Overview of Toxicological impacts of UV filters to fish

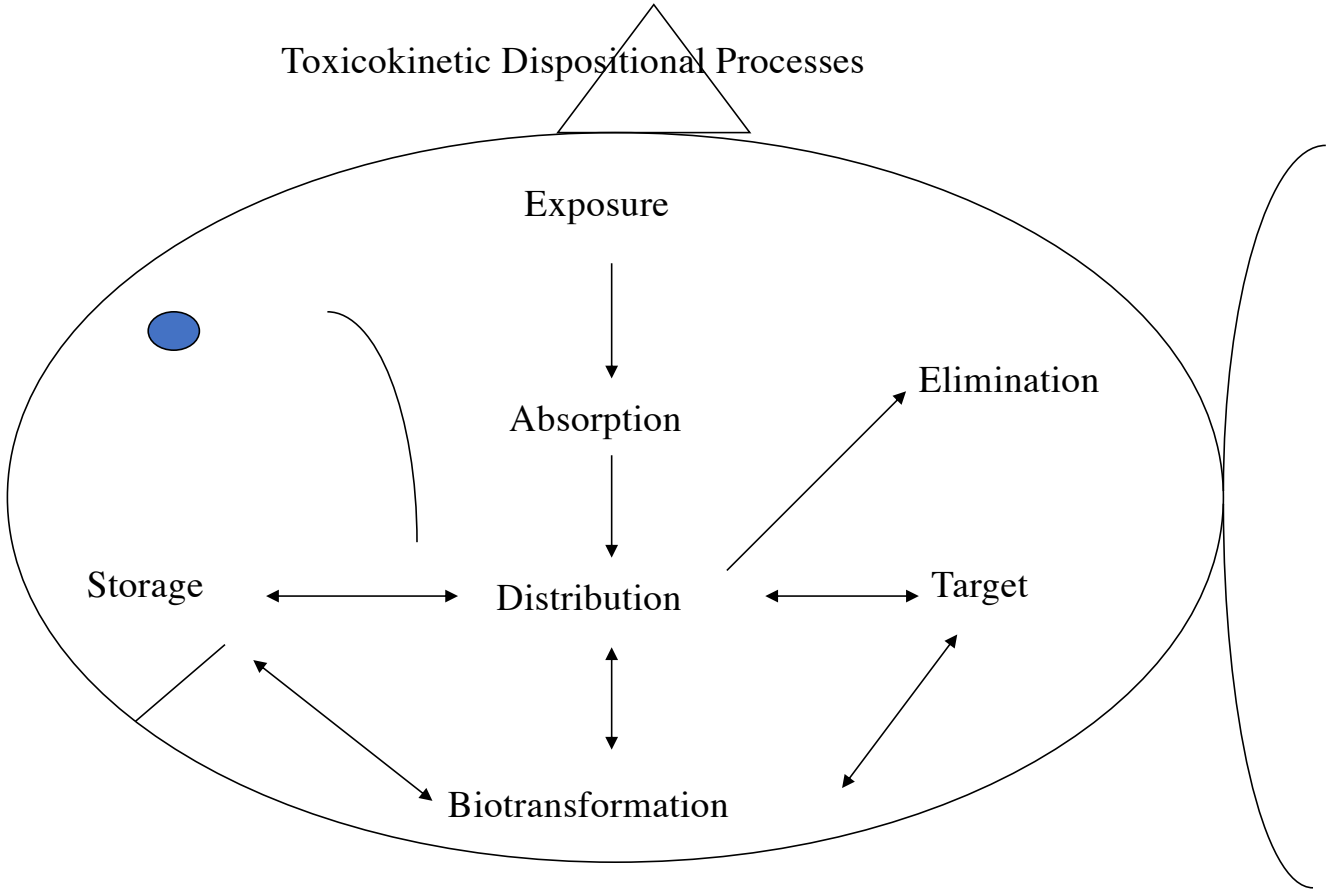
Daniel Schlenk

Department of Environmental Sciences

University of California, Riverside

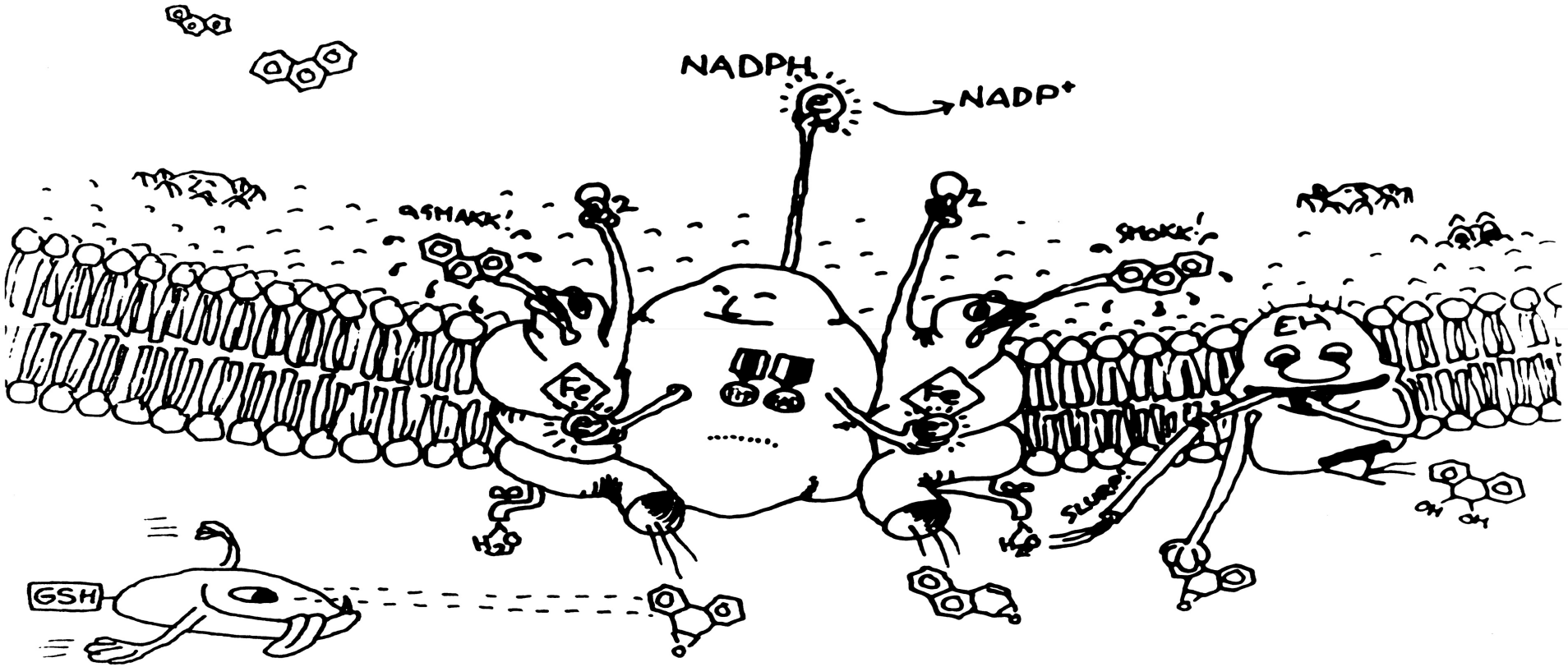
questions

- How do biochemical factors in fish influence susceptibility to UV filter inputs?
- What are the acute or chronic toxicity endpoints?
  - What is the biological and environmental relevance of these endpoints?
  - How do they influence ecosystem and organism functions?


