

Cross-validation of disruptors

Target	Chemical disruptor	Exposure type and route	Adverse health effects	Current available evidence: References (includes those from human, animal and aquatic data)		
		<b>Horticultural Spray/application</b>				
<b>Growth Factor/Growth Factor Receptor</b>	Cyprodinil CSF1	Fungicide (pyrimidine). Used on grapes, almonds, stone fruits. Inhale/ Ingest/skin and mucous membranes (mm)	Pancreatic hyperplasia, liver and renal pathologies, dermal sensitizer (mice and rats) Persists in soil. Reference for stated effects – also see ERK/AhR <i>EPA carcinogenicity rating (not a likely carcinogen).</i>	EPA ToxCast data only, 2009		
	Etoxazole CSF1 EGFR	Insecticide (miticide and ovicide) Inhale/ingest/skin/mm	Liver toxicity. Genotoxic-chromosomal aberrations. Bioaccumulation potential. EDC potential unknown. <i>EPA carcinogenicity rating (not a likely carcinogen).</i>	(152)		
	<b>HPTE</b> CSF EGFR	<b>Metabolite</b> of methoxychlor pesticide	EDC. Reduced fertility, impaired testicular steroid production. Inhibits aromatase activity. Known teratogen. For further references see PPAR. <i>EPA carcinogenicity (not classified)</i>	(153,154)		
	Maneb CSF1 EGFR FGFR1 IGFR	Fungicide (EDBC) multiple crop use Inhale/ingest/skin/mm/eyes	Suspected EDC, Repro and developmental toxin (acquired Parkinson’s disease and proposed links to neuroblastoma and melanoma, 2013. Thyroid hyperplasia, decreased T4. Hepatotoxicity (rats). <i>EPA carcinogenicity rating (likely carcinogen)</i>	(155–159)		
Target	Chemical disruptor	Exposure type and route	Adverse health effects	Current available evidence: References (includes those from human, animal and aquatic data)		
		<b>Horticultural Spray/application</b>				
<b>Growth Factor/Growth Factor Receptor</b>	Methoxychlor	Insecticide. Inhale/ingest/skin/mm/eyes	EDC – reduced fertility. Developmental toxin (abortions	(153)		

			rodents). CNS pathologies. Metabolite = HPTE. Also see ERK/ER for effects references. <i>EPA carcinogenicity rating (not classified)</i>			
	Phosalone CSF1	Insecticide (OP). Inhale/ingest/skin/mm/eyes	ACH inhibitor, neurotoxin with CNS and G.I tract effects. Adverse health effects reference listed under PPAR. Potential ground water contaminant. <i>EPA carcinogenicity rating (not likely).</i>	EPA ToxCast data only, 2009		
Target	<b>Chemical disruptor</b>	<b>Exposure type and route</b>	<b>Adverse health effects</b>	<b>Current available evidence:</b>		
				<b>References (includes those from human, animal and aquatic data)</b>		
		<b>Horticultural Spray/application</b>				
<b>Growth Factor/Growth Factor Receptor</b>	Prochloraz CSF1 EGFR	Fungicide (azole). Fungicide (azole). Widely used. Inhale/ingest/skin/mm/eyes.	EDC (anti-androgen, anti-estrogen, potent aromatase inhibitor, inhibits fetal steroidogenesis). Adverse health effects also listed under AhR with reference. <i>EPA carcinogenicity rating (possible carcinogen)</i>	EPA ToxCast data only, 2009		
	Pyridaben CSF1 EGFR BMPR2 EGR1	Insecticide Inhale/ingest/skin/mm/eyes	Decreased body weight. Effects on several metabolic pathways involved in development. <i>EPA carcinogenicity rating (not a likely carcinogen)</i>	EPA ToxCast data 2009 (160)		
	<b>PFOS</b> CSF1 CSF1R EGFR	<b>Flame Retardant</b> Fluorosurfactant. Stain repellent classified as a POP (persistent in environment). Inhale/ingest. Can bio-accumulate.	Lipid bio-dysregulation. Liver tumours rodents and assoc. with bladder cancer (human). EDC. Bio-accumulates. References - effects see ERK/ER <i>EPA carcinogenicity rating (not classified)</i>	EPA ToxCast data only, 2009		
Target Cytokines and Cytokine Receptors	<b>Chemical disruptor</b>	<b>Exposure type and route</b> <b>Horticultural Spray Application</b>	<b>Adverse health effects</b>	<b>Current available evidence:</b>		
				<b>References (includes those from human, animal and aquatic data)</b>		

