Session C: Chemicals of Concern

TURI
TOXICS USE REDUCTION INSTITUTE
UMASS LOWELL

Overview

This session will focus on new information on human health effects, particularly those related to endocrine effects.

Overviews of the SAB's on-going review of per- and poly-fluorinated chemicals will be covered as well as recent work on Phthalate Esters.

Goals of Session

Share SAB process with examples of recent work

Learn key concerns about Phthalate Esters and PFAS

Learn more in depth about endocrine disruption in Phthalate Esters & PFAS

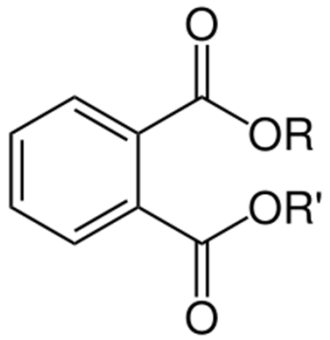
Phthalate Esters

CERCLA listed and TURA listed, not reportable by DEP Policy

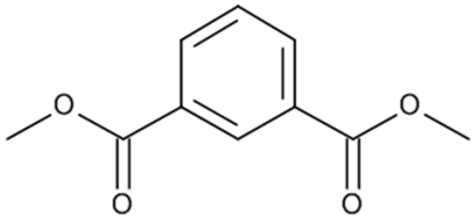
SAB review began in 2012, ended 2015

First Task: Define category

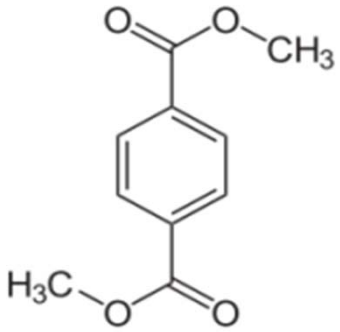
Phthalate Esters – Chemical Structure



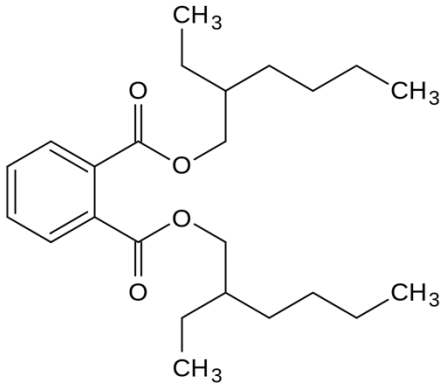
Ortho-phthalate ester



Isophthalate ester (meta-)



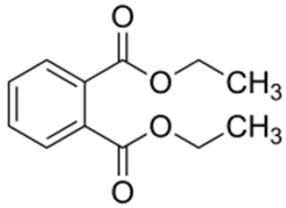
Terephthalate ester (para-)



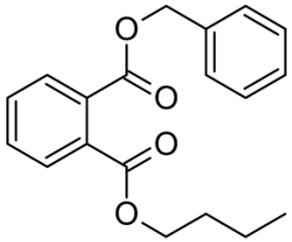
e.g., DEHP: di-2-ethylhexyl phthalate, Bis(2-ethylhexyl) phthalate (BEHP), Di-sec octyl phthalate (DOP)

Phthalate Esters - Uses

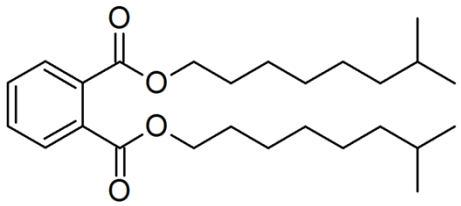
- Plasticizers in plastics
- solvents and emollients in personal care products and cosmetics



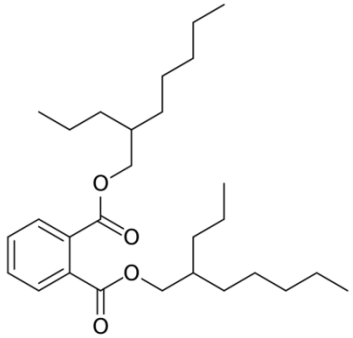
DEP – diethyl phthalate



BBP



DINP



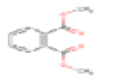
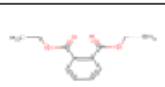
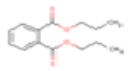
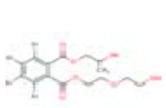
DPHP

- Commercial products are mixtures, with various chain lengths and configurations

SAB Process:
Collect Standard EHS Info on Substances

- Physical properties (FP, VP, etc)
- Acute toxicity
- Reproductive/developmental toxicity
- Liver toxicity/Target organs
- Carcinogenicity
- Neurotoxicity
- PBT

Standard EHS Info

Common Abbrev.	Common Chemical Name	CAS No.	Individual Chem Listed on TURA	Chemical Name (Synonyms)	Chemical Formula	Structure	Carbon Chain Length [Table 3 Tox Data Summary PE ACC 2001; T = Transitional Group = >/= 10% C4-C6]	Molecular Weight (mainly from ChemID Plus)	Viscosity in Centistokes (or otherwise noted) @ 20 deg C (HSDB, etc…)	Physical State at Room Temperature (HSDB, RTECS, CICAD, CHRIS)	Vapor Pressure mmHg at ~20C (HSDB, MSDS, ICSC)	PBT (from www.pbtprofiler.net) *Part of mixture not recommended for profiling ** May be no effect at saturation (Water solubility)						IARC	Neurotoxicity (Scorecard)	Other re health ef (Scoreca
												Water	Soil	Sediment	Air	BCF	Fish ChV			
DMP	Dimethyl phthalate	131-11-3	Yes	Phthalic acid, dimethyl ester	C10-H10-O4		C1	194.185	17.2 cP @ 25 deg C [HSDB]	Liquid; solid below 42F	0.0031 [HSDB]	15	30	140	28	5.3	3.3	n/f	Y [DAN, RTECS]	Immuno
	Dimethyl 4-aminophthalate	51832-31-6	No	1,2-Benzenedicarboxylicacid, 4-amino-, 1,2-dimethyl ester	C10H11NO4		C1 and the ring has an amine group	209.2	n/f	solid [MSDS]	n/a	15	30	140	2	2.6	0.65	n/f	n/f	
DEP	Diethyl phthalate	84-66-2	Yes	Phthalic acid, diethyl ester	C12-H14-O4		C2	222.239	12.1 cP [CHRIS] 31.3 centistokes at 0 deg C [HSDB]	Liquid	0.002 [HSDB]	15	30	140	4.6	18	0.82	n/f	Y [HSDB]	Endocri Liver [A' [HAZM Respirato
DPP	Di-n-propylphthalate	131-16-8	No	1,2-Benzenedicarboxylic acid, dipropyl ester	C14-H18-O4		C3	250.3	n/a	Liquid [MSDS]	0.000132 mm Hg [HAZMAP]	15	30	140	2.5	67	0.2	n/f	N	Er
DMEP	Bis(2-methoxyethyl) phthalate	117-82-8	No	Dimethylglycol phthalate	C14-H18-O6		C3 (w/ O)	282.29	32 cP [HSDB]	Liquid	0.000228 [HSDB]	15	30	140	0.83	2.5	14	n/f	n/f	Rep/Deve
DAP	Diallyl phthalate	131-17-9	No	1,2-Benzenedicarboxylic acid, di-2-propenyl ester	C14-H14-O4		C3 (double bond)	246.261	13 mPa s (dynamic) [RR]	Liquid (HAZMAP)	0.00116 mm Hg [HAZMAP]	15	30	140	0.18	63	0.014	n/f	N	Cardiova Carcino
	2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate	20566-35-2	No	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 2-(2-(2-hydroxyethoxy)ethyl) 1-(2-hydroxypropyl) ester	C15-H16-Br4-O7		C3 with hydroxyl group and C4 as ethyl ether with primary hydroxyl group	627.9	>= 80000 <= 135000 other: cps @ 25degC [RR]	Liquid [RR]	0 mm Hg @ 25deg C Estimated VP: 2.37E-14 mm Hg. [RR]	60	120	540	0.54	86	0.37	n/f	n/f	
DBP	Dibutyl phthalate	84-74-2	Yes	o-Benzenedicarboxylic acid,	C16-H22-O4		C4	278.346	12-14 mPas [IUCLID]	Liquid	2.01x10-5 [HSDB]	8.7	17	78	1.8	430	0.048	n/f	Y	De G

Chose Substances to Focus on

10 Phthalate Esters Selected for In-Depth Review		Carbon chain length	
		As understood in 2013	After further research
DAP	Diallyl phthalate	C3	C3
DMEP	Bis(2-methoxyethyl) phthalate	C3	C3
DIDP	Diisodecyl phthalate	C7-C11	C8-C10
DnOP	Di-n-octyl phthalate	C8	C8
DINP	Diisononyl phthalate	C9, C8–C10	C8-C9
Din911P	1,2-Benzenedicarboxylic acid, 1-nonyl 2-undecyl ester, branched and linear	C9-C11	C8-C11
DPHP	Di-2-propyl heptyl phthalate	C10	C7, C10
DUP	Diundecyl phthalate	C11	C10-C11
DIUP	Diundecyl phthalate, branched and linear	C11	C9-C11
DTDP	Ditridecyl phthalate	C13-rich	C10-C13

In Depth Study of Specific Phthalate Esters

- Gather studies on specific endpoints

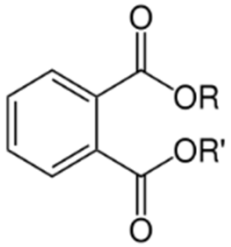
- Consult experts on Phthalate Esters
  - Experts from EPA
  - Experts from the American Chemistry Council
  - Experts from CSPC

Effects of Highest Concern

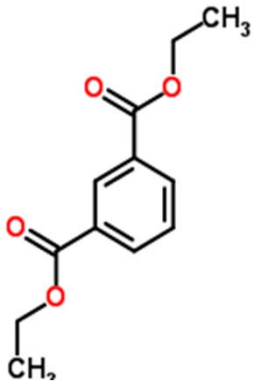
- Reproductive and developmental toxicity
- Liver effects
- Thyroid effects

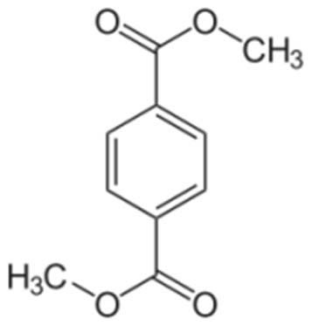
Additional Phthalate Ester Isomers

- Initial focus on ortho-phthalate esters;



- Review meta- and para- as well





Additional Considerations

Review studies on cumulative effects

Review studies on low doses

Phthalate Esters by carbon side chain backbone length: Regulatory and Policy Activity (as of 10/13/16)

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14
DMP	DEP		DBP	DnPP;DPP	DEHP		DINP		DTDP				
TURA	TURA CoRAP WA CHCC		TURA, CA Prop 65, CPSC, SVHC Auth, EPA CAP, EU Restrict, RoHS, ME CHC*, WA CHCC	SVHC EPA CAP SNUR CPSC*	TURA SVHC Auth CA Prop 65 CPSC EPA CAP EU Restrict RoHS WA CHCC		CA Prop 65 CPSC EPA CAP EU Restrict WA CHCC		CoRAP				
		DIBP		DIPP	TBPH		DnOP		DIUP				
		SVHC Auth EPA CAP CPSC* RoHS		SVHC	EPA TSCA CoRAP		TURA CPSC** EPA CAP EU Restrict WA CHCC		CoRAP				
		DMEP	BBP (ring)	PIPP		DIOP	DIDP						
		SVHC	TURA, SVHC Auth CA Prop 65 CPSC, EPA CAP, EU Restrict, RoHS, ME CHC*, WA CHCC	SVHC		CPSC*	CA Prop 65 CPSC** EPA CAP EU Restrict WA CHCC						
		DAP	DCHP (ring)	DnHP; DHP		Benzyl C7-C9			DUP, DnUP				
		CoRAP	EPA TSCA, CPSC*, ME CHC	SVHC, CA Prop 65, CPSC*, WA CHCC		CoRAP			CoRAP				
			DHNUP 7-11 branched and linear 68515-42-4										
			SVHC										
				C6-8, C7 rich			C9-C11						
				SVHC			CoRAP						
				DPHP					DPHP				
				CoRAP					CoRAP				
				DiHepP									
				SVHC									
							Din911P						
				610P; Di C6-10PE									
				SVHC									

Summary Findings: Ortho PEs

C1-C3 (includes individually TURA listed DMP and DEP, and non-listed DPP, DMEP, and DAP, among others):

C1-C3 chain length substances have significant health effects, but not always the same effects as other PEs. These substances often are used as film-forming solvents; most of the known commercial plasticizer products are not in this range.