Toxicokinetic Dispositional Processes
Exposure
Absorption
Elimination
Storage
Distribution
Target
Biotransformation

Toxicokinetics (ADME) and Susceptibility

- Exposure
  - Wastewater dominated systems
  - Low dilution low turnover water bodies
  - UV light (increases toxicity)
    - Photodegradates→similar biological activity
  - DOC? Log Kow=3-4
    - Tropical environments?
  - Chemical confirmation very important (esp. static systems)
- Absorption
  - pH (climate change)—increase absorption?
  - Log Kow
  - ABC transporters- affect elimination as well
- Distribution
  - Plasma binding/Blood Flow
- Storage
  - Log Kow-lipid storage?---metabolism….
  - Lipid status (off-loading to gonads)
  - Reproductive strategies



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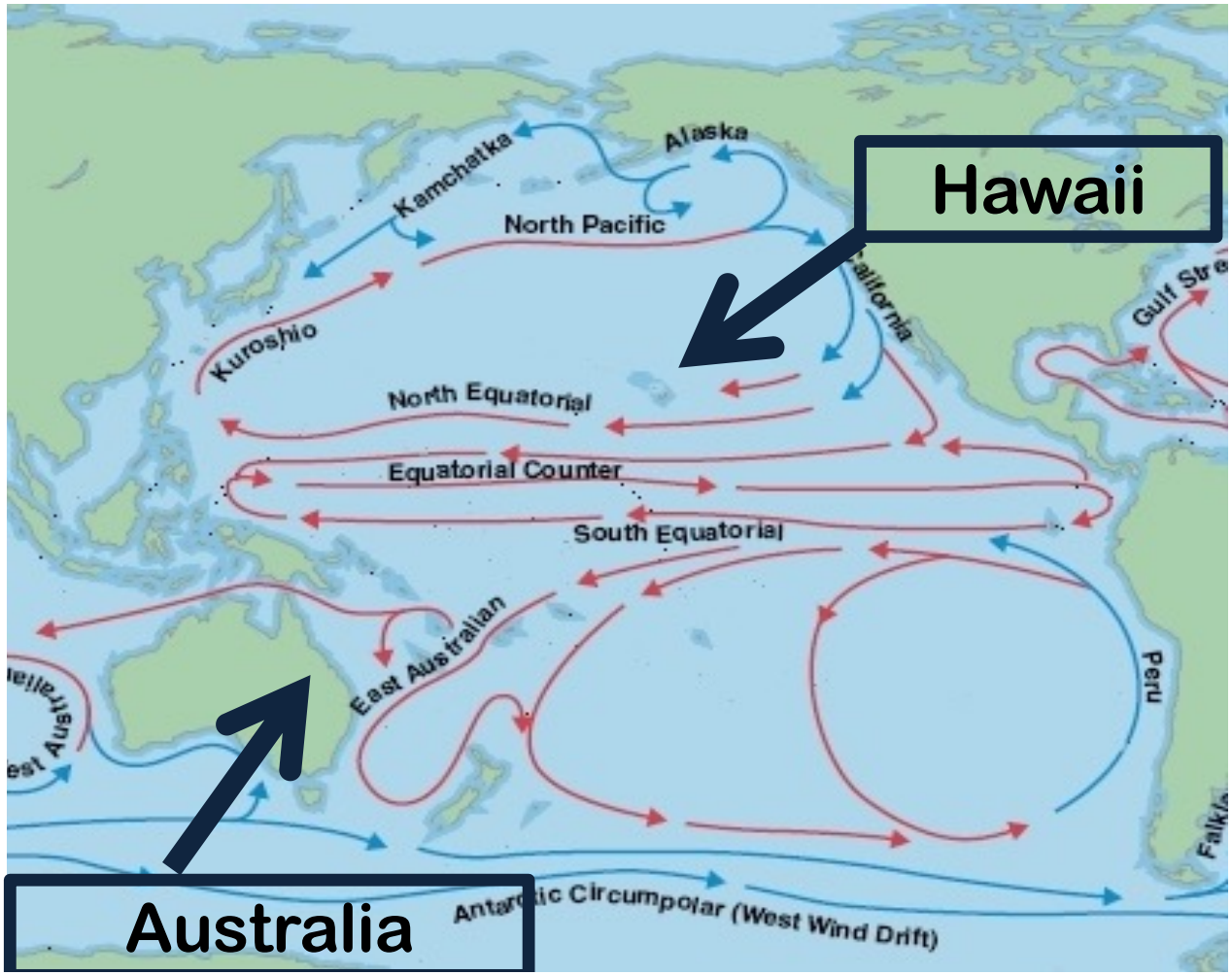
Collection Sites



ɔligate soft coral *(Lobophytum spp.)* VS. Plankton, facultative hard coral

Australian *C. lunulatus*
Obligate hard coral (*Acorapora spp.)*

VS.

Hawaiian *C. lunulatus*
Obligate hard coral (*Porities spp.)*

Australian *C. auriga*
Generalist

VS.

Hawaiian *C. auriga*
Generalist

Australian *C. unimaculatus*
Obligate Soft coral
(*Lobophytum spp & Sinularia spp* .)

VS.

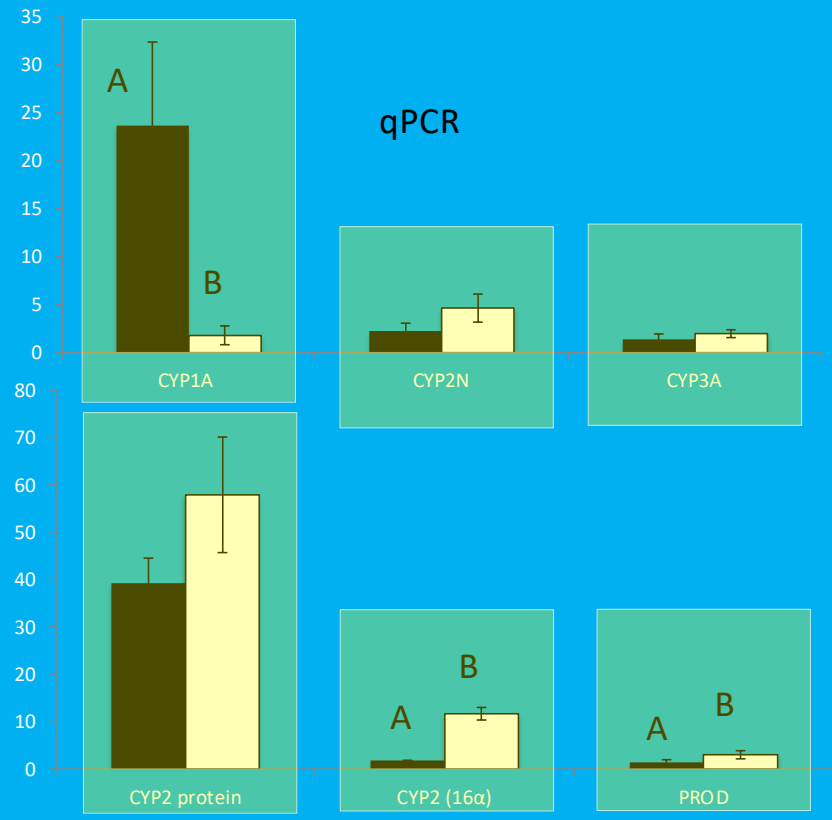
Hawaiian *C. unimaculatus*
Obligate Hard coral (*Montipora spp.*)

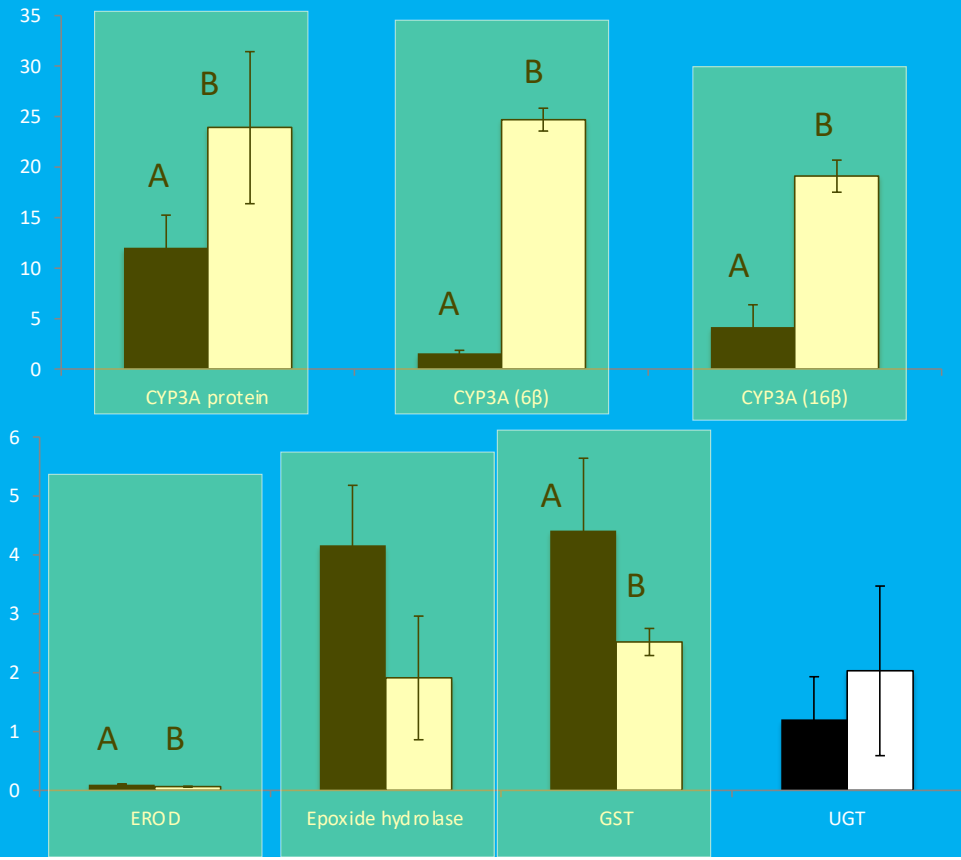
C. auriga

Both Generalist

CYP2, CYP3A= AU/mg protein
CYP2 (16α), CYP3 (6β), (16β)= pmol/min/mg protein
EROD=nmol/min/mg protein
PROD, EH, GST, GST= pmol/min/mg protein
Hawaii Australia

