abnet, R.L. Tanguay, M.E. Hahn, W. Heideman, R.E. Peterson, Two forms of aryl hydrocarbon receptor type 2 in rainbow trout (Oncorhynchus mykiss) - Evidence for differential expression and enhancer specificity. Journal of Biological Chemistry 274 (1999) 15159-15166.
[28] T. Bresolin, M. de Freitas Rebelo, A. Celso Dias Bainy, Expression of PXR, CYP3A and MDR1 genes in liver of zebrafish. Comp Biochem Physiol C Toxicol Pharmacol 140 (2005) 403-407.
[29] D.A. Terreros, J. Coombs, Cyclosporine nephropathy: inhibition of osmoregulatory renal cell transport. Ann Clin Lab Sci 19 (1989) 337-344.
[30] G.T. Ankley, K.M. Jensen, E.A. Makynen, M.D. Kahl, J.J. Korte, M.W. Hornung, T.R. Henry, J.S. Denny, R.L. Leino, V.S. Wilson, M.C. Cardon, P.C. Hartig, L.E. Gray, Effects of the androgenic growth promoter 17-beta-trenbolone on fecundity and reproductive endocrinology of the fathead minnow. Environ Toxicol Chem 22 (2003) 1350-1360.
[31] P.I. Petkov, S. Temelkov, D.L. Villeneuve, G.T. Ankley, O.G. Mekenyan, Mechanism-based categorization of aromatase inhibitors: a potential discovery and screening tool. http://dx.doi.org/10.1080/10629360903438347 (2009).
[32] W. Zhang, Y. Ramamoorthy, T. Kilicarslan, H. Nolte, R.F. Tyndale, E.M. Sellers, Inhibition of cytochromes P450 by antifungal imidazole derivatives. Drug Metab Dispos 30 (2002) 314-318.
[33] J.W. Gooch, A.A. Elskus, P.J. Kloepper-Sams, M.E. Hahn, J.J. Stegeman, Effects of ortho- and non-ortho-substituted polychlorinated biphenyl congeners on the hepatic monooxygenase system in scup (Stenotomus chrysops). Toxicol Appl Pharmacol 98 (1989) 422-433.
[34] M.L. Haasch, L.A. Sutherland, P.J. Wejksnora, J.J. Lech, Effect of acrylamide monomer on hepatic CYP1A1 monooxygenase induction in rainbow trout. Comp Biochem Physiol C 102 (1992) 281-286.

[35] D.E. Watson, L. Menard, J.J. Stegeman, R.T. Di Giulio, Aminoanthracene is a mechanism-based inactivator of CYP1A in channel catfish hepatic tissue. Toxicol Appl Pharmacol 135 (1995) 208-215.
[36] R.D. White, D. Shea, J.J. Stegeman, Metabolism of the aryl hydrocarbon receptor agonist 3,3',4,4'-tetrachlorobiphenyl by the marine fish scup (Stenotomus chrysops) in vivo and in vitro. Drug Metab Dispos 25 (1997) 564-572.
[37] J.E. Casida, Pest Toxicology: The Primary Mechanisms of Pesticide Action. Chemical Research in Toxicology 22 (2009) 609-619.
[38] R.M. Waterhouse, F. Tegenfeldt, J. Li, E.M. Zdobnov, E.V. Kriventseva, OrthoDB: a hierarchical catalog of animal, fungal and bacterial orthologs. Nucleic Acids Research 41 (2013).
[39] M.B. Čolović, D.Z. Krstić, T.D. Lazarević-Pašti, A.M. Bondžić, V.M. Vasić, Acetylcholinesterase Inhibitors: Pharmacology and Toxicology, Curr Neuropharmacol, 2013, pp. 315-335.
[40] J.E. Casida, Neonicotinoids and Other Insect Nicotinic Receptor Competitive Modulators: Progress and Prospects. Annu Rev Entomol 63 (2018) 125-144.
[41] M. Ihara, S.D. Buckingham, K. Matsuda, D.B. Sattelle, Modes of Action, Resistance and Toxicity of Insecticides Targeting Nicotinic Acetylcholine Receptors. Curr Med Chem 24 (2017) 2925-2934.
[42] N. Simon-Delso, V. Amaral-Rogers, L.P. Belzunces, J.M. Bonmatin, M. Chagnon, C. Downs, L. Furlan, D.W. Gibbons, C. Giorio, V. Girolami, D. Goulson, D.P. Kreutzweiser, C.H. Krupke, M. Liess, E. Long, M. McField, P. Mineau, E.A.D. Mitchell, C.A. Morrissey, D.A. Noome, L. Pisa, J. Settele, J.D. Stark, A. Tapparo, H. Van Dyck, J. Van Praagh, J.P. Van der Sluijs, P.R. Whitehorn, M. Wiemers, Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites. Environ Sci Pollut Res Int 22 (2015) 5-34.
[43] T.G. Davies, L.M. Field, P.N. Usherwood, M.S. Williamson, DDT, pyrethrins, pyrethroids and insect sodium channels. IUBMB Life 59 (2007) 151-162.
[44] L.M. Field, T.G. Emyr Davies, A.O. O'Reilly, M.S. Williamson, B.A. Wallace, Voltage-gated sodium channels as targets for pyrethroid insecticides, Eur Biophys J, 2017, pp. 675-679.
[45] N.C.f.B. Information, Home - HomoloGene - NCBI, 2018.
[46] K. Palmquist, J. Salatas, A. Fairbrother, Pyrethroid Insecticides: Use, Environmental Fate, and Ecotoxicology | IntechOpen, in: F.K. Perveen (Ed.), Insecticides, IntechOpen, 2012.
[47] K. Silver, K. Dong, B.S. Zhorov, Molecular Mechanism of Action and Selectivity of Sodium Channel Blocker Insecticides. Current Medicinal Chemistry 24 (2017) 2912-2924.
[48] Y. Zhang, Y. Du, D. Jiang, C. Behnke, Y. Nomura, B.S. Zhorov, K. Dong, The Receptor Site and Mechanism of Action of Sodium Channel Blocker Insecticides. J Biol Chem 291 (2016) 20113-20124.
[49] L.W. Pisa, V. Amaral-Rogers, L.P. Belzunces, J.M. Bonmatin, C.A. Downs, D. Goulson, D.P. Kreutzweiser, C. Krupke, M. Liess, M. McField, C.A. Morrissey, D.A. Noome, J. Settele, N. Simon-Delso, J.D. Stark, J.P. Van der Sluijs, H. Van Dyck, M. Wiemers, Effects of neonicotinoids and fipronil on non-target invertebrates. Environ Sci Pollut Res Int 22 (2015) 68-102.
[50] A. Sturm, P. Cunningham, M. Dean, The ABC transporter gene family of Daphnia pulex. BMC Genomics 10 (2009) 170.
[51] A.J. Wolstenholme, A.T. Rogers, Glutamate-gated chloride channels and the mode of action of the avermectin/milbemycin anthelmintics. Parasitology 131 Suppl (2005) S85-95.

