Development of a strategy to substitute acute fish toxicity tests: Status of the CEFIC-LRI CEllSens-Eco8 project

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LRI The Long-range Research initiative

Goal of work package 1 (due 10/07):

Construct an inventory of available *in vivo-in vitro* and chemical exposure data; Select chemicals for testing and validation.

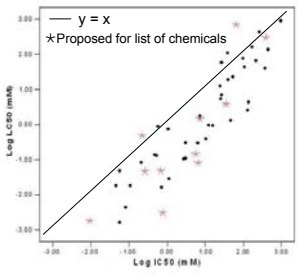
Selected chemicals should have:

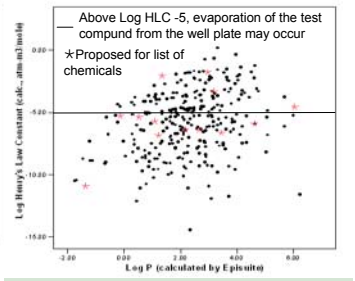
→ a wide range of chemico-physical properties:
- logP (octanol-water partition coefficient)
- logHLC (Henry's law constant)

→ different modes of toxic action

Data bases used:
- U.S. EPA Duluth fathead minnow database for fish acute toxicity data
- Halle database for in vitro toxicity data as well as own data
- Data colletion by the German Environmental Protection Agency (UBA) for embryo toxicity values

Selection of narcotic compounds:



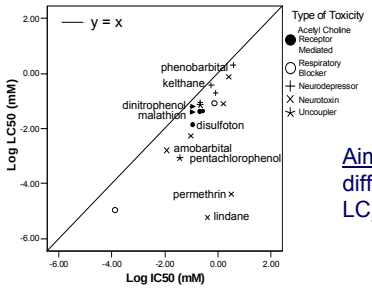


Aim:
- a wide range of differences between LC_{50}s and IC_{50}s;
- a wide range of Henry's Law Constants and Log P's

All narcotic compounds found in both the Halle Registry of Cytotoxicity and the EPA Fathead Minnow Database

All compounds of the EPA database for which Log P and Log HLC could be calculated with EPISuite

Specifically acting compounds:

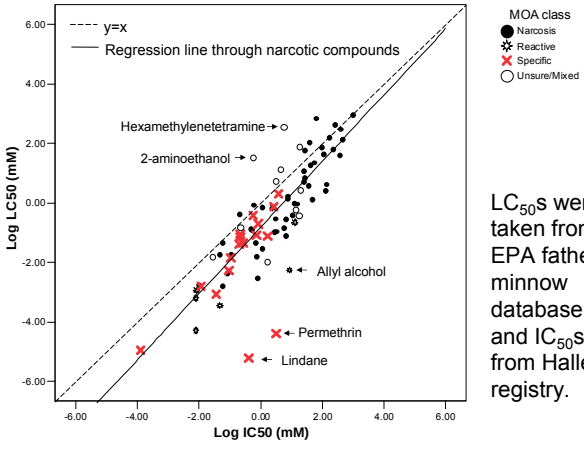


Aim: a wide range of differences between LC_{50}s and IC_{50}s

LC_{50}s were taken from EPA fathead minnow database and IC_{50}s from Halle registry.

Selection of outliers:

Aim: pick compounds with 2 and 3 standard deviation difference from y = x, i.e. Log LC_{50} = Log IC_{50}



LC_{50}s were taken from EPA fathead minnow database and IC_{50}s from Halle registry.

List of TOP33:

Reg. #	Name	CAS #	MOA	log P	log HLC (atm-m3/mol)	log LC50 (mM) fathead minnow	log IC50 (mM) Halle database	log IC50 (mM) embryo test
1	ethanol	64175	NPN	-0,14	-5,25	2,49	2,58	2,40
2	2,2,2-trichloroethanol	115208	NPN	1,21	-6,81	0,30	n/a	
3	diethylphthalate	84662	NPN	2,65	-6,4	-0,84	0,74	
4	di-n-butylorthophthalate	84742	NPN	4,61	-5,91	-2,52	-0,12	
5	4-decylaniline	37529309	NPN	6,04	-5,22	-3,58	n/a	
6	naphthalene	91203	NPN	3,17	-3,28	-1,32	-1,32	
7	1,2-dichlorobenzene	95501	NPN	3,28	-2,53	-1,19	n/a	
8	dichloromethane	75092	NPN	1,35	-2,04	0,59	1,54	
9	tetrachloroethylene	127184	NPN	2,97	-1,78	-1,09	0,82	1,14 (96h)
10	1,2,4-trichlorobenzene	120821	NPN	4,02	-2,66	-1,78	-0,15	
11	aniline	62533	PN	1,08	-5,72	0,16	0,86	0,48
12	4-chlorophenol	106489	PN	2,16	-6,38	-1,32	-0,17	-0,57
13	2,4,6-trichlorophenol	88062	PN	3,45	-6,64	-1,33	-0,58	
14	3,4-dichloroaniline	95761	PN	2,69	-5,98	-1,36	n/a	-1,77
15	ally alcohol	107186	Reactive	0,21	-5,25	-2,26	0,93	
16	ethanal #1	75070	Reactive	-1,17	-4,17	-0,16	0,39	
17	acrolein #1	107028	Reactive	0,19	-4,45	-3,45	-1,33	-1,94
18	2-methyl-1,4-Naphthoquinone	58275	Reactive	2,21	-8,51	-3,19	-2,10	
19	2,3-dimethyl-1,3-butadiene	513815	Reactive	3,13	-0,72	-1,08	n/a	
20	2,2'-methylenebis(4-chlorophenol)	97234	Reactive	4,34	-11,54	-2,94	-2,08	
21	4-fluoroaniline	371404	Reactive	1,28	-5,65	-0,82	n/a	
22	2,2'-methylenebis(3,4,6-trichlorophenol)	70304	Reactive	6,92	-12,07	-4,29	-2,08	
23	malathion	121755	ACHE	2,29	-9,08	-1,37	-0,7	-1,68
24	disulfoton #1	298044	ACHE	3,86	-5,68	-1,84	-0,98	
25	rotenone #1	83794	R.BLOCKER	4,31	-12,95	-4,94	-3,90	
26	2,4-dinitrophenol #9	51285	UNCOUPLER	1,73	-7,56	-1,14	-0,67	-2,10
27	pentachlorophenol #7	87865	UNCOUPLER	4,74	-6,9	-3,08	-1,44	-3,47
28	permethrin	52645531	NEUROTOX	7,43	-6,54	-4,39	0,51	
29	lindane	58899	NEUROTOX	4,26	-3,59	-5,23	-0,39	-4,56 (LC_{10})
30	phenobarbital	50066	NEURODEP	1,33	-13,78	0,32	0,58	
31	parathion-ethyl	56382	NEUROTOX	3,73	-6,53	n/a	-1,03	
32	Hexamethylenetetramine (aliphatic)	100970	UNSURE	-4,15(2,46)	-0,79	2,55	0,74	
33	2-Aminoethanol	141435	UNSURE	-1,61	-9,43	1,53	-0,25	1,78

Schirmer et al. Toxicology 127 (1998) 129-141
Johnson and Finley (1980) Handbook of Acute Toxicity of Chemicals to Fish & Aquatic Invertebrates

Non-toxic compounds:

Aim: pick compounds *without* reported toxicity up to 100 mg/L

Candidates: contrast media, e.g. iopromid; salts; search still ongoing

Further steps:

- modelling to correlate physico-chemical parameters with toxicity
- evaluation of dosing schemes and true availability of chemicals to cells/embryos