qPCR

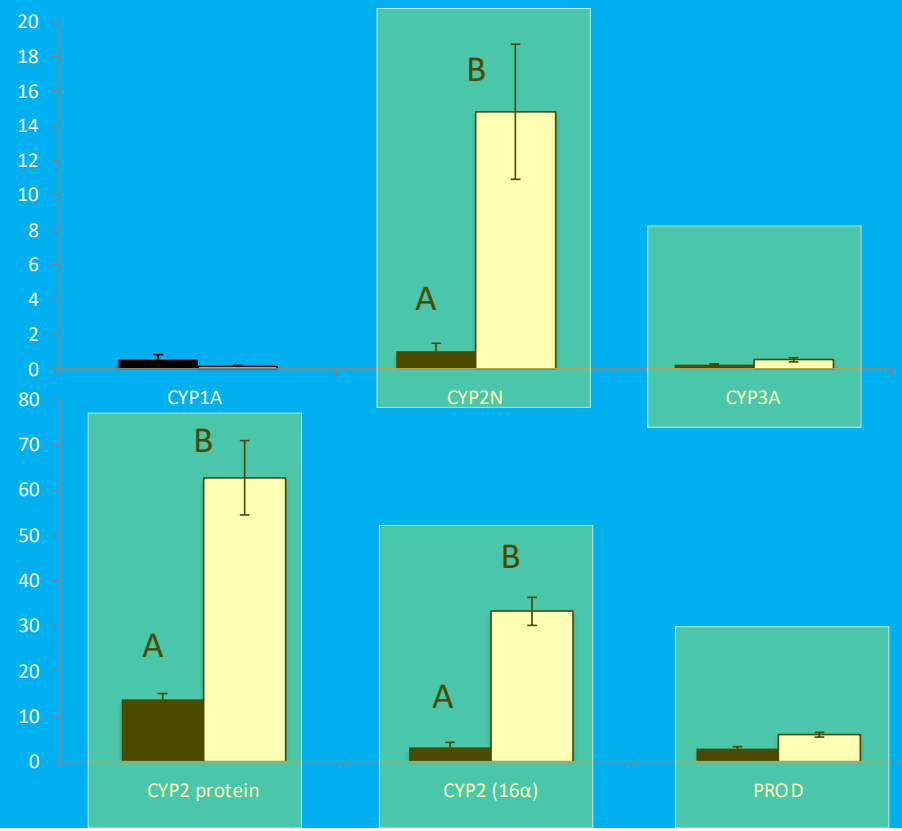


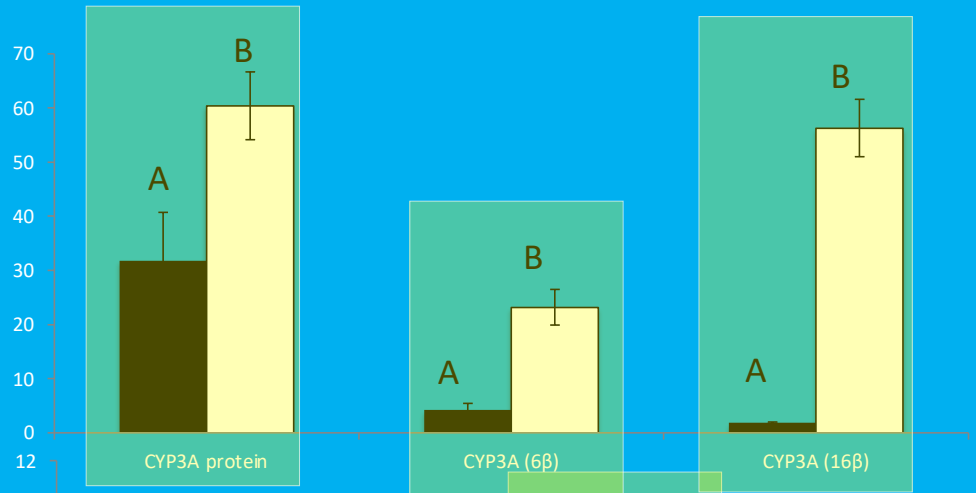


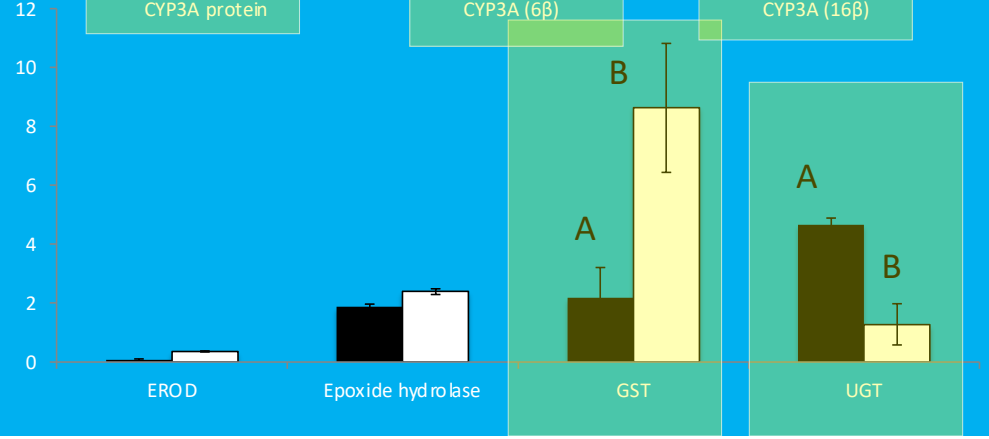
C. unimaculatus

A-Soft Coral H-Hard coral

CYP2, CYP3A= AU/mg protein
CYP2 (16α), CYP3 (6β), (16β)= pmol/min/mg protein
EROD=nmol/min/mg protein
PROD, EH, GST, GST= pmol/min/mg protein
Hawaii Australia

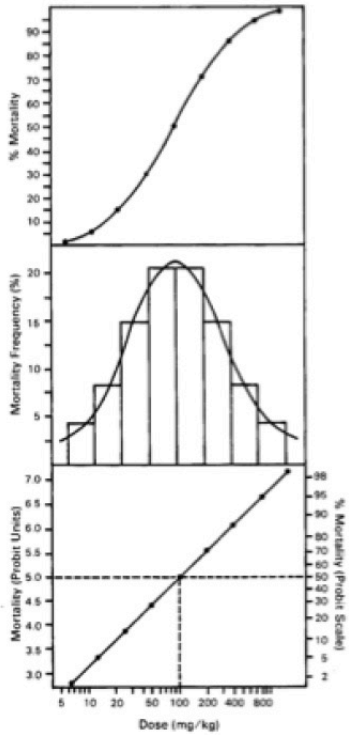






Acute vs. Chronic Toxicity Endpoints

- Acute Toxicity
  - Short duration of exposure
    - 96 h for fish
  - Rapid response endpoints
    - Lethality—LC50
    - Growth ?--EC50
  - Usefulness tied to rapidly acting agents
    - (Neurotoxic or Narcosis Agents)