[52] B.J. Troczka, M.S. Williamson, L.M. Field, T.G.E. Davies, Rapid selection for resistance to diamide insecticides in Plutella xylostella via specific amino acid polymorphisms in the ryanodine receptor. Neurotoxicology 60 (2017) 224-233.
[53] H. Xu, Z. Sun, Ryanodine Receptors for Drugs and Insecticides: An Overview. Mini Rev Med Chem (2018).
[54] M. Broser, C. Glöckner, A. Gabdulkhakov, A. Guskov, J. Buchta, J. Kern, F. Müh, H. Dau, W. Saenger, A. Zouni, Structural Basis of Cyanobacterial Photosystem II Inhibition by the Herbicide Terbutryn*, J Biol Chem, 2011, pp. 15964-15972.
[55] H. Hiranpradit, C.L. Foy, Effect of 4 triazine herbicides on growth of non-target green algae. Weed Science 40 (1992) 134-142.
[56] A. Marchler-Bauer, M.K. Derbyshire, N.R. Gonzales, S. Lu, F. Chitsaz, L.Y. Geer, R.C. Geer, J. He, M. Gwadz, D.I. Hurwitz, C.J. Lanczycki, F. Lu, G.H. Marchler, J.S. Song, N. Thanki, Z. Wang, R.A. Yamashita, D. Zhang, C. Zheng, S.H. Bryant, CDD: NCBI's conserved domain database. Nucleic Acids Research 43 (2015) D222-D226.
[57] H.G. Peterson, C. Boutin, P.A. Martin, K.E. Freemark, N.J. Ruecker, M.J. Moody, Aquatic phyto-toxicity of 23 pesticides applied at expected environmental concentrations. Aquatic Toxicology 28 (1994) 275-292.
[58] P.S. Boger, Gerhard, Target Sites of Herbicide Action, 2018.
[59] A. Marchler-Bauer, S. Lu, J.B. Anderson, F. Chitsaz, M.K. Derbyshire, C. DeWeese-Scott, J.H. Fong, L.Y. Geer, R.C. Geer, N.R. Gonzales, M. Gwadz, D.I. Hurwitz, J.D. Jackson, Z. Ke, C.J. Lanczycki, F. Lu, G.H. Marchler, M. Mullokandov, M.V. Omelchenko, C.L. Robertson, J.S. Song, N. Thanki, R.A. Yamashita, D. Zhang, N. Zhang, C. Zheng, S.H. Bryant, CDD: a Conserved Domain Database for the functional annotation of proteins. Nucleic Acids Research 39 (2011) D225-D229.
[60] M. Hiraki, S. Ohki, Y. Sato, I. Jablonkai, P. Boger, K. Wakabayashi, Protoporphyrinogen-IX oxidase inhibitors: Bioactivation of thiadiazolidines. Pesticide Biochemistry and Physiology 70 (2001) 159-167.
[61] Y. Miyamoto, Y. Ikeda, K. Wakabayashi, Synthesis and phytotoxic activities of N-substituted phenyl isothiazolone derivatives. Journal of Pesticide Science 28 (2003) 293-300.
[62] T. Nagai, S. Ishihara, A. Yokoyama, T. Iwafune, Effects of four rice paddy herbicides on algal cell viability and the relationship with population recovery. Environ Toxicol Chem 30 (2011) 1898-1905.
[63] D.A. Witkowski, B.P. Halling, Inhibition of plant protoporphyrinogen oxidase by the herbicide acifluorfen-methyl. Plant Physiol 90 (1989) 1239-1242.
[64] C.A. Lalone, D.L. Villeneuve, L.D. Burgoon, C.L. Russom, H.W. Helgen, J.P. Berninger, J.E. Tietge, M.N. Severson, J.E. Cavallin, G.T. Ankley, Molecular target sequence similarity as a basis for species extrapolation to assess the ecological risk of chemicals with known modes of action. Aquat Toxicol 144-145 (2013) 141-154.
[65] H. Ogawa, I. Yamada, K. Arai, K. Hirase, K. Moriyasu, C. Schneider, G. Sandmann, P. Boger, K. Wakabayashi, Mode of bleaching phytotoxicity of herbicidal diphenylpyrrolidinones. Pest Management Science 57 (2001) 33-40.
[66] P. Castelfranco, T. Bisalputra, Inhibitory effect of amitrole on *Scenedesmus quadricauda*. Am J Bot 52 (1965) 222-227.
[67] F. Ndikuryayo, B. Moosavi, W.-C. Yang, G.-F. Yang, 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors: From Chemical Biology to Agrochemicals. (2017).
[68] E. Filiz, I. Koc, Genome-wide identification and comparative analysis of EPSPS (aroA) genes in different plant species. Journal of Plant Biochemistry and Biotechnology 25 (2016) 21-29.