C4-C7

- Includes individually TURA listed DBP, BBP, DEHP (C8 total: C6 backbone w/ C2 branch), and non-listed DIBP, DinHP, DnPP, DnHP, DCHP, DiHepP, among others:
- Are the most well studied substances;
  - there is a significant body of animal evidence of adverse reproductive and developmental health effects, as well as some human evidence from epidemiological studies. (CPSC, 2010g)

Endocrine Pathways (C4-C7)

- There is a general consensus from animal studies that some C4 and longer ortho-PEs are anti-androgens, interrupting the testosterone synthesis pathway.
- While the mechanisms for these effects are not well understood, there is general concern regarding the impact on hormone pathways.

Liver Effects (C4-C7)

- Liver is a primary target organ for most ortho-PEs, showing effects in chronic and subchronic animal studies.
- There is concern, and no general agreement, about whether the liver effects involving peroxisome proliferation, including carcinogenicity, seen in animal studies are relevant to humans.

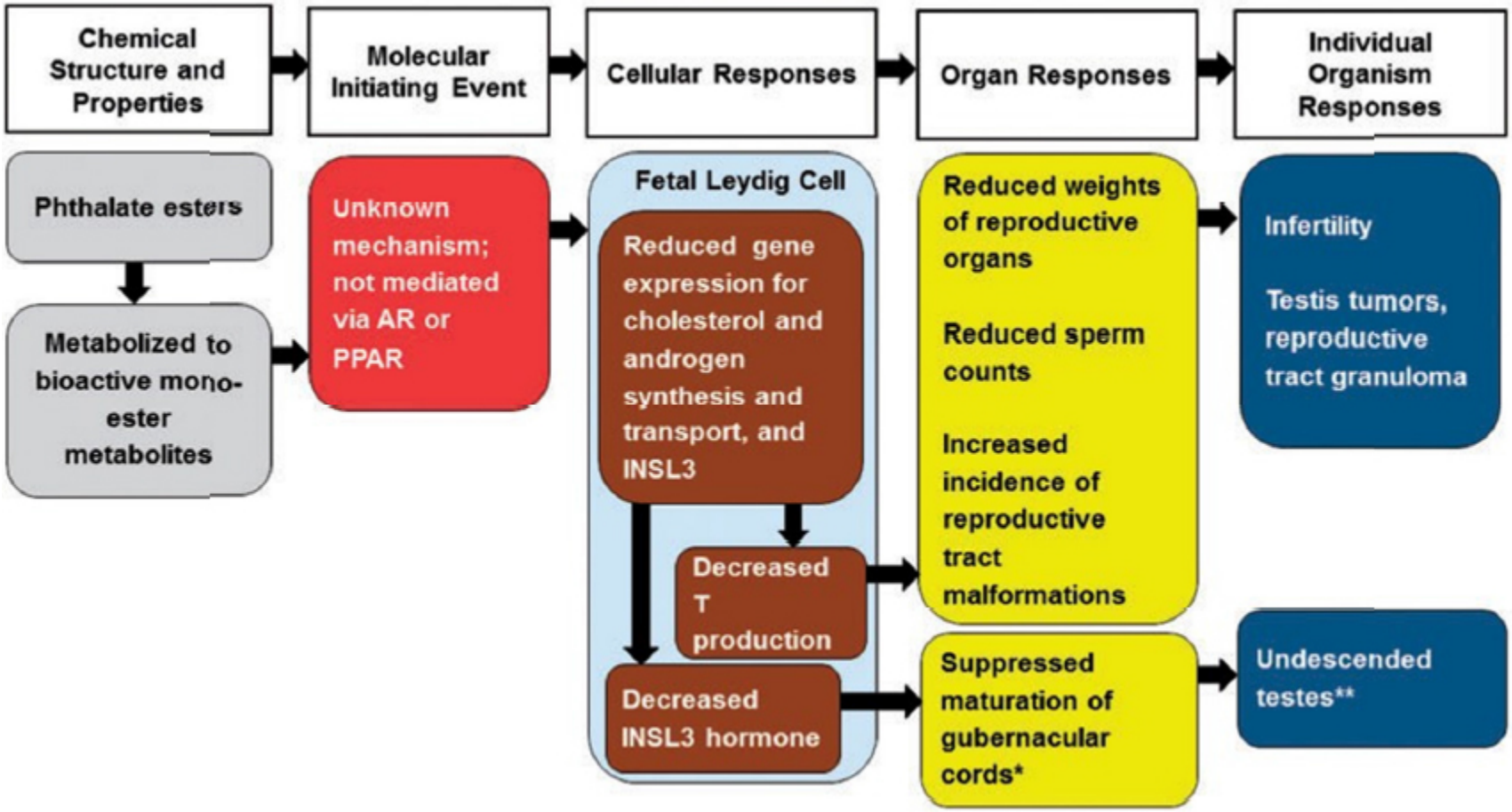
Thyroid (C4-C7)

- While not systematically evaluated by the SAB, thyroid effects were noted in a few of the reproductive studies reviewed
  - May indicate an area of concern

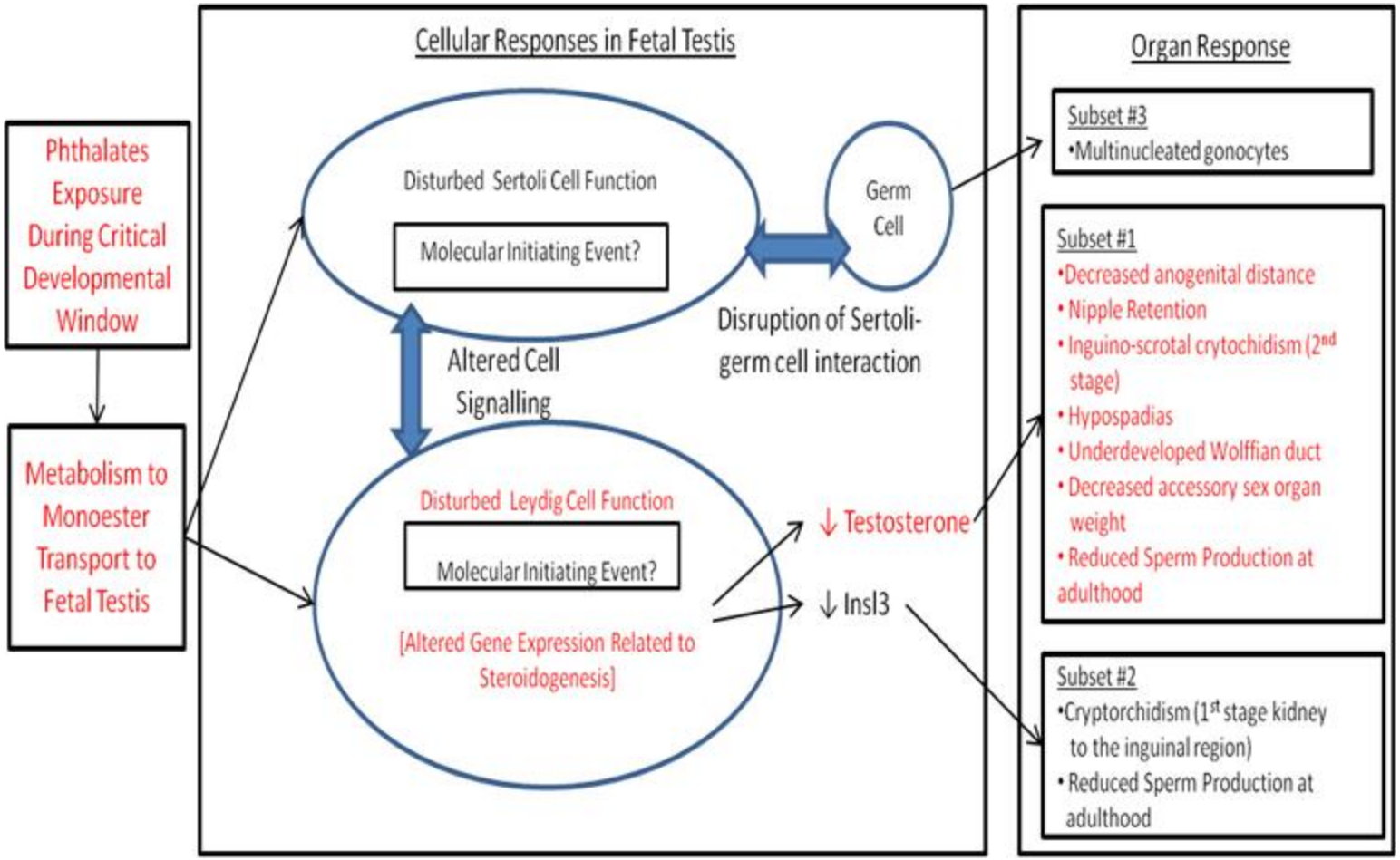
> C7

- Includes individually TURA listed DnOP, and non-listed DINP, DIOP, DIDP, DNP, Din911P, DIUP, DUP, DPHP, DTDP, among others):
- After C7, there is a general tendency as the carbon backbone chain length increases, for the adverse effects to diminish and for there to be fewer scientific studies.