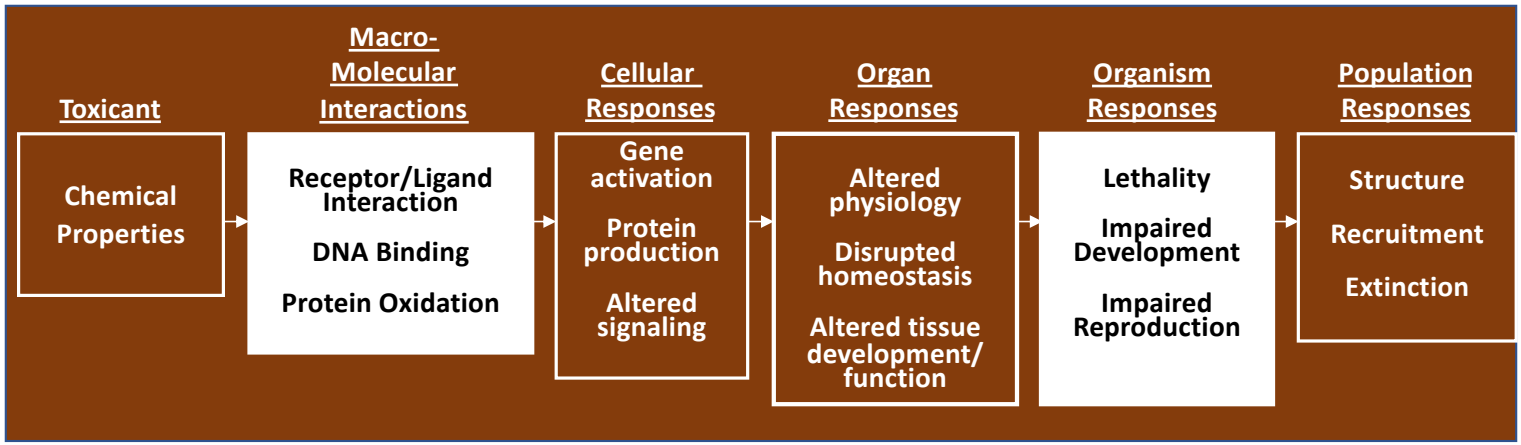
Acute vs. Chronic Toxicity Endpoints (cont)

- Chronic Toxicity
  - Longer duration of exposure
    - 28 d for fish (represents ~one life cycle)
  - Longer term response endpoints (NOEC/LOEC)
    - Monotonicity vs. non-monotonicity (EDC MOA)
    - Reproduction
      - Fecundity
      - Hatch rate/success
    - Growth
      - Life stage matrix parameter
    - Histology
      - Reproductive organs
    - Survival
    - Development

Adverse Outcome Pathways

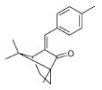
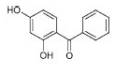
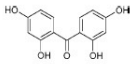
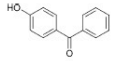
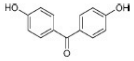
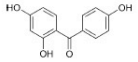
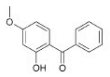
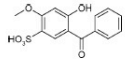
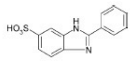
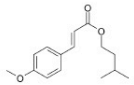
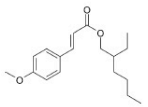
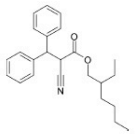
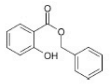
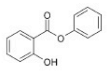
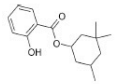
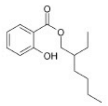
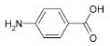
An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome, at a level of biological organization relevant to risk assessment.

(Ankley et al. 2010, Environ. Toxicol. Chem., 29(3): 730-741.)



- Helps us organize what we know
- And utilize that knowledge to support risk-based decision-making

TABLE 1
Chemical Structures, Molecular Weight, and CAS Numbers of Compounds Analyzed

Compound MW, (CAS)	Chemical structure	Compound MW, (CAS)	Chemical structure
4MBC 254.37 (36861-47-9)		3BC 240.34 (15087-24-8)	
BP1 214.22 (131-56-6)		BP2 246.22 (131-55-5)	
4HB 198.22 (1137-42-4)		4DHB 214.22 (611-99-4)	
THB 230.22 (1470-79-7)		BP3 228.25 (131-57-7)	
BP4 308.31 (4065-45-6)		PBS 274.30 (27503-81-7)	
IMC 248.32 (71671-10-2)		OMC 290.40 (5466-77-3)	
OC 361.48 (6197-30-4)		BS 228.25 (118-58-1)	
PS 214.22 (118-55-8)		HMS 262.35 (118-56-9)	
OS 250.33 (118-60-5)		PABA 137.10 (150-13-0)	

ER activation----------→ Vitellogenin

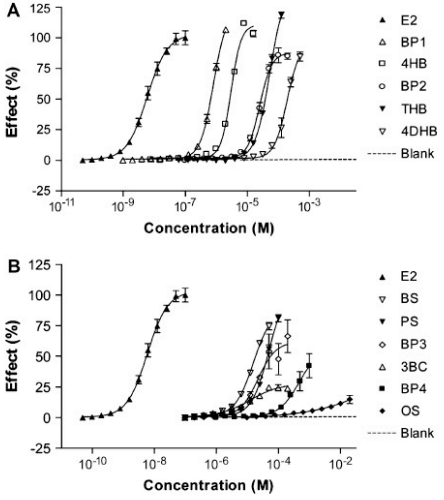


FIG. 1. Estrogenic activity of UV filters in the rtERα assay, shown in two panels (A, B) for clarity. Data shown are means ± SEM (three experiments with four replicates each). Effect (%) represents percentage of β-galactosidase induction of UV filters versus solvent (0%) and E2 (100%) controls. Results for inactive chemicals are not shown for clarity. Compound abbreviations see Table 1.

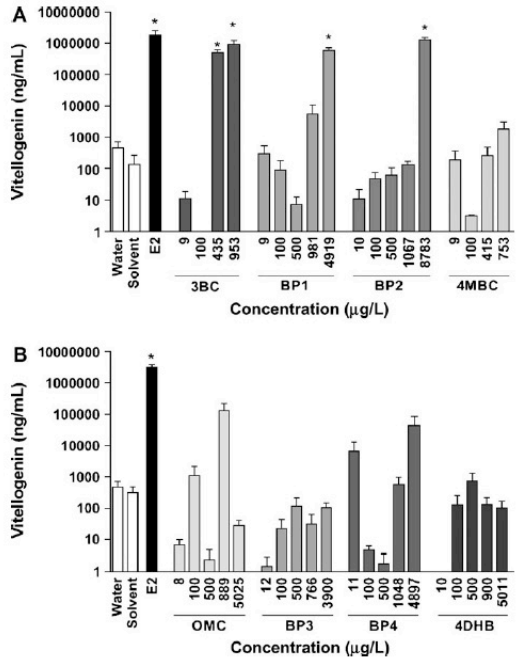


FIG. 3. Vitellogenin concentration in juvenile fathead minnows exposed to eight UV filters. Values are means ± SEM ($n = 10$). Asteric denotes a significant difference from control (solvent) at $p \leq 0.05$. Concentrations given as actual median measured, except 100 and 500 µg/l.

Kunz et al. Toxicological Sci. 2006

Table 2. Hormonal activities of UV filters *in vitro* in the recombinant hERα and hAR assay[25]

Compound	Estrogenic activity	Anti-estrogenic activity	Androgenic activity	Anti-androgenic activity
4-Methylbenzylidene camphor (4MBC)	--	+++	--	**+++**
3-Benzylidene camphor (3BC)	+	+++	--	**+++**
Benzophenone-1 (BP1)	+++	--	--	**+++**
Benzophenone-2 (BP2)	+++	--	+++	**+++**
4-Hydroxy benzophenone (4HB)	**+++**	--	--	**+++**
4,4'-Dihydroxybenzophenone (4DHB)	**+++**	--	--	**+++**
Benzophenone-3 (BP3)	+	+++	--	**+++**
Benzophenone-4 (BP4)	**+**	+++	--	+++
Isopentyl-4-methoxycinnamate (IMC)	--	+++	++	**+++**
Ethyl hexyl methoxycinnamate (EHMC)	--	+++	++	**+++**
Octocrylene (OC)	--	+++	+	**+++**
Benzyl salicylate (BS)	+	**+++**	--	+++
Phenyl salicylate (PS)	++	+++	--	**+++**
Homosalate (HMS)	--	+++	+++	**+++**
Octyl salicylate (OS)	--	+++	++	**+++**
Para amino-benzoic acid (PABA)	--	+++	--	--
Ethyl-4 amino benzoate (Et-PABA)	**+++**	--	--	++
Octyl dimethyl para amino benzoate (OD-PABA)	--	+++	--	**+++**
Ethoxylated ethyl 4-amino benzoate (Peg25-PABA)	--	+	--	--

+++, maximal dose-response curves with ≥ 80% efficacy; ++, submaximal dose-response curves with ≥ 30% efficacy; +, submaximal dose-response curves with < 30% efficacy. Bold, most potent hormonal activity found for each compound; --, not detected.