[69] E. Smedbol, M. Lucotte, M. Labrecque, L. Lepage, P. Juneau, Phytoplankton growth and PSII efficiency sensitivity to a glyphosate-based herbicide (Factor 540 (R)). Aquatic Toxicology 192 (2017) 265-273.
[70] C. Delye, A. Duhoux, J.A.C. Gardin, J. Gouzy, S. Carrere, High conservation of the transcriptional response to acetolactate-synthase-inhibiting herbicides across plant species. Weed Research 58 (2018) 2-7.
[71] X.H. Lv, Z.L. Ren, H. Liu, H.D. Li, Q.S. Li, L. Wang, L.S. Zhang, X.K. Yao, H.Q. Cao, Design, Synthesis and Biological Evaluation of Novel Pyrazole Sulfonamide Derivatives as Potential AHAS Inhibitors. Chemical & Pharmaceutical Bulletin 66 (2018) 358-362.
[72] B. Nystrom, H. Blanck, Effects of the sulfonylurea herbicide metsulfuron methyl on growth and macromolecular synthesis in the green alga Selenastrum capricornutum. Aquatic Toxicology 43 (1998) 25-39.
[73] H. Nakashita, K. Watanabe, O. Hara, T. Hidaka, H. Seto, Studies on the biosynthesis of bialaphos. Biochemical mechanism of C-P bond formation: discovery of phosphonopyruvate decarboxylase which catalyzes the formation of phosphonoacetaldehyde from phosphonopyruvate. J Antibiot (Tokyo) 50 (1997) 212-219.
[74] I. Ujváry, Chapter 3 - Pest Control Agents from Natural Products, in: R. Krieger (Ed.), Hayes' Handbook of Pesticide Toxicology (Third Edition), Academic Press, New York, 2010, pp. 119-229.
[75] R.C. Eng, G.O. Wasteneys, The microtubule plus-end tracking protein ARMADILLO-REPEAT KINESIN1 promotes microtubule catastrophe in Arabidopsis. Plant Cell 26 (2014) 3372-3386.
[76] D.P. Oliver, R.S. Kookana, R.B. Miller, R.L. Correll, Comparative environmental impact assessment of herbicides used on genetically modified and non-genetically modified herbicide-tolerant canola crops using two risk indicators. Sci Total Environ 557-558 (2016) 754-763.
[77] D. Van Damme, K. Van Poucke, E. Boutant, C. Ritzenthaler, D. Inze, D. Geelen, In vivo dynamics and differential microtubule-binding activities of MAP65 proteins. Plant Physiol 136 (2004) 3956-3967.
[78] J. Holy, Chlorpropham [isopropyl N-(3-chlorophenyl) carbamate] disrupts microtubule organization, cell division, and early development of sea urchin embryos. J Toxicol Environ Health A 54 (1998) 319-333.
[79] M. Passananti, M. Lavorgna, M.R. Iesce, M. DellaGreca, E. Criscuolo, A. Parrella, M. Isidori, F. Temussi, Chlorpropham and phenisopham: phototransformation and ecotoxicity of carbamates in the aquatic environment. Environ Sci Process Impacts 16 (2014) 823-831.
[80] W. Ahrens, Herbicide handbook, Seventh edition ed., Weed Science Society of America, Champaign, IL, 1994.
[81] W. Chotpatiwetchkul, K. Boonyarattanakalin, D. Gleeson, M.P. Gleeson, Exploring the catalytic mechanism of dihydropteroate synthase: elucidating the differences between the substrate and inhibitor. Org Biomol Chem 15 (2017) 5593-5601.
[82] R. Huerlimann, K. Heimann, Comprehensive guide to acetyl-carboxylases in algae. Crit Rev Biotechnol 33 (2013) 49-65.
[83] N. Wagner, S. Lotters, M. Veith, B. Viertel, Acute toxic effects of the herbicide formulation and the active ingredient used in cycloxydim-tolerant maize cultivation on embryos and larvae of the African clawed frog, Xenopus laevis. Bull Environ Contam Toxicol 94 (2015) 412-418.
[84] N. Wagner, S. Lotters, M. Veith, B. Viertel, Acute Toxic Effects of the Herbicide Formulation Focus((R)) Ultra on Embryos and Larvae of the Moroccan Painted Frog, Discoglossus scovazzi. Arch Environ Contam Toxicol 69 (2015) 535-544.
[85] R.C. Bromilow, K., Pathways and Mechanisms of Transport of Herbicides in Plants | SpringerLink, in: K. R.C. (Ed.), Target Sites for Herbicide Action. Topics in Applied Chemistry, Springer, Boston, MA, 1991.