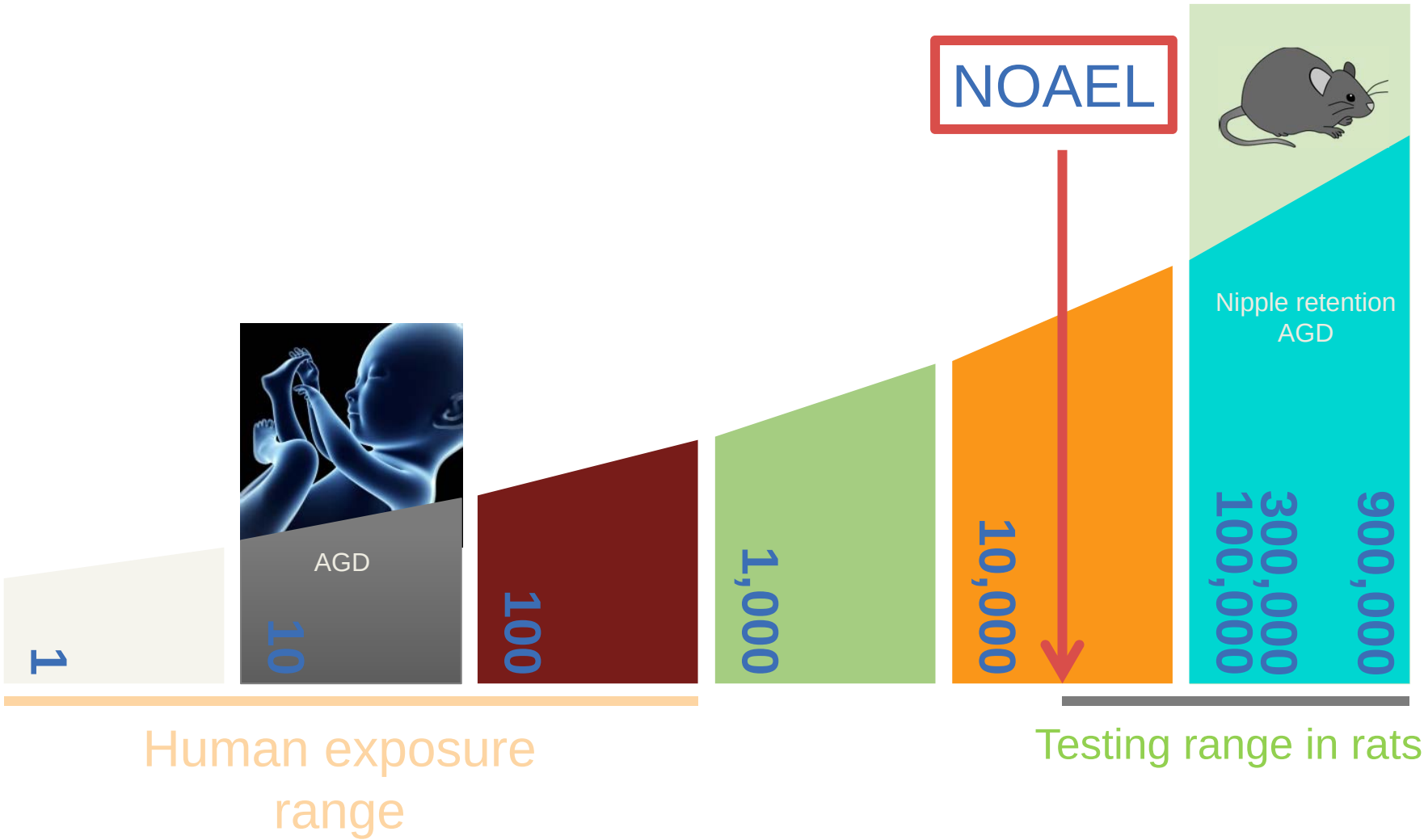
Phthalates: an endocrine perspective



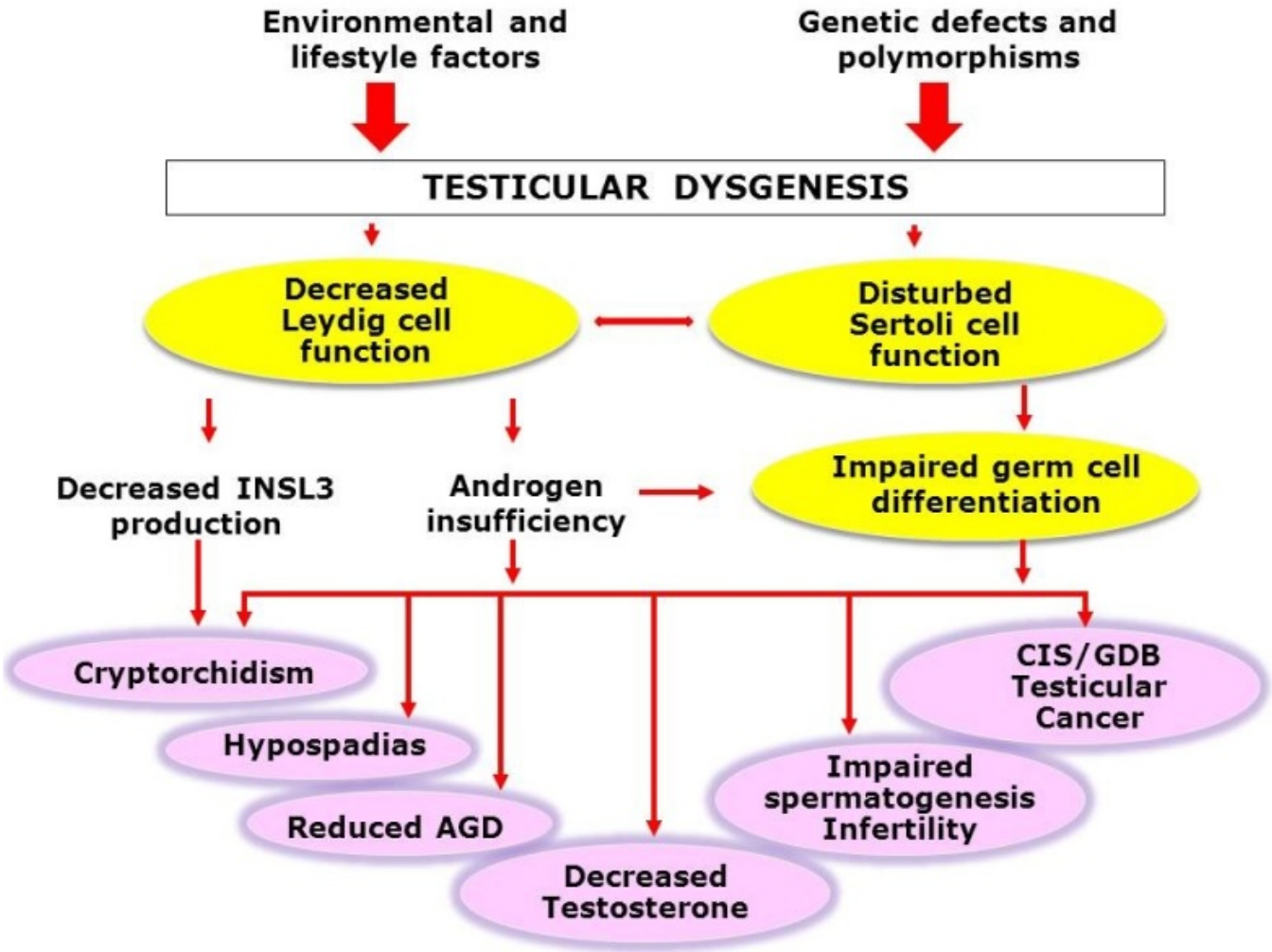
Phthalates: male reproductive syndrome



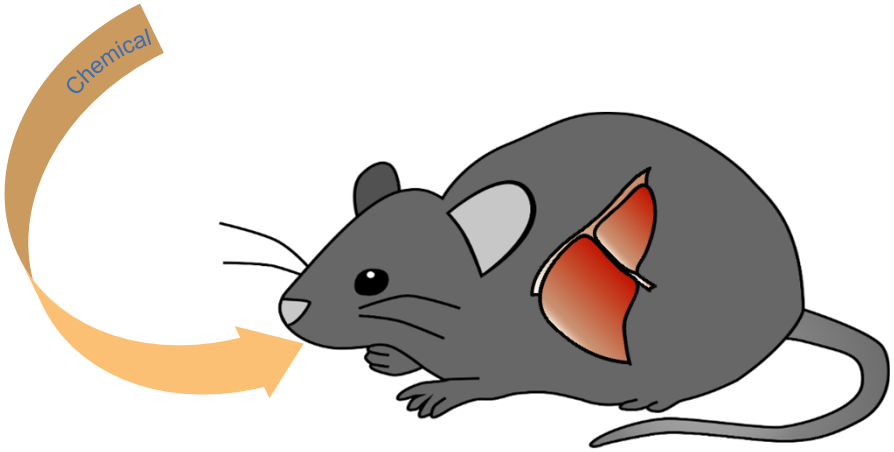
DIISONONYL PHTHALATE (DINP)



Importance of AGD

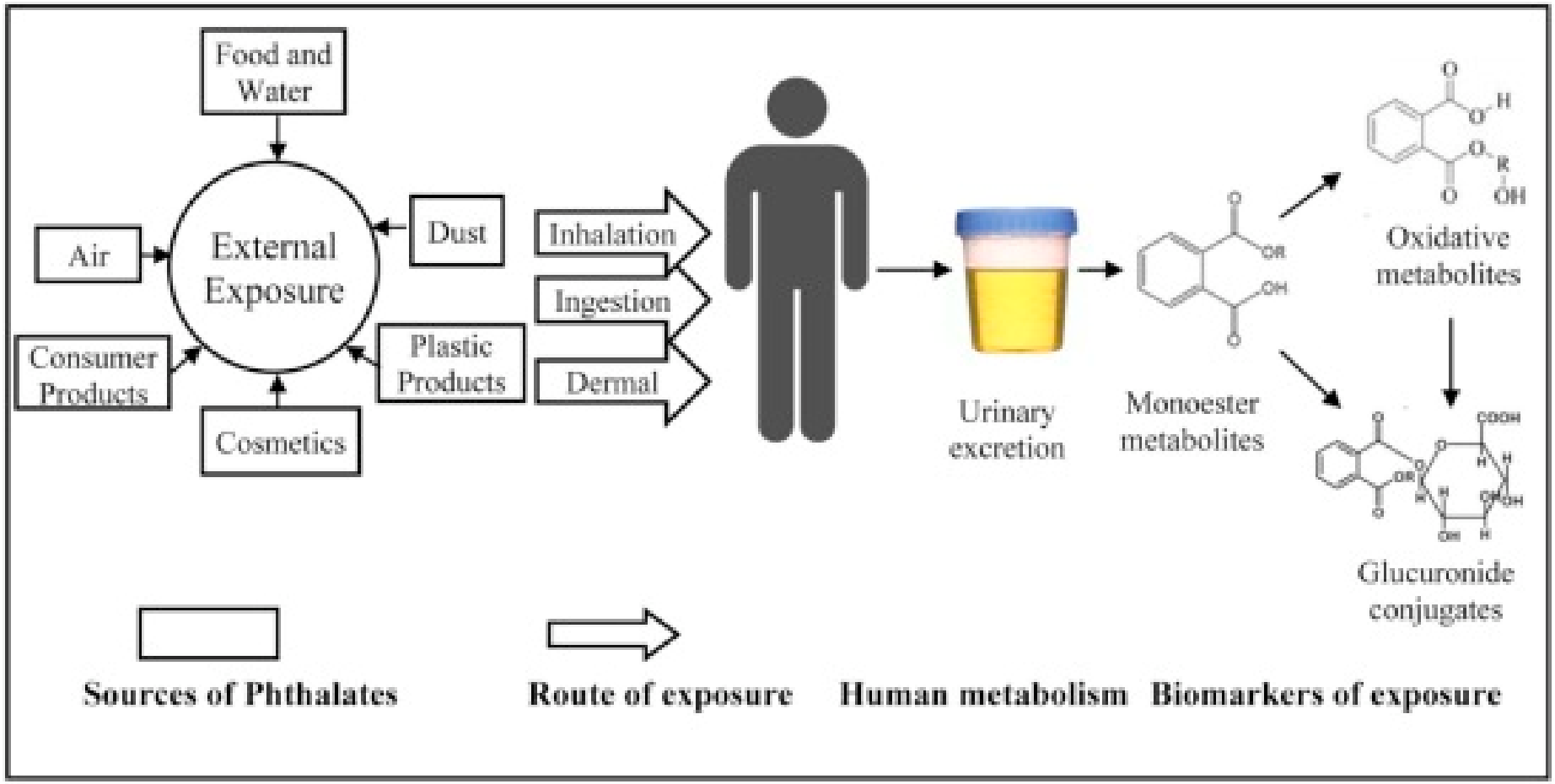


Risk assessment FOR ENDOCRINE DISRUPTORS: IS IT SUFFICIENT?