Fent et al. 2008

Table 4
Endocrine disrupting activities of benzophenone-3 and its relevant derivatives in vitro.

Compounds	Hormonal activity	Cell line	Assay	Endpoints	Conc. (μM)	Reference
BP-3	Estrogenic	MCF-7 cells	MCF-7 cell proliferation assay	6 d, cell proliferation EC50	3.73	Schlumpf et al. (2001)
			MCF-7 cell proliferation assay	6 d, cell proliferation LOEC	>100	Nakagawa and Suzuki (2002)
			pS2 protein assay	pS2 protein secretion, LOEC	10	Schlumpf et al. (2001)
			ERE-luciferase reporter assay	Estrogenic EC50	19.5	Suzuki et al. (2005)
		Recombinant yeast	Recombinant yeast assay	Agonism toward rtER, EC50	21.9	Kunz et al. (2006)
			Recombinant yeast assay	Agonism toward hERα, EC50	18.6	Kunz and Fent (2006b)
		MELN cells	Luciferase assay	Transactivation for hERα, EC50	20.315	Molina-Molina et al. (2008)
		HELN cells	Luciferase assay	Transactivation of hERα, NOEC	10	Gomez et al. (2005)
			Luciferase assay	Transactivation of hERβ, NOEC	10	Gomez et al. (2005)
			Luciferase assay	Transactivation for hERα, EC50	>30	Molina-Molina et al. (2008)
			Luciferase assay	Transactivation for hERβ, NOEC	0.01	Molina-Molina et al. (2008)
			Luciferase assay	Transactivation for rtERα, EC50	18.426	Molina-Molina et al. (2008)
		HEK293 cells	Gene expression assay	Transactivation for hERα, EC50	2.9	Schreurs et al. (2005)
			Gene expression assay	Transactivation for hERβ, EC50	25	Schreurs et al. (2005)
			Gene expression assay	Transactivation for hERα, LOEC	10	Schreurs et al. (2002)
			Gene expression assay	Transactivation for hERβ, LOEC	10	Schreurs et al. (2002)
	Antiestrogenic	Recombinant yeast	Recombinant yeast assay	Antagonism toward hERα, IC50	17.8	Kunz and Fent (2006b)
			Recombinant yeast assay	Antagonism toward hERα, IC50	3.68	Kunz and Fent (2006b)
		HELN cells	Luciferase assay	Antagonism toward hERα, NOEC	0.01	Molina-Molina et al. (2008)
			Luciferase assay	Antagonism toward hERβ, NOEC	0.01	Molina-Molina et al. (2008)
			Luciferase assay	Antagonism toward rtERα, NOEC	0.01	Molina-Molina et al. (2008)
	Antiprogestagenic	U2-OS cells	Gene expression assay	Transrepression for hPR, IC50	5.2	Schreurs et al. (2005)
	Antiandrogenic	U2-OS cells	Gene expression assay	Transrepression for hAR, IC50	2	Schreurs et al. (2005)
		NIH3T3 cells	ARE-luciferase reporter assay	Antiandrogenic IC50	>100	Suzuki et al. (2005)
		HEK293 cells	Gene expression assay	Transrepression for hAR, IC50	3.1	Nashev et al. (2010)

Kim & Choi 2014

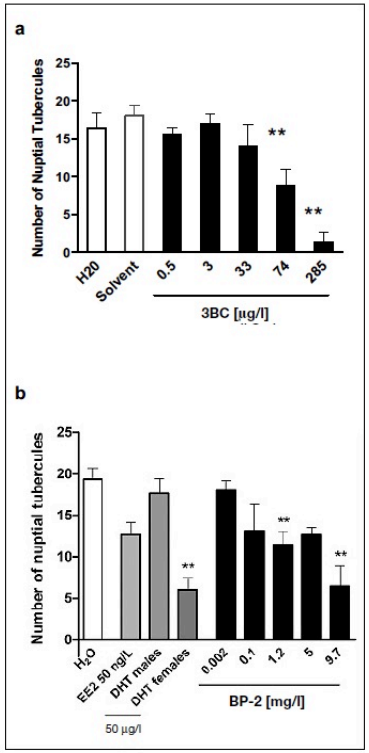


Fig. 3. Feminization of male secondary sex characteristics by 3-benzylidene camphor (3BC) (a) and benzophenone-2 (BP2) (b). Nuptial tubercles in male fish show dose-related decrease.[15,16]

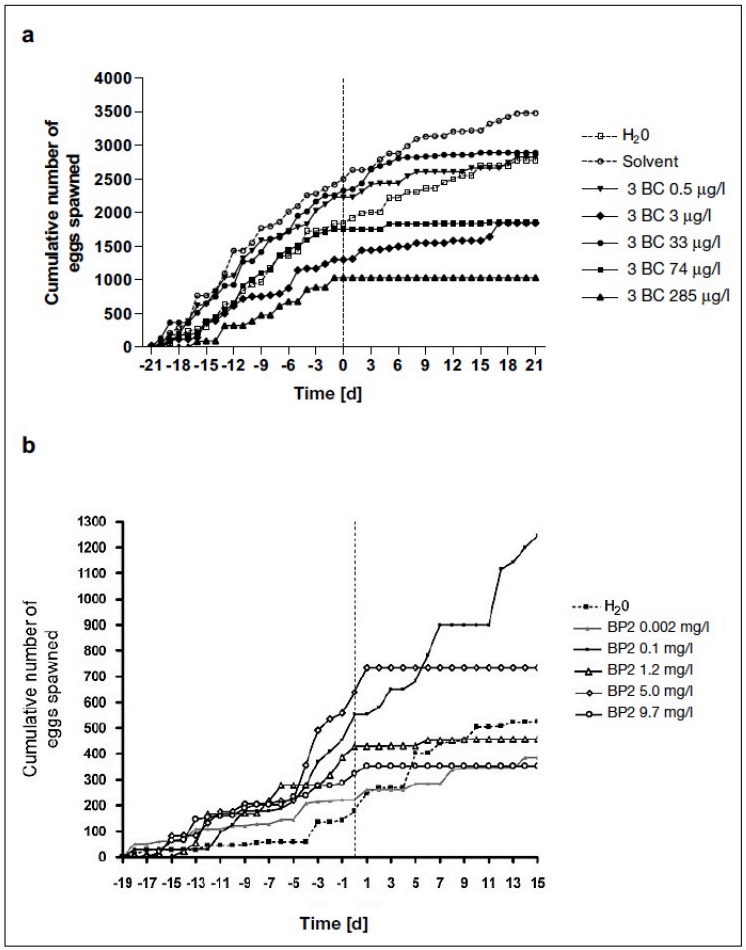


Fig. 4. Negative effects of 3-benzylidene camphor (3BC) (a) and benzophenone-2 (BP2) (b) on fish reproduction. Shown are egg numbers in the pre-exposure and exposure period.[15,16]

Hazard assessments of individual UV filters using predicted river concentrations

Table 3. PEC values in surface water and PNEC values based on water concentrations in our experiments on hormonal activity of 3BC and BP2 (LOEC)

UV filter	Toxicity acute [mg/l]	chronic [mg/l]	LOEC Our exper. [µg/l]	Safety factor	PNEC [µg/l]	PEC [µg/l]	PEC/ PNEC	Risk Assessment
3BC	0.141[a]	>1	3.0	100	0.03	0.082[d]	2.73	YES
BP1	3.882[b]	>5	4'919	100	49.2	0.125[e]	0.003	NO
BP2	3.882[b]	>10	1'200	100	12.0	0.125[e]	0.010	NO
Et-PABA	62.00[c]	>10	4'393	100	43.9	0.125[e]	0.003	NO

[a]3BC, LC_{50} in fish 96 h, rainbow trout, SciFinder Scholar 2006; [b]BP3, LC_{50} in fish 96 h, rainbow trout, SciFinder Scholar 2006; [c]Et-PABA, LC_{50} in fish 24 h, rainbow trout, Invest Fish Control Rep. No. 87, Fish Wildl. Serv., Bur. Sport Fish. Wildl., U.S.D.I., Washington, D.C.; 50, 1979; [d] ref. [9]: Highest concentration of 4MBC found in Swiss lakes (summer 1998, 82 ng/l in Hüttensee); [e] ref. [9]: Highest concentration of BP3 found in Swiss lakes (summer 1998, 125 ng/l in Hüttensee)