[86] J.R. Cashman, L.D. Olsen, R.S. Nishioka, E.S. Gray, H.A. Bern, S-oxygenation of thiobencarb (Bolero) in hepatic preparations from striped bass (Morone saxatilis) and mammalian systems. Chem Res Toxicol 3 (1990) 433-440.
[87] E.G. Magnucka, Y. Suzuki, S.J. Pietr, A. Kozubek, R. Zarnowski, Cycloate, an inhibitor of fatty acid elongase, modulates the metabolism of very-long-side-chain alkylresorcinols in rye seedlings. Pest Manag Sci 65 (2009) 1065-1070.
[88] Y. Shimasaki, M. Tsuyama, R. Tasmin, X. Qiu, M. Shimizu, Y. Sato, Y. Yamasaki, Y. Kato-Unoki, A. Nukata, T. Nakashima, H. Ichinose, H. Wariishi, T. Honjo, Y. Oshima, Thiobencarb herbicide reduces growth, photosynthetic activity, and amount of Rieske iron-sulfur protein in the diatom Thalassiosira pseudonana. J Biochem Mol Toxicol 27 (2013) 437-444.
[89] T.M. Tate, R.N. Jackson, F.A. Christian, Effects of glyphosate and dalapon on total free amino acid profiles of Pseudosuccinea columella snails. Bull Environ Contam Toxicol 64 (2000) 258-262.
[90] T. Gotz, P. Boger, The very-long-chain fatty acid synthase is inhibited by chloroacetamides. Z Naturforsch C 59 (2004) 549-553.
[91] A. Lazartigues, C. Fratta, R. Baudot, L. Wiest, C. Feidt, M. Thomas, C. Cren-Olive, Multiresidue method for the determination of 13 pesticides in three environmental matrices: water, sediments and fish muscle. Talanta 85 (2011) 1500-1507.
[92] A. Ozkara, D. Akyil, Y. Eren, S.F. Erdogmus, Potential cytotoxic effect of Anilofos by using Allium cepa assay. Cytotechnology 67 (2015) 783-791.
[93] M. Tateno, C. Brabham, S. DeBolt, U.o.K. Department of Horticulture, 309 Plant Science Building, 1405 Veterans Drive, Lexington, KY 40546-0312, USA, Cellulose biosynthesis inhibitors – a multifunctional toolbox. Journal of Experimental Botany 67 (2018) 533-542.
[94] M.L. Tran, T.W. McCarthy, H. Sun, S.Z. Wu, J.H. Norris, M. Bezanilla, L. Vidali, C.T. Anderson, A.W. Roberts, Direct observation of the effects of cellulose synthesis inhibitors using live cell imaging of Cellulose Synthase (CESA) in Physcomitrella patens. Scientific Reports 8 (2018) 9.
[95] G.I. Lepesheva, M.R. Waterman, Sterol 14α-Demethylase Cytochrome P450 (CYP51), a P450 in all Biological Kingdoms. Biochim Biophys Acta 1770 (2007) 467-477.
[96] N.C.f.B.I. NCBI, Home - HomoloGene - NCBI, 2018.
[97] A.G. Warrilow, J.E. Parker, D.E. Kelly, S.L. Kelly, Azole Affinity of Sterol 14α-Demethylase (CYP51) Enzymes from Candida albicans and Homo sapiens. (2013).
[98] S. Zhao, P. Wei, M. Wu, X. Zhang, L. Zhao, X. Jiang, C. Hao, X. Su, D. Zhao, M. Cheng, Design, synthesis and evaluation of benzoheterocycle analogues as potent antifungal agents targeting CYP51. Bioorg Med Chem (2018).
[99] D. Debieu, J. Bach, A. Lasseron, C. Malosse, P. Leroux, Effects of sterol biosynthesis inhibitor fungicides in the phytopathogenic fungus, Nectria haematococca: Ergosterol depletion versus precursor or abnormal sterol accumulation as the mechanism of fungitoxicity. Pesticide Science 54 (1998) 157-167.
[100] M. Nowosielski, M. Hoffmann, L.S. Wyrwicz, P. Stepniak, D.M. Plewczynski, M. Lazniewski, K. Ginalski, L. Rychlewski, Detailed mechanism of squalene epoxidase inhibition by terbinafine. J Chem Inf Model 51 (2011) 455-462.
[101] A. Marchler-Bauer, S.H. Bryant, CD-Search: protein domain annotations on the fly. Nucleic Acids Research 32 (2004) W327-W331.
[102] N.C.f.B.I. NCBI, Conserved Domains Database (CDD) and Resources, 2018.
[103] E. Spazier, V. Storch, T. Braunbeck, Cytopathology of spleen in eel Anguilla-anguilla exposed to a chemical spill in the Rhine river. Diseases of Aquatic Organisms 14 (1992) 1-22.