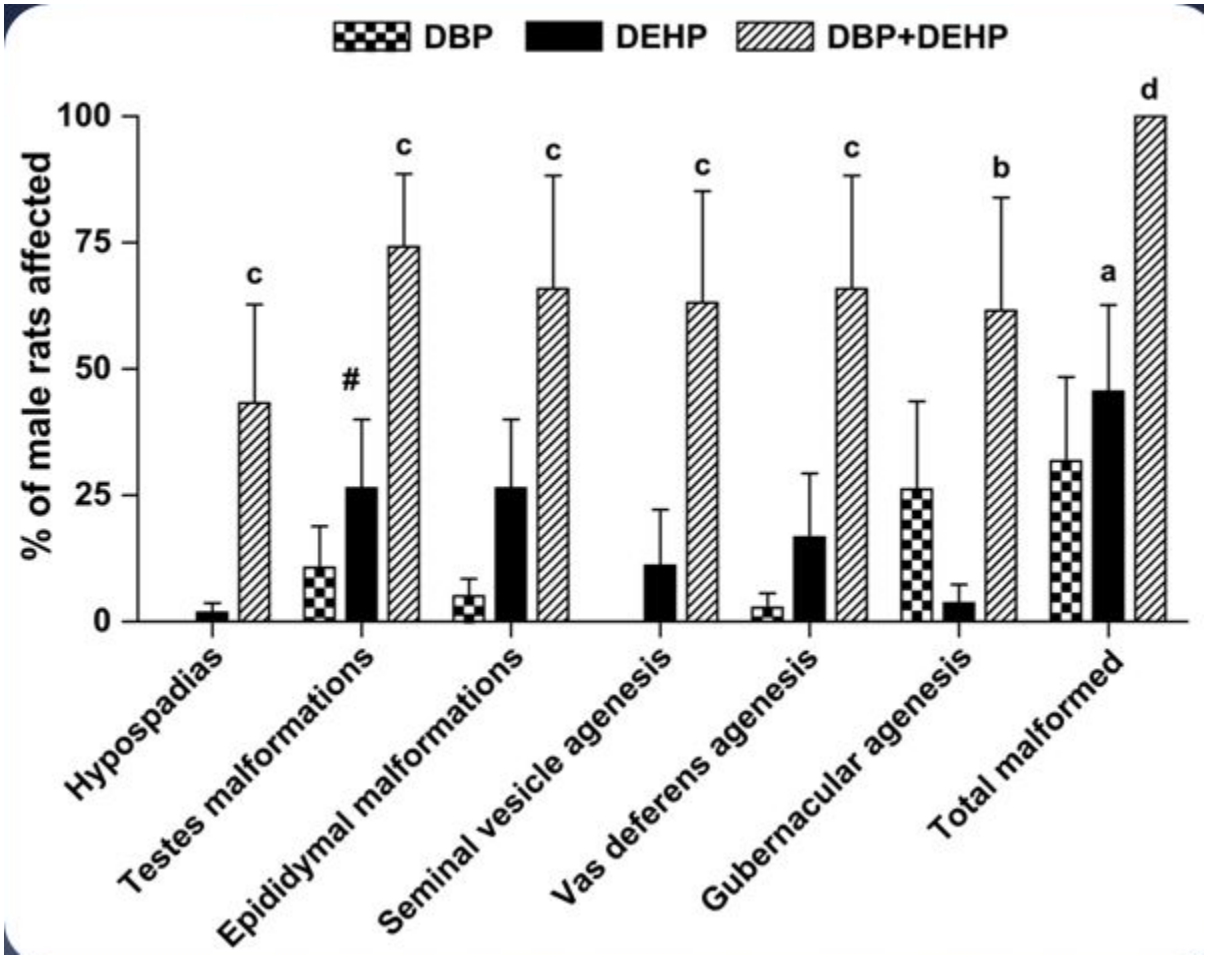
- IDENTIFY LD50, MTD, LOAEL, NOAEL
- CALCULATE **RFD** (NOAEL/10, 100 OR 1,000)
- COMPARE THE **RFD** TO HUMAN EXPOSURE LEVELS

Exposure Equivalency

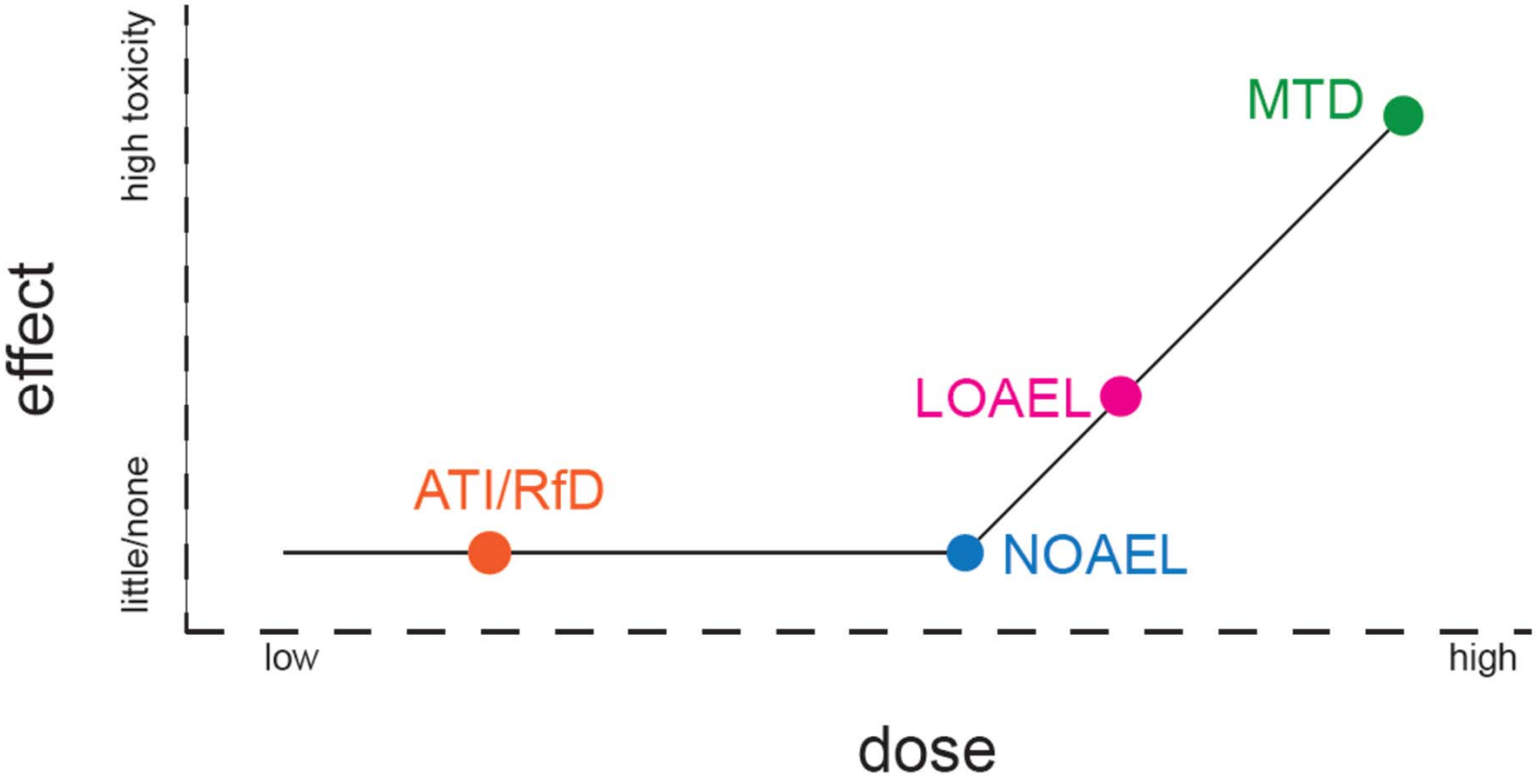


Cumulative effects: lessons from phthalates

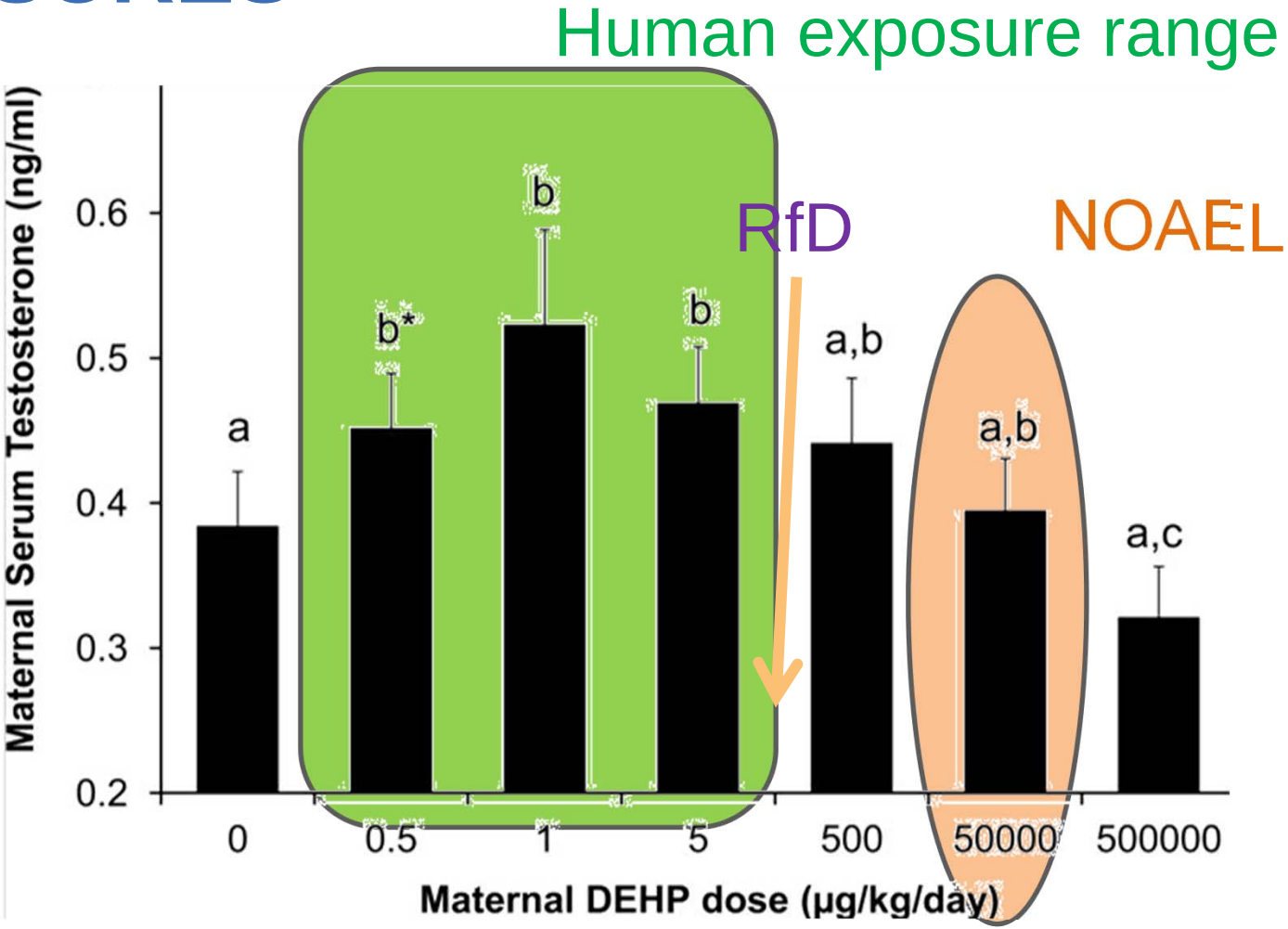
Howdeshell et al. 2007



ATI/RFD DOSES ARE CALCULATED FROM NOAELs WITH AN ASSUMPTION OF LINEARITY



EXAMPLES IN THE CONTEXT OF THE NOAEL, RFD & HUMAN EXPOSURES



Do et al. 2013

Summary of Phthalate Esters

Widely used in consumer products. Widespread human exposures to mixtures.