Table 4. PEC values based on residues in fish in rivers and PNEC values based on body burdens in fish in our experiments on hormonal activity of 3BC and BP2 (LOEC)

UV filter	Toxicity acute [mg/l]	chronic [mg/l]	LOEC Our exper. [ng/g]	Safety factor	PNEC [ng/g]	PEC [ng/g]	PEC/ PNEC	Risk Assessment
3BC	0.141[a]	>1	360	100	3.6	90[d]	25	YES
BP1	3.882[b]	>5	2000	100	20.0	5.9[e]	0.295	NO
BP2	3.882[b]	>10	2000	100	20.0	5.9[e]	0.295	NO
Et-PABA	62.00[c]	>10	2000	100	20.0	5.9[e]	0.295	NO
3BC					3.6	11.5[f]	3.19	YES
BP1					20.0	11.5[f]	0.575	NO
BP2					20.0	11.5[f]	0.575	NO
Et-PABA					20.0	11.5[f]	0.575	NO

[a]3BC, LC_{50} in fish 96 h, rainbow trout, SciFinder Scholar 2006; [b]BP3, LC_{50} in fish 96 h, rainbow trout, SciFinder Scholar 2006; [c]Et-PABA, LC_{50} in fish 24 h, rainbow trout, Invest Fish Control Rep. No. 87, Fish Wildl. Serv., Bur. Sport Fish. Wildl., U.S.D.I., Washington, D.C.; 50, 1979; [d]ref. [6]: lipid weight based concentration of 1800 ng/g 4MBC in brown trout from a small Swiss river, divided by 20 as an approximation for whole body concentration; [e]ref. [6]: lipid weight based concentration of 118 ng/g BP3 in roach from Lake Greifen (Switzerland), divided by 20 as an approximation for whole body concentration; [f]Zenker A. (pers. communication): Highest concentration of UV filter EHMC in fish from river Glatt was 229 ng/g lipids, divided by 20 as an approximation for whole body concentration

Fent et al. 2008

Mixtures?

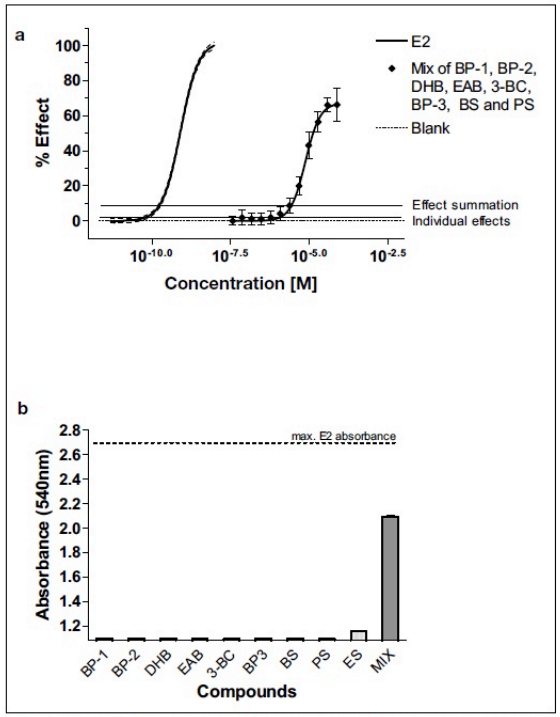


Fig. 5. Estrogenic activity of UV filter mixtures *in vitro* in the hERα assay. (a) Activity of a mixture of eight UV filters that were individually mixed at their no observed effect concentrations. (b) Effects of individual compounds and their activity as a mixture summing up the individual contribution (ES) and the measured effect (MIX) are shown.[40]

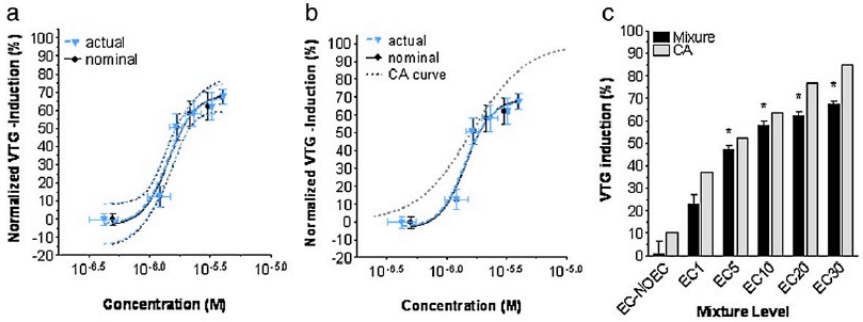


Fig. 5. (a) Pooled concentration–response data and nonlinear hill regression curves for nominal (solid line) and actual (dashed line) exposure concentrations of each of the ternary UV filter mixture, dashed lines represent the 95% confidence intervals. Data shown are means ± SEM and 95% CI band (three replicates per concentration with 6 fish each). (b) Comparison between the observed and CA-predicted mixture effects of three UV filters in juvenile fathead minnow. The solid (nominal) and dashed (actual) line represents the best-fit of the observed effect data, and the dotted grey line represents the CA prediction. (c) Comparison between the observed and CA-predicted mixture effects at 6 equi-effective concentration levels. Values are means ± SEM. Asterisk denotes a significant difference from solvent control at $p \leq 0.05$.

Table 1. Measured Concentrations (Mean ± Standard Deviation, ng/g of Dry Weight, n = 3) of BP-3, EHMC, and OC in Artemia and Zebrafish at Environmental Cases (EC, 5.5 μg/L BP-3, 4 μg/L EHMC, and 7 μg/L OC), at Worst-Case (WC, 550 μg/L BP-3, 400 μg/L EHMC, and 700 μg/L OC), and after Single/Mixture Exposures[a]

	measured concentrations (ng/g of dry weight)		
exposures	BP-3	EHMC	OC
		Blank Control	
artemia	n.d.	n.d.	n.d.
zebrafish	n.d.	n.d.	n.d.
		EC Single	
artemia	27.4 ± 5.6 a	126.9 ± 2.7 a	87.4 ± 11.6 a
zebrafish	17.0 ± 1.8 a	23.5 ± 0.7 a	23.0 ± 3.3 a
		EC Mixture	
artemia	28.7 ± 3.6 a	161.0 ± 52.5 a	142.8 ± 32.2 a
zebrafish	18.0 ± 4.3 a	26.2 ± 2.7 a	30.8 ± 4.2 a
		WC Single	
artemia	4873.7 ± 2200.0 b	35 382.4 ± 1503.2 b	23 655.3 ± 1919.8 b
zebrafish	130.3 ± 14.9 b	94.5 ± 24.3 a	147.7 ± 3.1 b
		WC Mixture	
artemia	9415.4 ± 188.8 c	92 378.0 ± 351.8 c	35 187.3 ± 2451.2 c
zebrafish	191.6 ± 52.8 c	400.4 ± 130.0 b	496.2 ± 41.0 c

[a]Values with different letters denote significantly different means (p < 0.05, Student-Newman-Keuls test) in artemia and zebrafish. n.d.: <LOD (signal-to-noise ratio of 3, 0.3−6.0 ng/g dry weight).

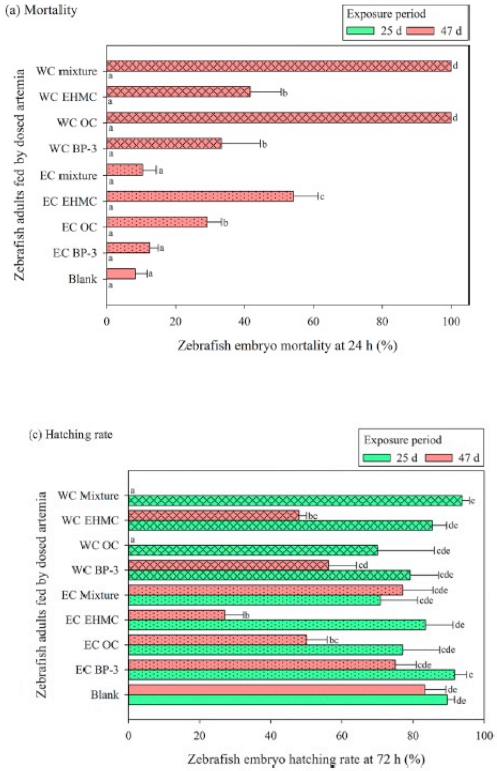


Figure 2. Apical end points (mean ± standard error) of (a) mortality at 24 h (n = 4), (b) heart rate at 48 h (n = 5), and (c) hatching rate (n = 4) at 72 h, of zebrafish *Danio rerio* embryos produced from zebrafish adults fed artemia dosed with different UV filters at environmental-case (EC) and worst-case (WC) single/mixture levels. Bars with different letters denote significantly different means (p < 0.05, Student−Newman−Keuls test).