[104] E.M.A. EMA, Oxolinic acid, Summary Report (http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2013/11/WC500155305.pdf), in: C.f.V.M. Products (Ed.), London, 2002.
[105] L. Wollenberger, B. Halling-Sorensen, K.O. Kusk, Acute and chronic toxicity of veterinary antibiotics to Daphnia magna. Chemosphere 40 (2000) 723-730.
[106] B. Halling-Sorensen, Algal toxicity of antibacterial agents used in intensive farming. Chemosphere 40 (2000) 731-739.
[107] C.P. van Buul, W. Visser, P.H. van Knippenberg, Increased translational fidelity caused by the antibiotic kasugamycin and ribosomal ambiguity in mutants harbouring the ksgA gene. FEBS Lett 177 (1984) 119-124.
[108] M. Arena, D. Auteri, S. Barmaz, G. Bellisai, A. Brancato, D. Brocca, L. Bura, H. Byers, A. Chiusolo, D.C. Marques, F. Crivellente, C. De Lentdecker, M. De Maglie, M. Egsmose, Z. Erdos, G. Fait, L. Ferreira, M. Goumenou, L. Greco, A. Ippolito, F. Istace, S. Jarrah, D. Kardassi, R. Leuschner, C. Lythgo, J.O. Magrans, P. Medina, I. Miron, T. Molnar, A. Nougadere, L. Padovani, J.M.P. Morte, R. Pedersen, H. Reich, A. Sacchi, M. Santos, R. Serafimova, R. Sharp, A. Stanek, F. Streissl, J. Sturma, C. Szentes, J. Tarazona, A. Terron, A. Theobald, B. Vagenende, A. Verani, L. Villamar-Bouza, A. European Food Safety, Peer review of the pesticide risk assessment of the active substance zoxamide. Efsa Journal 15 (2017) 25.
[109] M. Fujimura, T. Kamakura, H. Inoue, I. Yamaguchi, Amino-acid alterations in the beta-tubulin gene of Neurospora crassa that confer resistance to carbendazim and diethofencarb. Curr Genet 25 (1994) 418-422.
[110] M. Greenlee, A. Alonso, M. Rahman, N. Meednu, K. Davis, V. Tabb, R. Cook, R.K. Miller, The TOG protein Stu2/XMAP215 interacts covalently and non-covalently with SUMO. Cytoskeleton (Hoboken) (2018).
[111] P. Margot, F. Müller, P. Ackermann, Fungicides, Agricultural, 2. Individual Fungicides, in: B. Elvers (Ed.), *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2012.
[112] D.H. Young, Anti-tubulin Agents, in: H.H. Ishii, D. (Ed.), Fungicide Resistance in Plant Pathogens, Springer, Tokyo, 2015.
[113] P.R. Binks, G.D. Robson, M.W. Goosey, A. Humphreys, A.P.J. Trinci, Chitin Synthesis in fusarium-graminearum and its inhibition by edifenphos (Hinosan). Journal of General Microbiology 137 (1991) 615-620.
[114] Y. Hashimoto, Y. Nishiuchi, Establishment of bioassay methods for evaluation of acute toxicity of pesticides to aquatic organisms. Journal of Pesticide Science 6 (1975) 4.
[115] M. Katagiri, Y. Uesugi, Similarities Between the Fungicidal Action of Isoprothiolane and Organophosphorus Thiolate Fungicides. Phytopathology 67 (1977) 3.
[116] O. Kodama, K. Yamashita, T. Akatsuka, Mechanisms of action of organo-phosphorus fungicides .2. Edifenphos, inhibitor of phosphatidylcholine biosynthesis in *Pyricularia oryzae*. Agricultural and Biological Chemistry 44 (1980) 1015-1021.
[117] U.R. Sachin, S.K., Effect of fungicides on neck blast incidence and grain yield of rice in mid hills of Himachal Pradesh. Plant Diseas Res 26 (2003).
[118] T. Dalu, R.J. Wasserman, M. Jordaan, W.P. Froneman, O.L.F. Weyl, An Assessment of the Effect of Rotenone on Selected Non-Target Aquatic Fauna. PLoS One 10 (2015).
[119] R.C. Gupta, D. Milatovic, Chapter 23 - Insecticides, Biomarkers in Toxicology, Academic Press, Boston, 2014, pp. 389-407.