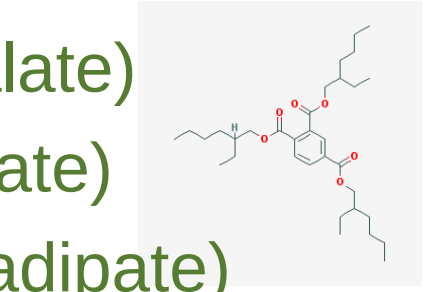
High concern effects: liver, reproductive, developmental toxicity

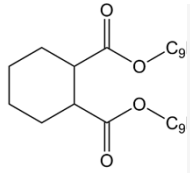
Policy Considerations

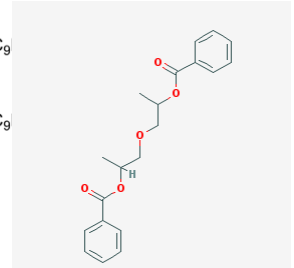
- Massachusetts evaluated the class of phthalate esters.
- For Ortho-PEs:
  - Reproductive health effects across ortho-PEs, variable potency
  - Commercial products are mixtures; not feasible to categorize by carbon chain length
  - New products continue to come on the market with similar constituents and different CAS no.
  - Additive health effects

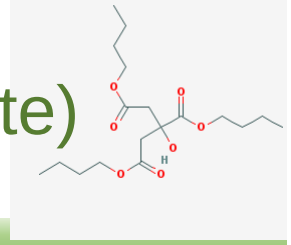
Plasticizer Alternatives

- Tere-phthalates (e.g., DOTP: Dioctyl terephthalate, bis(2-ethylhexyl) terephthalate)
- Trimellitates (e.g., TOTM: Trioctyl trimellitate)
- Aliphatics (e.g., DEHA: Di(2-ethyl hexyl) adipate)
- Epoxies (e.g., ESBO: Epoxidized soybean oil)
- Cyclic esters (e.g., DINCH: Di-isononyl cyclohexane-1,2-dicarboxylate)
- Benzoates (e.g., dipropylene glycol (DPG) dibenzoate)
- Citrates (e.g., tributyl citrate, Acetyl tributyl citrate)



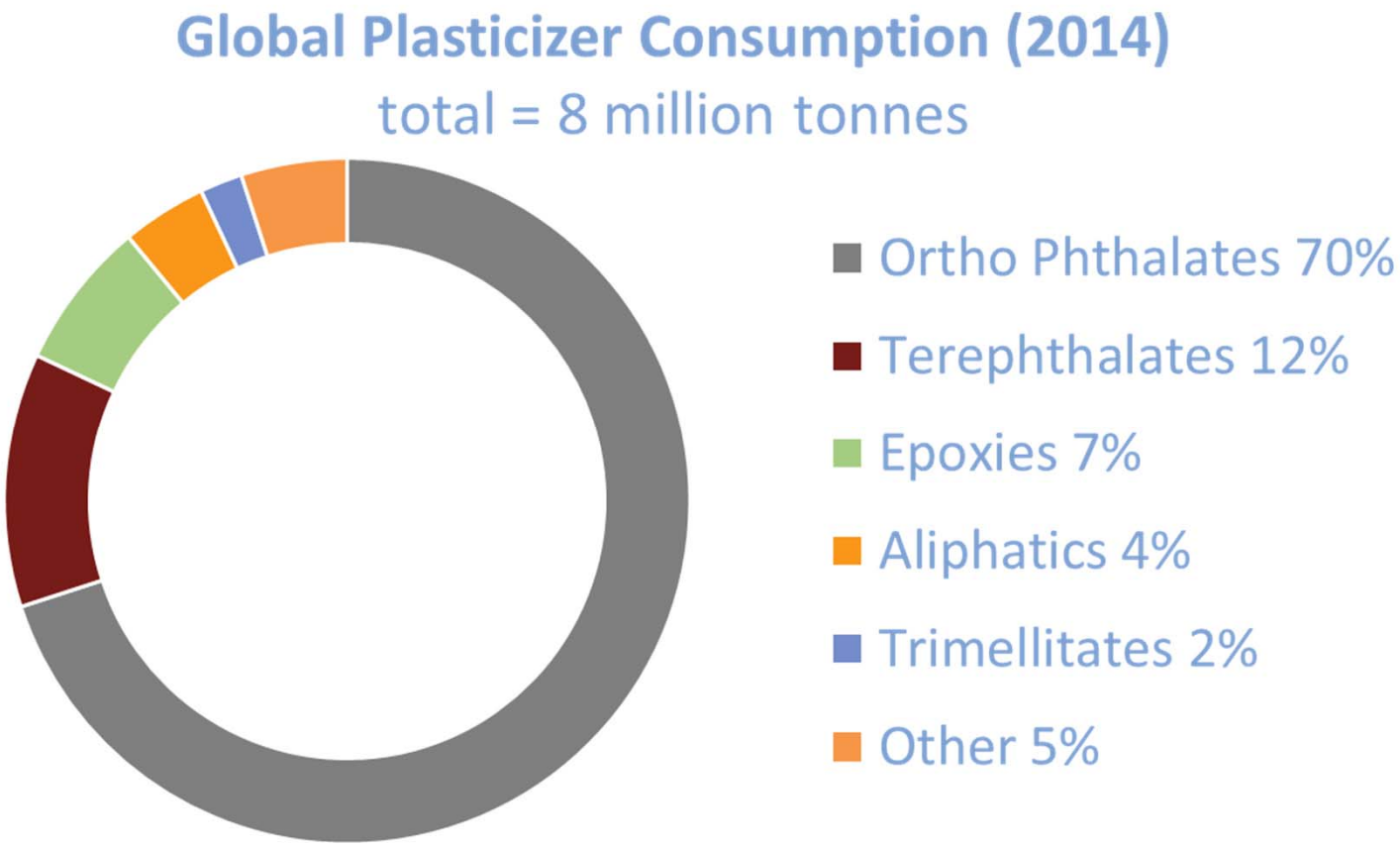






PHTHALATE ESTERS

USED AS PLASTICIZERS, OTHER

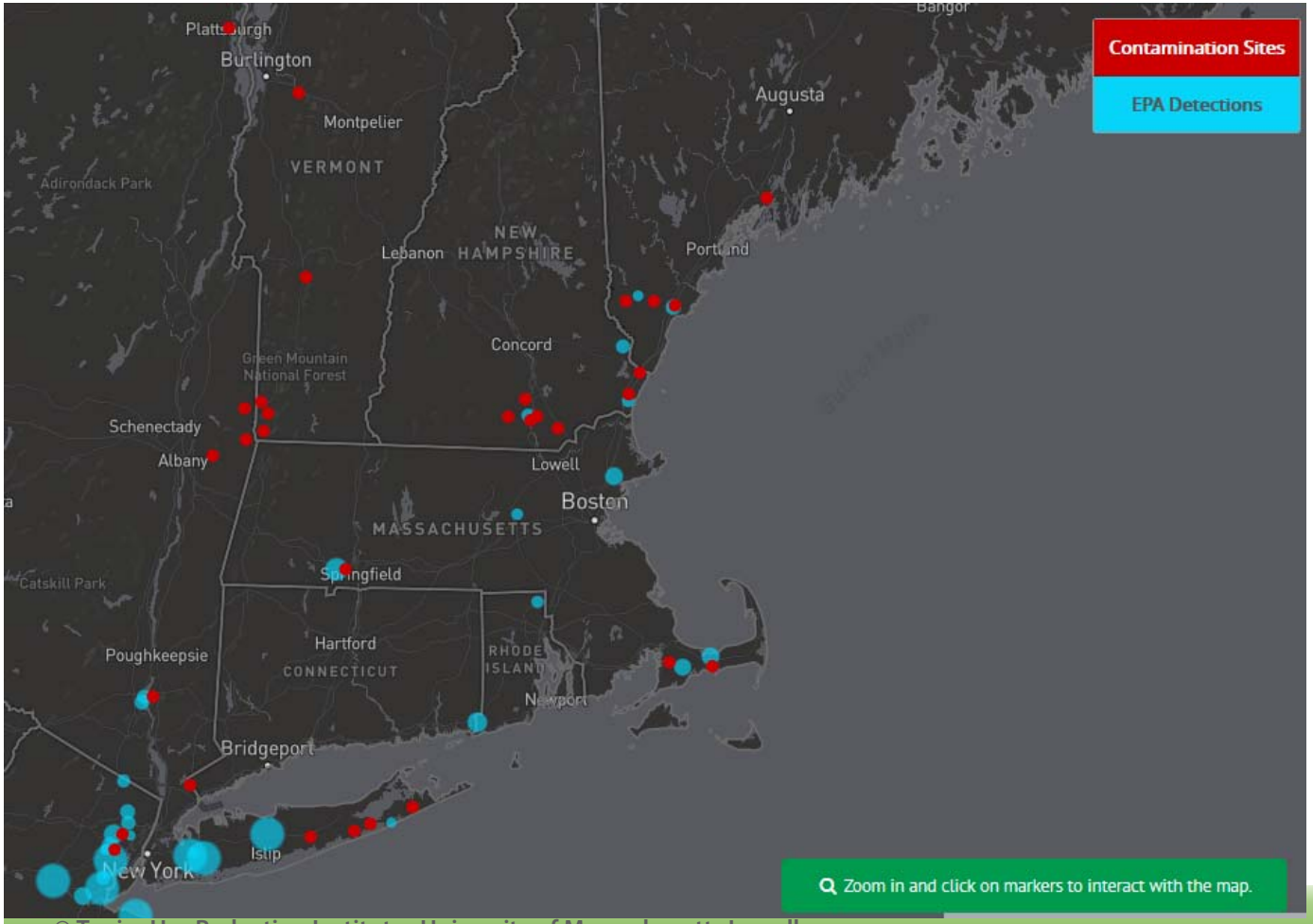


95% of plasticizers are used to make flexible PVC

http://cen.acs.org/articles/93/i25/Plasticizer-Makers-Want-Piece-Phthalates.html ; IHS Chemical, Chemical Economics Handbook

PFAS - Per- and Polyfluoroalkyl Substances

- Showing up in water in New England states and across the country



Environmental Working Group's Interactive PFAS map:

https://www.ewg.org/interactive-maps/2017_pfa/

PFAS

- Historical concern with PFOS, PFOA
  - PFOA: Perfluorooctanoic acid
  - PFOS: Perfluorooctanesulfonic acid
- Initial review showed replacement substitutes (with longer or shorter carbon chains) have similar concerns to historical PFOS and PFOA

PFAS - Where are they used?