BP3 assessments

In vivo estrogenic activity in sediments

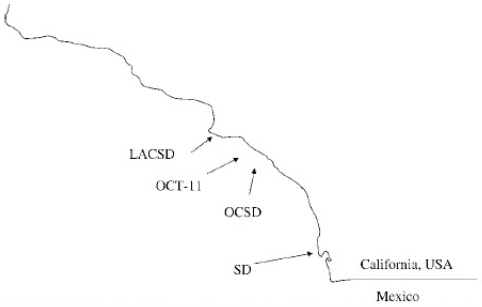


Fig. 1. Map of the Southern California Bight, USA, and sampling locations (see Table 1 for description of sites). LACSD = outfall for the Los Angeles County Sanitation District; OCT-11 = reference location; OCSD = outfall for the Orange County Sanitation District; SD = outfall for the City of San Diego.

Table 3. In vivo (California halibut [CH] vitellogenin [VTG]) estrogenic activity of sediment extracts collected near outfalls of three wastewater discharge outfalls and a reference site in the Southern California Bight, USA, in 2003. Each value represents the mean ± standard deviation of seven (CH vitellogenin) replicates. ND = not detected; NM = not measured[a]

	Extract		Sediment only
	CH VTG (μg/g) plasma protein	CH VTG EEQ (μg/kg wet wt) fish	CH VTG (μg/g) plasma protein
LACSD	17.7 ± 4.1	90.4 ± 48.3	NM
SD	6.8 ± 1.4	13.7 ± 2.9	NM
OCSD	2.8 ± 0.4	1.3 ± 0.12	2.0 ± 0.2
OCT-11 reference	ND	<1.0	ND
Sand	ND	<1.0	ND

[a] LACSD = Los Angeles County Sanitation District; SD = city of San Diego; OCSD = Orange County Sanitation District; EEQ = estradiol equivalents. Detection limits (1 μg/kg CH).

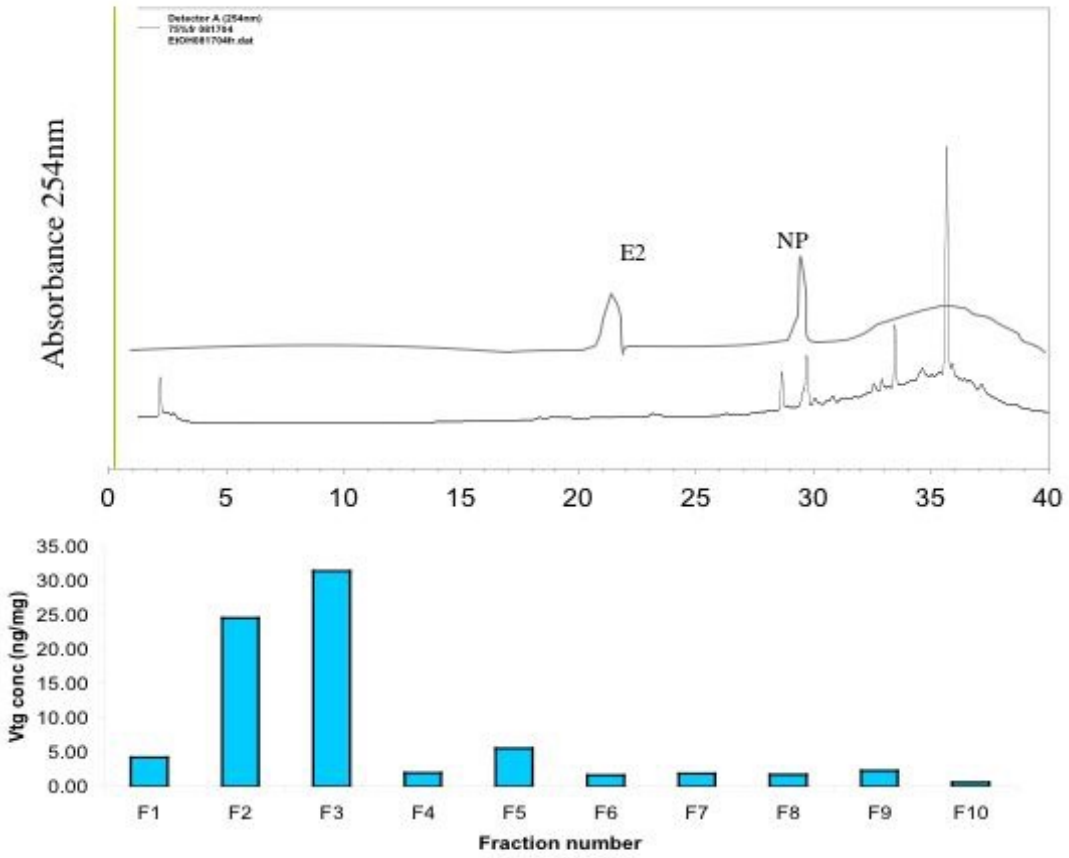
Table 2. 17β-Estradiol, estrone, alkyl phenol, and alkylphenol ethoxylate concentrations (ng/g dry wt) of sediments collected from the Southern California Bight, USA, in 2003 (<cal = detected by instrument, but below calibration curve; <DL = below detection limit[a]

	LACSD	SD	OCSD	OCT-11 (reference)
E1	0.6	<0.03	<0.03	<0.03
E2	0.3	0.3	0.45	0.16
NP	198	122	3200	130
NPC1	<DL	<DL	100	<DL
NPBr	<DL	<DL	<DL	<DL
NP 1EO	36	11.6	330	76
NP 2EO	19.2	3.2	600	92
NP 3EO	15.6	1.9	3900	92
OP	8.2	1.9	<DL	<DL
OP 1EO	<DL	<DL	<cal	21
OP 2EO	<DL	<DL	<cal	8
OP 3EO	<DL	<DL	42	58

[a] E2 = 17β-estradiol; E1 = estrone; NP = nonylphenol; NP (X)EO ethoxylate = nonylphenol (carbon chain) ethoxylate; OP (X)EO ethoxylate = octylphenol (carbon chain) ethoxylate; LACSD = Los Angeles County Sanitation District; SD = city of San Diego; OCSD = Orange County Sanitation District.

Schlenk et al. 2005

TIE of Estrogenic Sediment Extracts from LACSD outfall



Schlenk et al. 2005

Table 4
Compounds qualitatively and quantitatively identified by GC-MS/MS or LC-MS/MS

Compound name	Concentration, ng/g	Compound class
Pyrene	5	Polyaromatic hydrocarbon
Phenanthrene	7.5	Polyaromatic hydrocarbon
Oxybenzone	19	Sunscreen agent, UV filter
Galaxolide	6	Musk odorant
Triclosan	26	Antibacterial chemical
Bisphenol A like Phenols	?	Plasticizers
Diethylphlalate	?	Plasticizers
Dibutyl phlalate	?	Plasticizers
Nonylphenol isomers	?	Detergent derivatives

See Sapozhnikova et al. (2005) and (Vanderford et al., 2003) for methods.