[120] C.-W. Huang, K.-M. Lin, T.-Y. Hung, Y.-C. Chuang, S.-N. Wu, Multiple Actions of Rotenone, an Inhibitor of Mitochondrial Respiratory Chain, on Ionic Currents and Miniature End-Plate Potential in Mouse Hippocampal (mHippoE-14) Neurons. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 47 (2018) 330-343.
[121] H. Zhou, F. Zhang, S.H. Chen, D. Zhang, B. Wilson, J.S. Hong, H.M. Gao, Rotenone activates phagocyte NADPH oxidase by binding to its membrane subunit gp91(phox). Free Radical Biology and Medicine 52 (2012) 303-313.
[122] H.J. Song, Y.X. Liu, L.X. Xiong, Y.Q. Li, N. Yang, Q.M. Wang, Design, Synthesis, and Insecticidal Activity of Novel Pyrazole Derivatives Containing alpha-Hydroxymethyl-N-benzyl Carboxamide, alpha-Chloromethyl-N-benzyl Carboxamide, and 4,5-Dihydrooxazole Moieties. Journal of Agricultural and Food Chemistry 60 (2012) 1470-1479.
[123] E.F.S.A. EFSA, Conclusion on the peer review of the pesticide risk assessment of the active substance bixafen, in: E.F.S. Authority (Ed.), Parma, Italy, 2012.
[124] A. Marchler-Bauer, Y. Bo, L. Han, J. He, C.J. Lanczycki, S. Lu, F. Chitsaz, M.K. Derbyshire, R.C. Geer, N.R. Gonzales, M. Gwadz, D.I. Hurwitz, F. Lu, G.H. Marchler, J.S. Song, N. Thanki, Z. Wang, R.A. Yamashita, D. Zhang, C. Zheng, L.Y. Geer, S.H. Bryant, CDD/SPARCLE: functional classification of proteins via subfamily domain architectures. Nucleic Acids Research 45 (2017) D200-D203.
[125] M.D.o.A. MDA, Fluxapyroxad (http://www.mda.state.mn.us/chemicals/pesticides/regs/~/media/7328555591A7441FA677AD52A7A80858.ashx), Minnesota Department of Agriculture, Minnesota, 2012.
[126] M.D.o.A. MDA, Sedaxane (http://www.mda.state.mn.us/chemicals/pesticides/regs/~/media/Files/chemicals/reviews/nair-sedaxane.ashx), Minnesota Department of Agriculture, Minnesota, 2012.
[127] S. Strathmann, S. Walker, J. Barnes, Fluxapyroxad: A new broad-spectrum fungicide. Phytopathology 101 (2011) S172-S172.
[128] Y. Yang, W.X. Liu, X.Y. Mu, S.Z. Qi, B. Fu, C.J. Wang, Biological response of zebrafish embryos after short-term exposure to thifluzamide. Scientific Reports 6 (2016) 11.
[129] F. Cui, T.T. Chai, X.X. Liu, C.J. Wang, Toxicity of three strobilurins (kresoxim-methyl, pyraclostrobin, and trifloxystrobin) on Daphnia magna. Environmental Toxicology and Chemistry 36 (2017) 182-189.
[130] N. Fisher, B. Meunier, Molecular basis of resistance to cytochrome bc1 inhibitors. FEMS Yeast Res 8 (2008) 10.
[131] X. Liu, Y. Wang, H. Chen, J. Zhang, C. Wang, X. Li, S. Pang, Acute toxicity and associated mechanisms of four strobilurins in algae. Environ Toxicol Pharmacol. 60 (2018) 5.
[132] R.P.A. van Wijngaarden, G.H.P. Arts, J.D.M. Belgers, H. Boonstra, I. Roessink, A.F.W. Schroer, T.C.M. Brock, The species sensitivity distribution approach compared to a microcosm study: A case study with the fungicide fluazinam. Ecotoxicology and Environmental Safety 73 (2010) 109-122.
[133] K. Fent, W. Meier, EFFECTS OF TRIPHENYLTIN ON FISH EARLY-LIFE STAGES. Archives of Environmental Contamination and Toxicology 27 (1994) 224-231.
[134] E. Fioramonti, R.D. Semlitsch, H.U. Reyer, K. Fent, Effects of triphenyltin and pH on the growth and development of Rana lessonae and Rana esculenta tadpoles. Environmental Toxicology and Chemistry 16 (1997) 1940-1947.
[135] J. Ma, F. Lin, W. Qin, P. Wang, Differential response of four cyanobacterial and green algal species to triazophos, fentin acetate, and ethephon. Bull Environ Contam Toxicol 73 (2004) 890-897.

[136] J.Y. Ma, Differential sensitivity of three cyanobacterial and five green algal species to organotins and pyrethroids pesticides. Science of the Total Environment 341 (2005) 109-117.
[137] M. Strmac, T. Braunbeck, Effects of triphenyltin acetate on survival, hatching success, and liver ultrastructure of early life stages of zebrafish (Danio rerio). Ecotoxicology and Environmental Safety 44 (1999) 25-39.
[138] L. Yu, X.L. Zhang, J. Yuan, Q.Z. Cao, J.Q. Liu, P. Zhu, H.H. Shi, Teratogenic effects of triphenyltin on embryos of amphibian (Xenopus tropicalis): A phenotypic comparison with the retinoid X and retinoic acid receptor ligands. Journal of Hazardous Materials 192 (2011) 1860-1868.
[139] Z.B. Zhang, J.Y. Hu, H.J. Zhen, X.Q. Wu, C. Huang, Reproductive Inhibition and Transgenerational Toxicity of Triphenyltin on Medaka (Oryzias latipes) at Environmentally Relevant tip Levels. Environmental Science & Technology 42 (2008) 8133-8139.
[140] H.Y. Wang, A.W. Olmstead, H. Li, G.A. LeBlanc, The screening of chemicals for juvenoid-related endocrine activity using the water flea Daphnia magna. Aquatic Toxicology 74 (2005) 193-204.
[141] R. Nauen, G. Smagghe, Rapid report - Mode of action of etoxazole. Pest Management Science 62 (2006) 379-382.
[142] J.P.d.S.M. Souza, Louise. Winkaler, Elissandra. Machado-Neto, Joaquim., Acute toxicity and environmental risk of diflubenzuron to Daphnia magna, Poecilia reticulata and Lemna minor in the absence and presence of sediment. Pesticidas: revista de ecotoxicologia e meio ambiente 21 (2011) 13.