(See www.sixclasses.org)

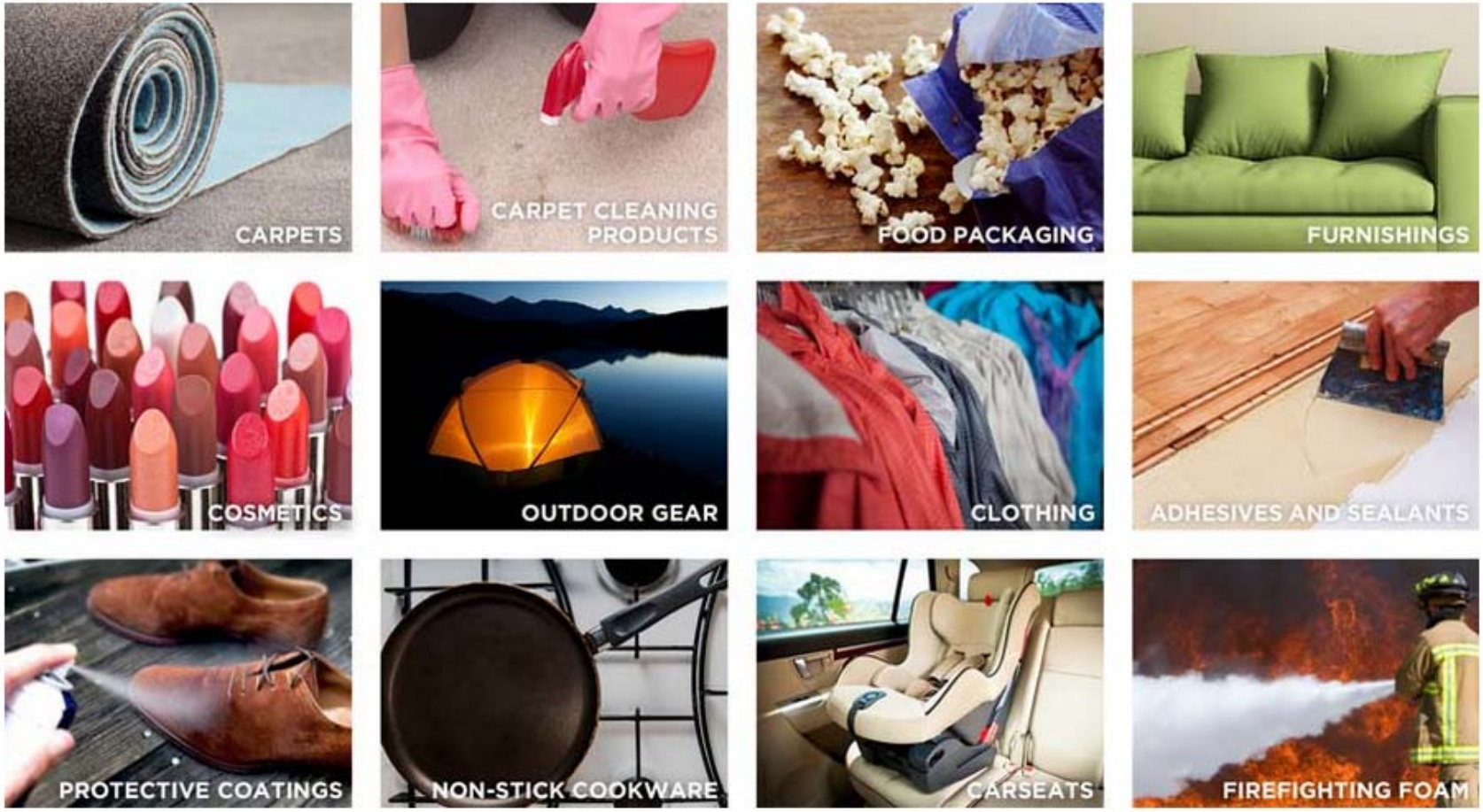


Image: www.sixclasses.org

PFAS - Where Are They Used?

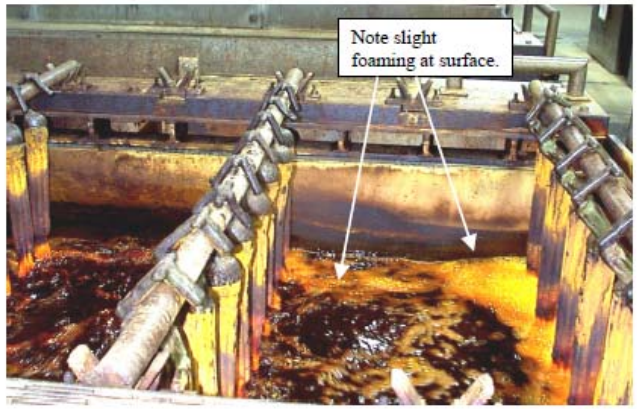
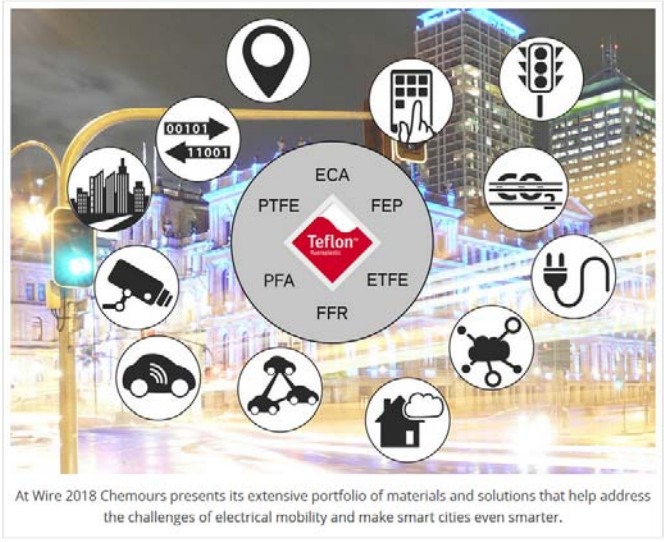


Figure 7. TINKER AFB, TANK NO. 222 WITH FUMETROL® 140

Image: NAVFAC 2004

Wetting agents/fume suppressants for Cr+6 plating tanks



At Wire 2018 Chemours presents its extensive portfolio of materials and solutions that help address the challenges of electrical mobility and make smart cities even smarter.

Image: Wire and Tube News, Chemours booth

Fluorinated resin processing aids and feedstock chemicals

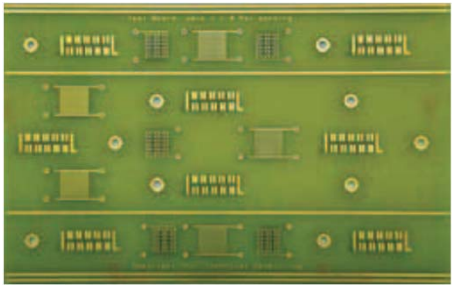
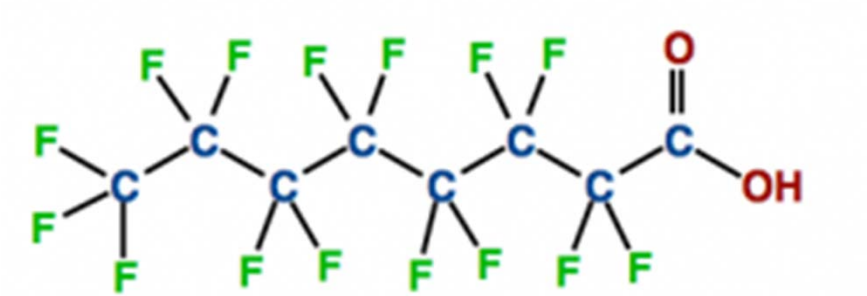


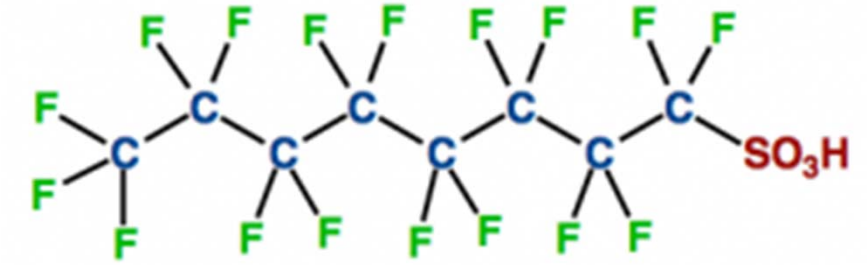
Image: 3M

PWB conformal coatings

PFAS chemicals



PFOA - perfluorooctanoic acid



PFOS - perfluorooctanesulfonic acid

ITRC PFAS Fact Sheets
https://pfas-1.itrcweb.org/fact-sheets/

An Introductory document has been prepared that briefly describes the contents of each of the fact sheets.

- Naming Conventions and Physical and Chemical Properties (updated 3-16-18)
- Regulations, Guidance, and Advisories (updated 1-4-18)
  - Section 4 Tables Excel file – (published November 2017)
    - Table 4-1 presents the available PFAS water values established by the USEPA, each pertinent state, or country (Australia, Canada and Western European countries)
    - Table 4-2 presents the available PFAS soil values established by the USEPA, each pertinent state, or country (Australia, Canada and Western European countries)
  - Section 5 Tables Excel file (published November 2017)
    - Table 5-1 summarizes the differences in the PFOA values for drinking water in the United States.
    - Table 5-2 summarizes the differences in the PFOS values for drinking water in the United States.
- History and Use (published 11-13-17)
- History and Use (Spanish Version)
- Environmental Fate and Transport (published 3-16-18)
  - Table 3-1 Log Koc values for select PFAS Excel file (coming soon)
- Site Characterization Considerations, Sampling Precautions, and Laboratory Analytical Methods (published 3-15-18)
- Remediation Technologies and Methods (published 3-15-18)
  - Remediation Comparison Tables Excel file (coming soon)
    - Table 1 – Solids Comparison
    - Table 2 – Liquids Comparison
- Aqueous Film Forming Foam (to be published August 2018)

SAB Review

Review began September 2016

Began with PFOA & PFOS

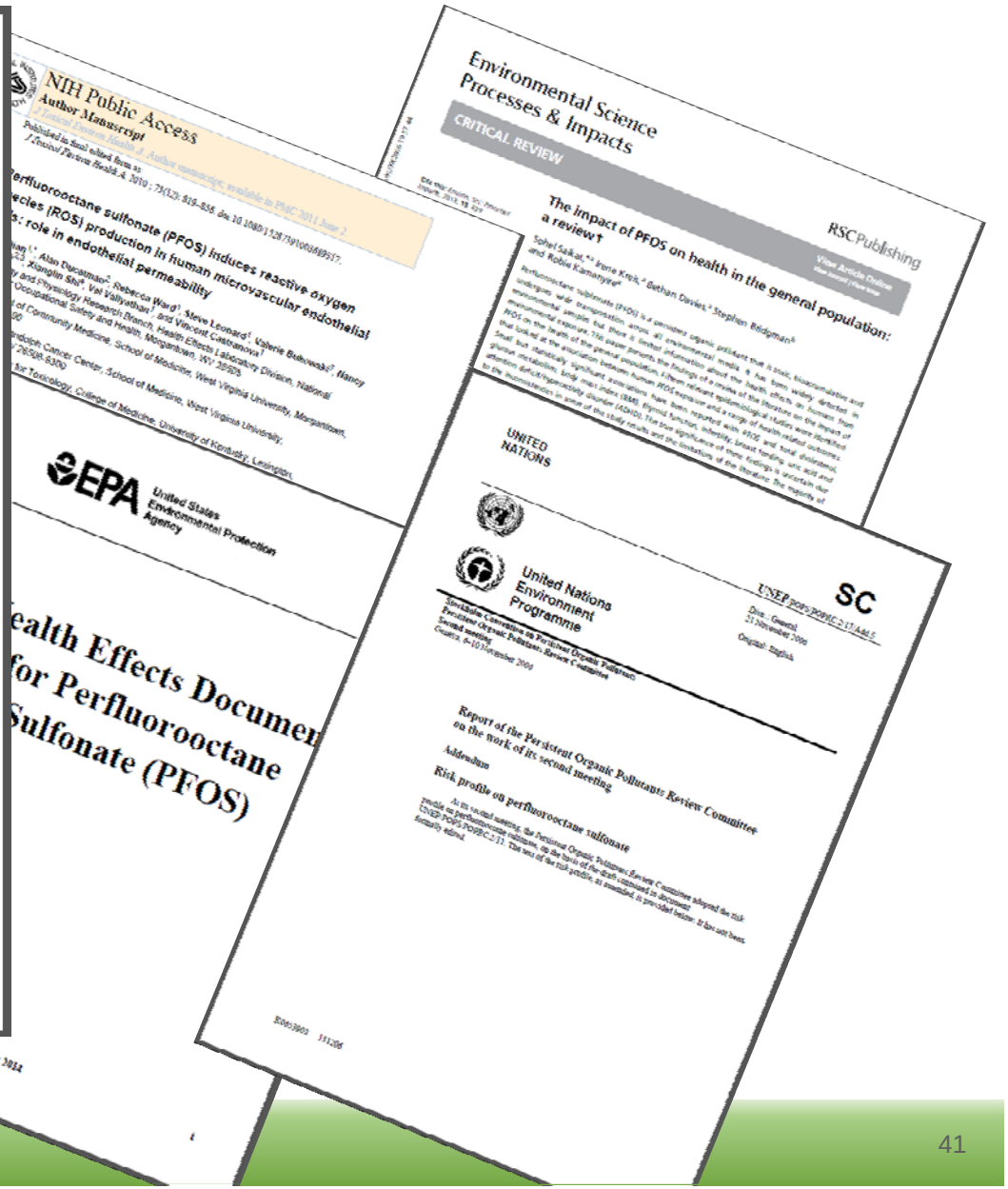
Expert for presentation Dr. Richard Clapp