BP-3

Threshold estimates for BP3 in medaka

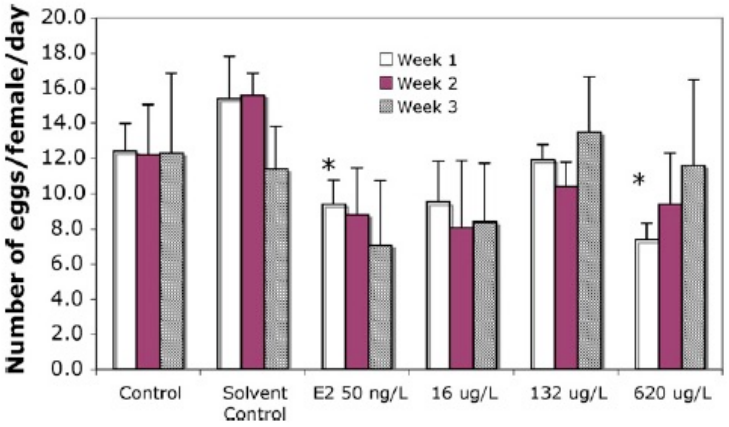


Fig. 1. Effects of oxybenzone on the cumulative number of eggs produced per female Japanese medaka during 21 days of treatment. Solvent control consisted of 0.1% acetone. Each value represents the mean of five replicates ± S.E. $^{*}p \leq 0.05$.

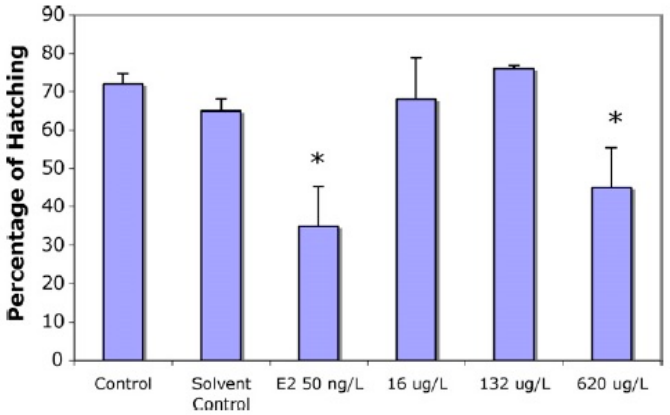


Fig. 2. Effects of oxybenzone on the percentage of eggs that hatched from Japanese medaka treated for 21 days. Solvent control consisted of 0.1% acetone. Each value represents the mean of five replicates ± S.E. $^{*}p \leq 0.05$.

M. Coronado et al. / Aquatic Toxicology 90 (2008) 182–187

Other studies (BP-3)

- Bluthgen et al. 2012
  - 14 d and embryonic exposures
  - No Vtg
  - BP3→BP1
  - Anti-androgenic based on gene expression in male testes
  - No histological changes
  - No embryonic effects up to 438 ug/L
- Kim & Choi 2014
  - PNEC 1.32 ug/L (all biota)
- Kinnberg et al. 2015 (ETC)
  - OECD TG 234
  - 0-60d post hatch exposure
    - Skewed sex monotonic females NOEC 191 ug/L; LOEC 388 ug/L
    - No Vtg
    - 12 d exposures to adults non-monotonic at 268 ug/L
- Tao et al 2020 (STOTEN)
  - Single dose 10 ug/L (nominal) embryonic exposure 6-24 hpf
    - Increased movement 21 and 24 hpf
    - Increased locomoter activity 5 **dpf**
    - Decreased shoaling behavior 11 **dpf**
    - Decreased axonal growth/apoptosis 27 hpf
    - RXR morpholinos reversed effects
    - Non-endocrine….neurotoxicity more important
- Sandoval-Gio 2021 (BECT)
  - 1-10 ug/L (nominal) embryonic exposure 4-72 hpf
  - No effect on hatch, survival
  - Decreases in Achase expression/activity (no positive control)
- Xu et al. 2021 (BECT)
  - exposure embryo-42 d (Fo) +/- 96 hr (F1) (0.056-38 ug/L)
  - Monotonic skewed sex ration to female F1 (LOEC 2.3 ug/L; NOEC 0.056 ug/L)
  - Decreased hatch rate from F1 embryos after parental exp0sures *** (no NOEC—LOEC 0.056 ug/L); identical response when F1 received parental and embryonic exposures
  - Decreased movement in F1 not receiving parental exposure (LOEC 0.056 ug/L) non-monotonic
  - Decreased heart beat and growth Fo embryos (no additional exposure) and F1 embryos with and without parental exposure. 0.056 ug/L non-monotonic

Table 7
Derivation of predicted no effect concentration (PNEC) for benzophenone-3 in fresh water environment.

Toxicity	Taxonomic group	EC50 or NOEC	Conc. (μg/L)	Reference	Assessment factor	PNEC (μg/L)
Acute	Algae	72 h, EC50	960	Sieratowicz et al. (2011)	100[a]	1.32
	Invertebrate	48 h, EC50	1670	Sieratowicz et al. (2011)		
Subchronic	Fish	21 d, NOEC	132[b]	Coronado et al. (2008)		
Chronic	Algae	72 h, EC10[c]	610	Sieratowicz et al. (2011)		
	Invertebrate	21 d, NOEC	500	Sieratowicz et al. (2011)		

[a] An assessment factor of 100 can be used in cases where the acutely most sensitive species has a lower toxicity than the two chronic toxicity data from two trophic levels (European Commission, 2003).
[b] Based on the lowest *Oryzias latipes* F1 hatchability NOEC after 21 days of parental exposure. The test duration of 21 days for fish was considered as acute with conservative perspectives.
[c] If no NOEC value is available for a long-term test, EC10 obtained by extrapolation using appropriate statistics can be considered as a NOEC (European Commission, 2003).

Species/Lab differences

- Static measured chem vs. Nominal
  - Before and after (cosmetic contamination?)
- Single dose vs. Dose response
- Inconsistent Non-montonicity
- Inconsistent Neurotoxicity
  - Dose?
- Metabolism species differences
  - Medaka and zf are different

Ecological Relevance

- Leslie's Matrix Population Estimate Model

(Miller and Ankley 2005)

  - Fathead Minnows

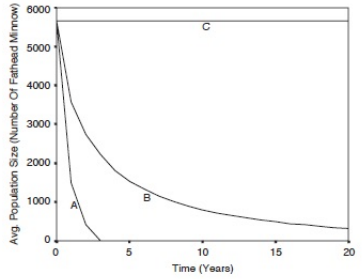


Fig. 2. Population projection for a fathead minnow population existing at a carrying capacity of 5665 and subsequently exposed to varying levels of 17β-trenbolone. Three exposure concentrations were evaluated: (A) ≥0.266 µg/L, (B) = 0.027 µg/L, and (C) ≤0.0015 µg/L.

- Age-structured life history Matrix Model (Baldwin et al. 2009)
  - Salmonid Feeding behavior/growth(length)

- Quantitative AOPs

(Conally et al. 2017)

TABLE 4. Organismal and population model outputs for each scenario examined.

	Organismal model (after 140 days)		Population model (after 20 years)			
Scenario	Mass (g)	Length (mm)	Calculated estuary survival	λ	Spawner abundance (% of control)	Spawner increase (%)
Control	6.1 (0.6)	80.9 (2.7)	0.170 (0.012)	1.10	100	523
OP pulse	4.4 (0.4)	72.4 (2.5)	0.134 (0.010)	1.03	27.0	68
OP continuous	5.1 (0.5)	76.0 (2.6)	0.148 (0.011)	1.06	47.3	195
CB pulse	5.9 (0.6)	79.8 (2.8)	0.165 (0.013)	1.09	85.6	433
CB four pulses	5.3 (0.5)	77.1 (2.7)	0.153 (0.012)	1.07	56.4	251

Notes: See Table 2 for definition of the scenarios. The intrinsic population growth rate is λ. Values in parentheses following means are standard deviations.

Conclusions

- Susceptibility
  - ADME toxicokinetic modifications
    - Factors that enhance body burdens
      - Climate impacts
    - Factors that reduce detox; enhance bioactivation
      - Mixtures
- Relevance of Acute or Chronic Effects
  - Acute impacts (lethality) high uncertainty with UV filters
    - Uncertainty factors warranted for compounds without chromic data
  - Chronic impacts (growth, survival, reproduction, development)
    - Better predictions to Population and Ecosystem impacts
      - Uncertainty associated with species differences (SSDs)
    - Adverse Outcome Pathways

Uncertainties with Laboratory estimates

- Static measured chem vs. Nominal
  - Before and after (cosmetic contamination?)
- Single dose vs. Dose response
- Inconsistent Non-montonicity
- Inconsistent Neurotoxicity
  - Dose?
- Metabolism species differences
  - Medaka and zf are different
- Models linking reproduction to population
  - Limited life history information/recruitment in the field
- Mixtures
  - Chemical—limited data indicate antagonistic response
    - Other contaminants unclear
  - Non-chemical stressors (climate change)

Questions

daniel.schlenk@ucr.edu