Table 2. Distribution of Aquatic toxicity classification by ECOSAR among mechanistic domains

Aquatic toxicity classification by ECOSAR	amount	Narcosis	Non-Specific Reactivity	Specific Toxicity
Acid moiety|Aliphatic Amines	6	x		x
Acid moiety|Aliphatic Amines|Amides	3			x
Acid moiety|Aliphatic Amines|Inorganic Compound	1			x
Acid moiety|Aliphatic Amines|Phenol Amines|Phenols	1		x	
Acid moiety|Amides	3			x
Acid moiety|Amides|Sulfonyl Ureas	1			x
Acid moiety|Esters	1			x
Acid moiety|Esters|Vinyl/Allyl Alcohols|Vinyl/Allyl Ethers	1			x
Acid moiety|Halopyrdines	1			x
Acid moiety|Pyrazoles/Pyrroles	2			x
Acid moiety|Sulfonyl Ureas|Triazines, Aromatic	1			x
Acrylamides	1			x
Acrylamides|Aliphatic Amines|Benzyl Alcohols|Inorganic Compound|Ketone alcohols|Phenol Amines|Phenols|Vinyl/Allyl Alcohols|Vinyl/Allyl Ketones	1			x
Acrylamides|Esters|Esters (phosphate)	2			x
Acrylamides|Esters|Esters (phosphate)|Vinyl/Allyl Halides	1			x
Acrylamides|Esters|Vinyl/Allyl Esters	1			x
Acrylamides|Vinyl/Allyl Ethers	1			x
Acrylamides|Vinyl/Allyl Ethers|Vinyl/Allyl Sulfones	1			x
Aldehydes (Mono)|Aliphatic Amines	1			x
Aliphatic Amines	45	x	x	x
Aliphatic Amines|Amides	4			x
Aliphatic Amines|Benzyl Alcohols|Ketone alcohols|Phenol Amines|Phenols|Vinyl/Allyl Alcohols|Vinyl/Allyl Ketones	1			x
Aliphatic Amines|Carbamate Esters	1			x
Aliphatic Amines|Carbonyl Ureas	1			x
Aliphatic Amines|Esters	2			x
Aliphatic Amines|Esters|Esters (phosphate)	1			x
Aliphatic Amines|Esters|Halopyrdines|Nicotinoids|Vinyl/Allyl Esters	1			x
Aliphatic Amines|Esters|Nereistoxin Analogues	1			x
Aliphatic Amines|Esters|Pyrazoles/Pyrroles	1			x
Aliphatic Amines|Esters|Vinyl/Allyl Alcohols|Vinyl/Allyl Esters|Vinyl/Allyl Ethers	1			x
Aliphatic Amines|Esters|Vinyl/Allyl Ethers	1			x
Aliphatic Amines|Esters|Vinyl/Allyl Ketones	2			x
Aliphatic Amines|Halopyrdines|Neonicotinoids	2			x

Aliphatic Amines|Halopyrdines|Nicotinoids	2			x
Aliphatic Amines|Neonicotinoids	1			x
Aliphatic Amines|Nereistoxin Analogues	3			x
Aliphatic Amines|Nicotinoids	3			x
Aliphatic Amines|Phenol Amines|Phenols|Polynitrobenzenes	1			x
Aliphatic Amines|Vinyl/Allyl Alcohols|Vinyl/Allyl Halides|Vinyl/Allyl Ketones	1			x
Aliphatic Amines|Vinyl/Allyl Alcohols|Vinyl/Allyl Ketones	1			x
Aliphatic Amines|Vinyl/Allyl Ethers|Vinyl/Allyl Ketones	1			x
Aliphatic Amines|Vinyl/Allyl Halides|Vinyl/Allyl Ketones	1			x
Aliphatic Amines|Vinyl/Allyl Ketones	3			x
Amides	54	x		x
Amides|Anilines (Unhindered)	1		x	
Amides|Benzyl Nitriles|Thiophenes	1			x
Amides|Carbamate Esters|Hydrazines	1			x
Amides|Carbonyl Ureas	1			x
Amides|Esters	4			x
Amides|Esters, Dithiophosphates	4			x
Amides|Esters, Monothiophosphates	1			x
Amides|Esters|Esters (phosphate)	3			x
Amides|Esters|Triazole Pyrimidine Sulfona	1			x
Amides|Halo Ketones (2 free H)	1			x
Amides|Halopyrdines	2			x
Amides|Halopyrdines|Pyrazoles/Pyrroles	2			x
Amides|Hydrazines	5			x
Amides|Imidazoles	1			x
Amides|Imides	1			x
Amides|Phenol Amines|Phenols	1		x	
Amides|Polynitrobenzenes	1			x
Amides|Pyrazoles/Pyrroles	10			x
Amides|Pyrazoles/Pyrroles|Thiophenes	1			x
Amides|Pyrazoles/Pyrroles|Vinyl/Allyl Halides	1			x
Amides|Sulfonyl Ureas	3			x
Amides|Thiophenes	1			x
Amides|Triazole Pyrimidine Sulfona	3			x
Amides|Triazoles (Non-Fused)	1			x
Anilines (Hindered)	2	x		
Anilines (Hindered)|Polynitroanilines	1			x
Anilines (Unhindered)	66	x	x	x
Anilines (Unhindered)|Carbamate Esters	1			x
Anilines (Unhindered)|Esters|Phenol Amines|Phenols	1	x		
Anilines (Unhindered)|Pyrazoles/Pyrroles	2			x