Reviewed Standard EHS Info

Updated EHS Summary of PFOS for the MA TURA Science Advisory Board Meeting – January 11, 2017

PNEL	
Health Based Exposure Limits	
NIOSH-REL/IDLH/Ceiling Limits	Not found
OSHA-PEL	Not found
ACGIH TLV-TWA	Not found
TLV-STEL	Not found
Biomonitoring Action Limits	Biomonitoring as part of US EPA Perfluorochemicals (PFCs)[40].
Drinking Water Standards	Perfluorooctane Sulfonate (PFOS) US EPA Drinking Water Health Advisory: 70 ppt.[41]
Other	Minnesota Department of Health existing Health Risk Limit (HRL) of 300 ppt for PFOA in drinking water (currently under review)[42].
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
PBT	See information in box on Lib Guide, e.g. EC 2006. PFOS is extremely persistent.[43]
BAF	PFOS bioaccumulates by binding preferentially to proteins in blood plasma (UNEP 2006 refs: Kerstner-Wood et al., 2003) and the liver (UNEP 2006 refs: Luebker et al., 2002).[44]
BMF	A biomagnification factor (BMF), which is the ratio of the concentration in the predator and the concentration in the prey: Hence, a BMF > 1 represents magnification up the food chain. • Polar bear, Canadian Arctic - Concentrations of PFOS in liver (1700->4000 ng/g) exceeding all other individual organohalogens – BMF > 160 based on concentrations in Arctic seals (Martin et al., 2004a) • Mink, US – Very high concentrations of PFOS in liver (40-4870 ng/g) – BMF ~ 145 to ~4000 based on data from their prey such as crayfish (whole body), carp (muscle) and turtles (liver) (Kannan et al 2005) BMF = 22 based on data from fish in the same area (Giesy and Kannan 2001) • Bald Eagle, US – Very high concentrations of PFOS in plasma (1-2570 ng/g) – BMF = 4-5 based on 400 ng/g liver ww, compared with fish (Giesy and Kannan 2001) • Seal in the Bothnian Sea, Finland – Very high concentrations of PFOS in liver (130 – 1100 ng/g) – BMF > 60 based on data from salmon in the same area (Kannan et al., 2002)[45]
Ecological/Aquatic Toxicity: LC_{50}, EC_{50}, ErC_{50}, NOAEC/NOEC	17 studies available in HSDB; Includes Honeybee data; 1,120 ug/L for 96 hr; *Danio rerio*, freshwater, static, 28 deg C; Effect: development, increased deformation[46] Chronic NOEC 0.3 mg/l fathead minnow (42d), based on mortality (OECD 2002)[47] NOEC 0.049 mg/L (10 day) aquatic midge, based on growth and

Revised 1/06/17 Page 5



SAB Recommendations

Recommendation to list PFOA/PFOS and salts due to PBT

Further review of C8 health study human health effects

Reviewed EHS Info for C6, C4 PFAS

Updated EHS Summary of Perfluorohexane sulfonic acid for the MA TURA Science Advisory Board Meeting – April 11, 2018

	studies are necessary to confirm these findings (Wang et al 2017).[29] Our results add to the evidence that exposure to PFOA and PFHxS, even at lower levels than previously reported, may reduce fecundability (Velez et al 2015).[30] Adjusted total testosterone concentrations were also higher in daughters with prenatal concentrations of PFOA (β = 0.24; 95% CI: 0.05, 0.43) and PFHxS (β = 0.18; 95% CI: 0.00, 0.35) in the upper tertile compared with daughters with concentrations in the lower tertile (Maisonet et al 2015).[31]
Genotoxicity/Mutagenicity	Not found in CCRIS or GENE-TOX
Endocrine Disruption/Thyroid Effects	Found on TEDX List of Potential Endocrine Disruptors[32] Data from National Health and Nutrition Examination Survey (NHANES) for the years 2007–2008 were used to evaluate the effect of PFOS, PFOA, PFNA, PFDA, PFHxS, and 2-(*N*-methyl-perfluorooctane sulfonamide) acetic acid on the levels of six thyroid function variables (Jain 2013). Levels of triiodothyronine were found to increase with the levels of PFOA (p=0.01), and total thyroxine levels were found to increase with increase in PFHxS levels (p<0.01).[33] In many PFAS toxicology studies decreased thyroid hormone levels are observed. The mechanism is a competitive binding to the thyroid hormone plasma transport protein transthyretin (TTR) that will alter/decrease the free thyroxine (T4) in blood. This competitive binding capacity of some poly- and perfluorinated compounds was studied by Weiss *et al.* (2009) with a radio-ligand-binding assay. The binding potency of the fluorinated chemicals was 12-300 times lower than for thyroxine itself and decreased in the order: PFHxS > PFOS/PFOA > PFHxA > PFBS.[34] PFHxS (and PFOS and PFOA) acts as a 17β-Estradiol (E2) agonist *in vitro* and enhanced significantly the E2-induced estrogen receptor (ER) response in human MVLN breast cancer cells (Kjeldsen *et al.* 2013).[35] "EC_{50} values of the three ER active test compounds were estimated to be in the range of $2.9X10^{-5}$ to $6.5X10^{-5}$M, indicating similar potencies of PFHxS, PFOS, and PFOA. However, the relative potencies of the three PFAAs were approximately 10^{6}-fold lower than the positive control 17β-Estradiol (E2, Table 2). Thus, the observed estrogenic effects of PFHxS, PFOS, and PFOA were relatively weak compared to the natural estrogen ligand."(Kjeldsen et al. 2013)[36]

Revised 03/01/18 Page 6

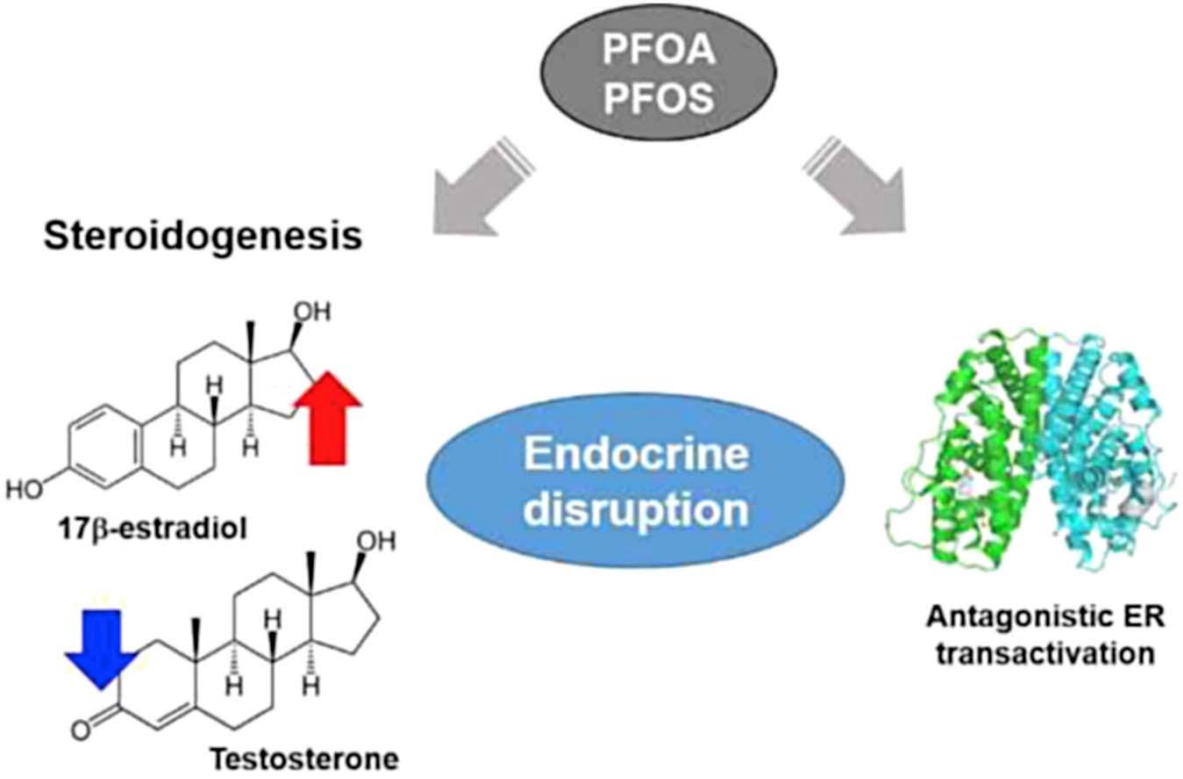
Review of C6, C4 PFAS

- Government reports, scientific studies, industry-provided studies and reports
- Some similarities and some differences in toxicity and environmental concerns
  - Still very persistent
  - Less bioaccumulation
  - Less acute toxicity
  - Less information

Other concerns

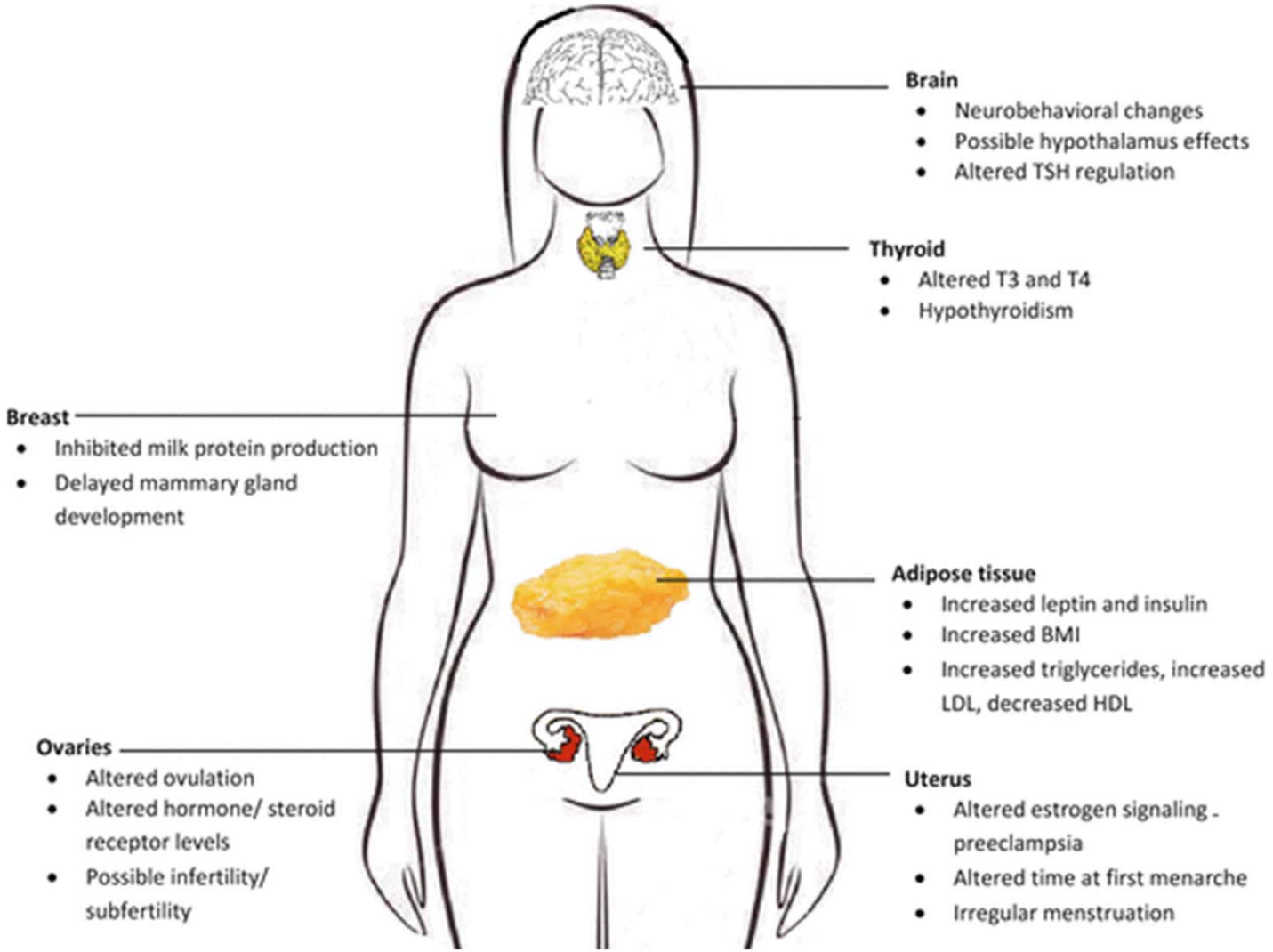
- Corrosivity
- Mobility
- Endocrine effects (liver, thyroid)
- Reproductive and developmental effects
- Hematological effects
- Presence in environment
- Presence in humans (serum, breastmilk)