Benzoylcyclohexanedione	2			x
Benzyl Alcohols	2			x
Benzyl Alcohols|Epoxides, mono	1		x	
Benzyl Alcohols|Triazoles (Non-Fused)	4			x
Benzyl Nitriles|Esters	3			x
Benzyl Nitriles|Esters|Pyrethroids	6			x
Benzyl Nitriles|Esters|Pyrethroids|Vinyl/Allyl Halides	10	x		x
Benzyl Nitriles|Triazoles (Non-Fused)	2			x
Carbamate Esters	4			x
Carbamate Esters|Carbamate Esters, Phenyl	2			x
Carbamate Esters|Carbonyl Ureas|Hydrazines	1			x
Carbamate Esters|Carbonyl Ureas|Thioureas	2			x
Carbamate Esters|Esters, Dithiophosphates	1			x
Carbamate Esters|Halopyrdines	1			x
Carbamate Esters|Imidazoles	1			x
Carbamate Esters|Imides	2			x
Carbamate Esters|Pyrazoles/Pyrroles	2			x
Carbonyl Ureas	9			x
Carbonyl Ureas|Esters|Salt	1			x
Carbonyl Ureas|Halopyrdines	1			x
Carbonyl Ureas|Hydrazines	1		x	
Epoxides, mono|Triazoles (Non-Fused)	1			x
Esters	75	x	x	x
Esters (phosphate)|Thiazolidinones|Thiocarbamates, Mono	1			x
Esters, Dithiophosphates	7			x
Esters, Dithiophosphates|Imides	1			x
Esters, Monothiophosphates	34	x		x
Esters, Monothiophosphates|Halopyrdines	2	x		x
Esters|Esters (phosphate)	11			x
Esters|Esters (phosphate)|Halo Alcohols	1			x
Esters|Esters (phosphate)|Peroxy Acids|Vinyl/Allyl Halides	1			x
Esters|Esters (phosphate)|Pyrazoles/Pyrroles	1			x
Esters|Esters (phosphate)|Vinyl/Allyl Halides	4			x
Esters|Esters, Dithiophosphates	2			x
Esters|Esters, Monothiophosphates	3			x
Esters|Esters, Monothiophosphates|Pyrazoles/Pyrroles	1			x
Esters|Haloacetamides	1			x
Esters|Halopyrdines	2			x
Esters|Imidazoles	1			x
Esters|Imides	1			x
Esters|Imides|Pyrethroids	1			x

Esters|Imides|Vinyl/Allyl Halides	1			x
Esters|Oxetanes|Sulfonyl Ureas	1			x
Esters|Polynitrobenzenes	2			x
Esters|Pyrazoles/Pyrroles	2			x
Esters|Pyrazoles/Pyrroles|Sulfonyl Ureas	2			x
Esters|Pyrazoles/Pyrroles|Vinyl/Allyl Esters|Vinyl/Allyl Nitriles	1			x
Esters|Pyrazoles/Pyrroles|Vinyl/Allyl Ethers	1			x
Esters|Pyrethroids	3			x
Esters|Pyrethroids|Vinyl/Allyl Esters	1			x
Esters|Pyrethroids|Vinyl/Allyl Esters|Vinyl/Allyl Ketones	2			x
Esters|Pyrethroids|Vinyl/Allyl Halides	8	x		x
Esters|Salt|Sulfonyl Ureas	1			x
Esters|Sulfonyl Ureas	3			x
Esters|Sulfonyl Ureas|Thiophenes|Triazines, Aromatic	1			x
Esters|Sulfonyl Ureas|Triazines, Aromatic	4			x
Esters|Triazines, Aromatic	1			x
Esters|Triazoles (Non-Fused)	1			x
Esters|Vinyl/Allyl Alcohols|Vinyl/Allyl Ethers	3			x
Esters|Vinyl/Allyl Esters	2			x
Esters|Vinyl/Allyl Ethers	6		x	x
Esters|Vinyl/Allyl Halides	1			x
Halo Acids	2			x
Halo Ethers	1			x
Halo Ethers|Sulfonyl Ureas|Triazines, Aromatic	1			x
Halo Ethers|Triazoles (Non-Fused)	1			x
Haloacetamides	10			x
Haloacetamides|Pyrazoles/Pyrroles	1			x
Haloacetamides|Thiophenes	2			x
Halopyrdines|Polynitrobenzenes	1			x
Hydrazines	1			x
Imidazoles	7			x
Imidazoles|Sulfonyl Ureas	2			x
Imidazoles|Thiophenes	1			x
Imidazoles|Vinyl/Allyl Ethers	1			x
Imides|Pyrazoles/Pyrroles	1			x
Inorganic Compound|SHOULD NOT BE PROFILED	1			x
Neutral Organics	252	x	x	x
Phenols	18	x		x
Phenols|Polynitrophenols	1			x
Phenols|Quinones	1		x	
Polynitrobenzenes	5			x
Propargyl Halide	1			x
Pyrazoles/Pyrroles	5			x

Pyrazoles/Pyrroles|Sulfonyl Ureas	1		x
SHOULD NOT BE PROFILED	5		x
Substituted Ureas	17		x
Sulfonyl Ureas	5		x
Sulfonyl Ureas|Triazines, Aromatic	4		x
Thiocarbamates, Mono	13		x
Thiocarbamates, Mono|Vinyl/Allyl Halides	1		x
Thioureas	1		x
Triazines, Aromatic	28	x	x
Triazoles (Non-Fused)	16		x
Triazoles (Non-Fused)|Vinyl/Allyl Alcohols	1		x
Vinyl/Allyl Ethers	2		x
Vinyl/Allyl Halides	12	x	x
Vinyl/Allyl Ketones	2		x

Appendix 3: Structural Alerts per domain

All structural alerts (developed as discussed in Chapter 5, or retrieved from literature) used in this studies are available on the USB stick attached to this thesis (Tab SAs, MIE Appendix.xlsx)