Endocrine effects (PFOA, PFOS)



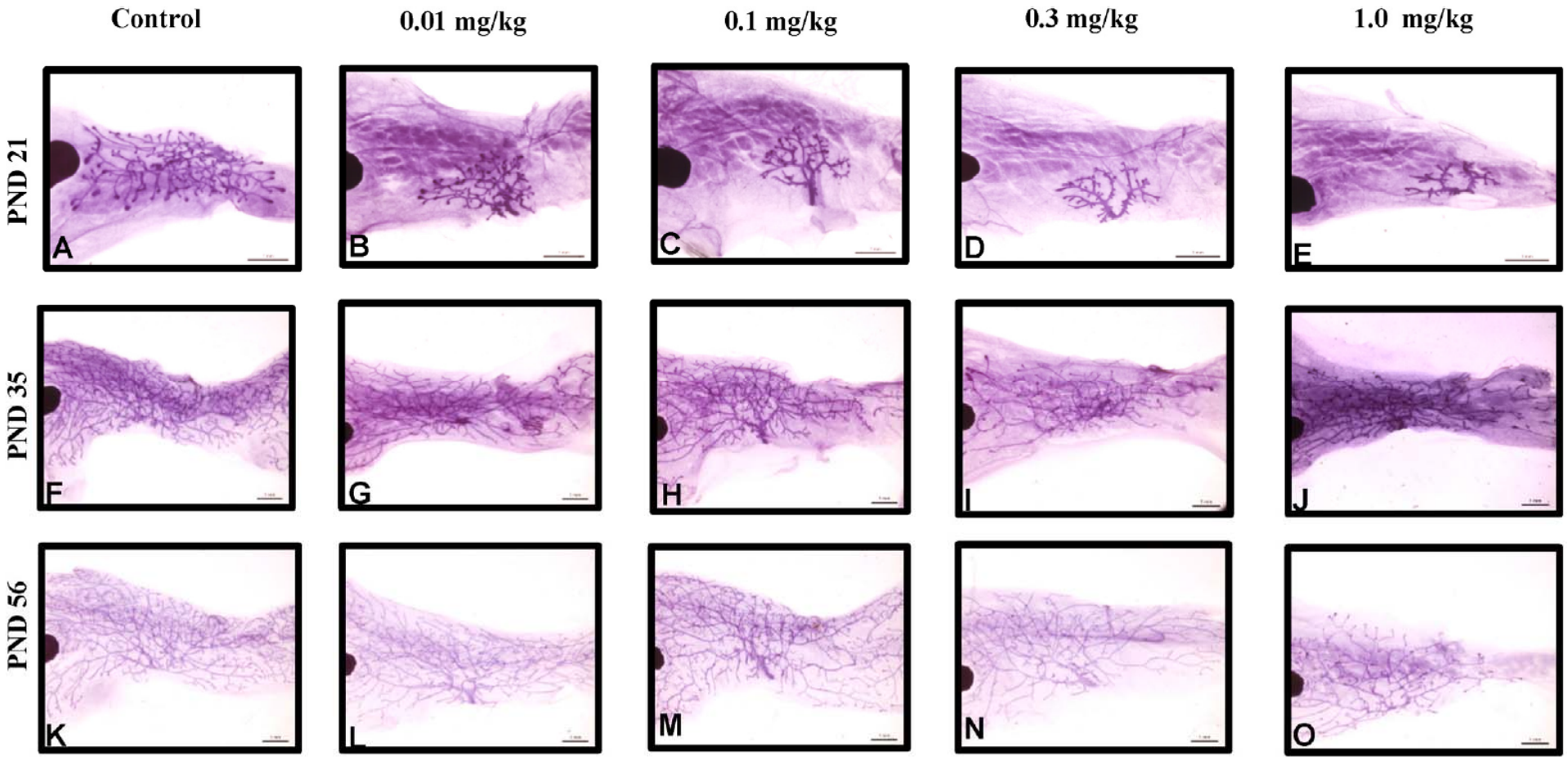
Kang et al. 2016

Targets of PFOA



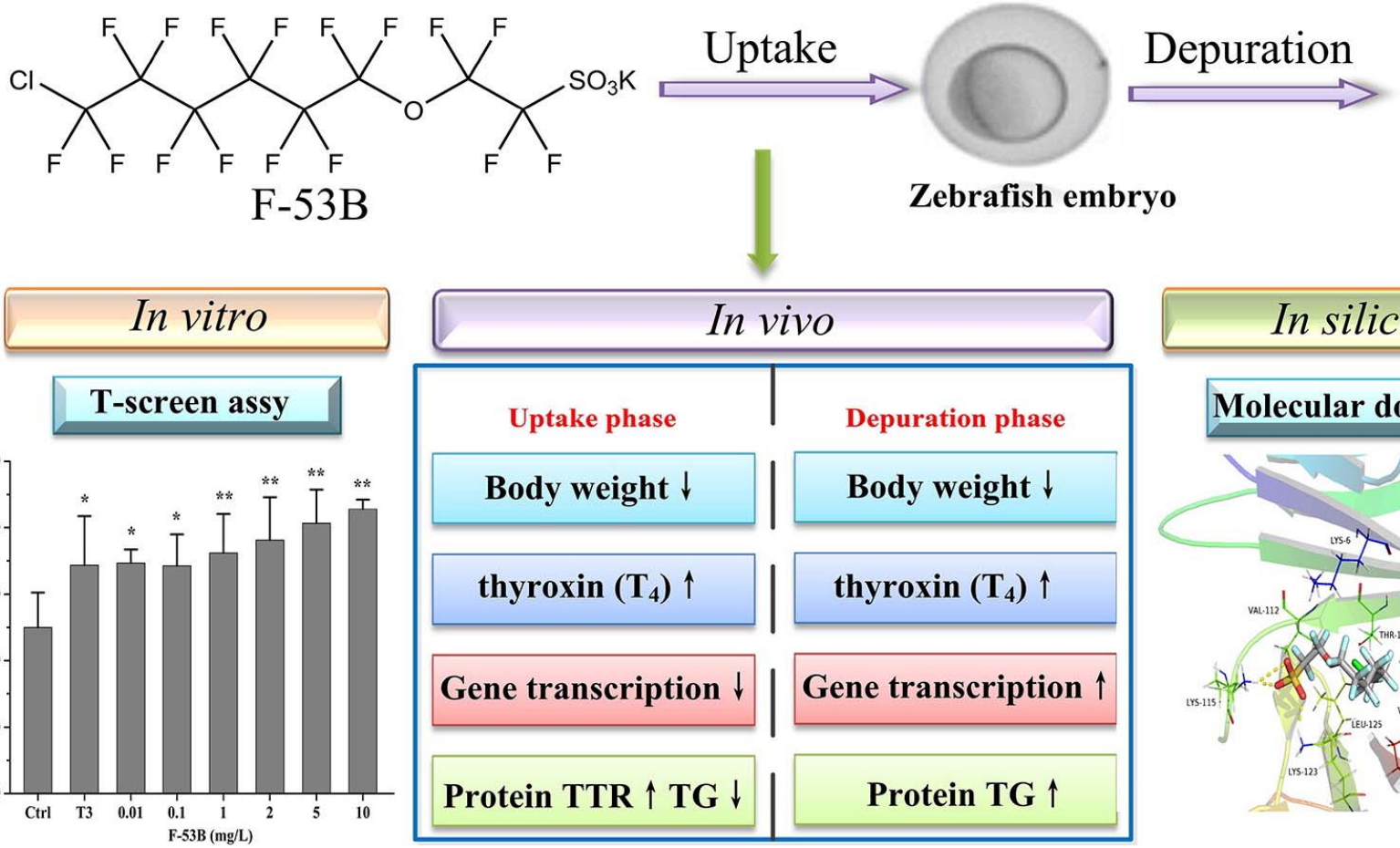
Reed & Fenton 2015

PFOA and the mammary gland



Tucker et al. 2015

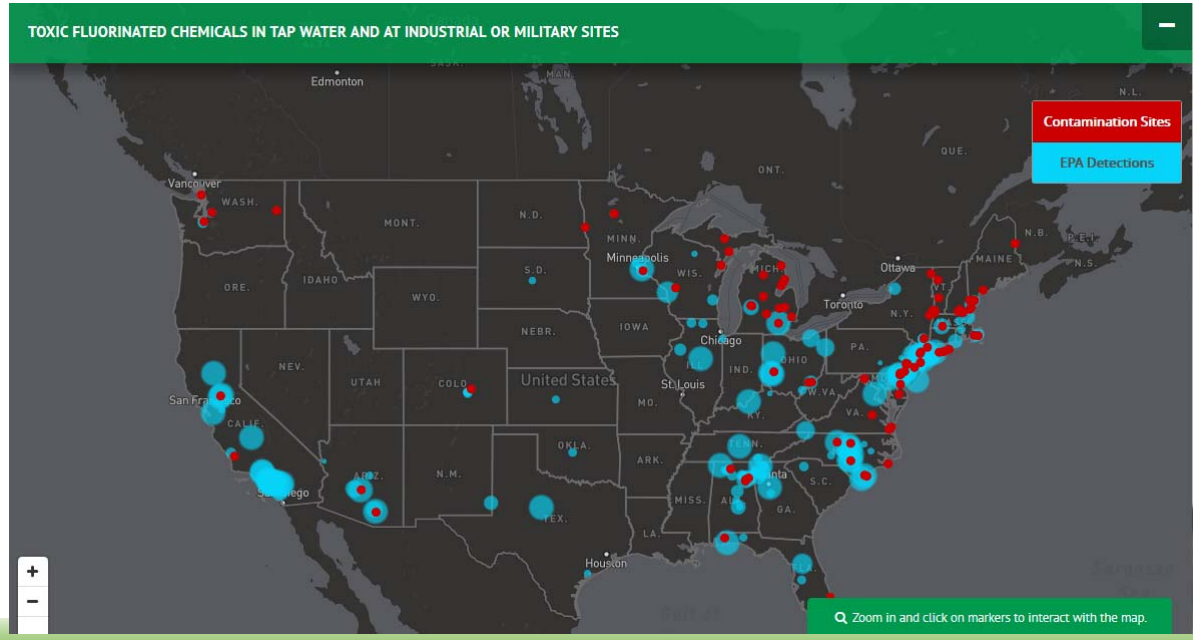
Endocrine outcomes – new PFCs



Deng et al. 2018

Other State's Actions

- NH – Pease, NH DES PFAS Investigation
- NJ drinking water MCL PFOA, PFNA
- MN, WA, OR
- collaborative research IC2 - AFFF



Source: Environmental Working Group

Resources for Endocrine Disruption Information

https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list

http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm#priority_list