IL1A IL8 CXCL10	Cyprodinil	Fungicide (pyrimidine). Used on grapes, almonds, stone fruits. Inhale/ Ingest/skin and mucous membranes (mm)	Listed above under Growth factors/ Growth Factor Receptors	EPA ToxCast data only, 2009
IL1A IL8 CXCL10	Etoxazole	Insecticide (miticide and ovicide) Inhale/ingest/skin/mm	Listed above under Growth factors/ Growth Factor Receptors	EPA ToxCast data only, 2009
IL1A IL8 CXCL10	HPTE	<b>Metabolite</b> of methoxychlor pesticide	Listed above under Growth factors/ Growth Factor Receptors	EPA ToxCast data only, 2009
IL1A IL8 CXCL10	Imazalil	Fungicide (azole) widely used for citrus fruit, bananas. Also used as topical fungicide in veterinary science. Inhale/ingest/skin/mm/eyes.	Developmental toxin and teratogen. Full references for effects see AhR/ER/PPAR <i>EPA carcinogenicity rating (likely carcinogen)</i>	EPA ToxCast data only, 2009
<b>Target Cytokines and Cytokine Receptors</b>	<b>Chemical disruptor</b>	<b>Exposure type and route</b>  <b>Horticultural Spray Application</b>	<b>Adverse health effects</b>	<b>Current available evidence: References (includes those from human, animal and aquatic data)</b>
IL8 CXCL10	Lactofen	Herbicide (nitrophenyl-ether). Commercial use on beans, in forestry control of broad leaf weeds. Inhale/ingest/skin/mm/eyes	Developmental toxin and teratogen. Hepatotoxic. Haematologic and kidney effects. References for effects -see AhR/ER/PPAR <i>EPA Carcinogenicity rating (likely carcinogen at higher doses)</i>	EPA ToxCast data only, 2009
IL1A IL6 IL8 CXCL10	Maneb	Fungicide (EDBC) multiple crop use Inhale/ingest/skin/mm/eyes	Listed above under Growth factors/ Growth Factor Receptors. Also see ER.	EPA ToxCast data only, 2009
IL1A IL8 CXCL10	Methoxychlor	Insecticide. Inhale/ingest/skin/mm/eyes	Listed above under Growth factors/ Growth Factor Receptors. Also see ER	EPA ToxCast data only, 2009

IL1A IL8 CXCL10	PFOS	Flame Retardant, Stain Repellant	Lipid bio-dysregulation. Liver tumours rodents and assoc. with bladder cancer (human). EDC. Bio-accumulates. References for effects see ERK/ER <i>EPA carcinogenicity rating (not classified)</i>	EPA ToxCast data only, 2009
Target Cytokines and Cytokine Receptors	Chemical disruptor	Exposure type and route	Adverse health effects	Current available evidence: References (includes those from human, animal and aquatic data)
IL8 CXCL10	Bisphenol A	Dietary intake Epoxy resins lining canned foods. Poly-carbonated plastic.	EDC (estrogen mimic) Reproductive and developmental toxin Perturbations Immune system and metabolism. Also see downstream signalling/ AhR/ER/ Jun/Fos/AP-1 <i>EPA carcinogenicity rating (not a likely carcinogen)</i>	EPA ToxCast data only, 2009
Target B Lymphocyte Markers	All the above-named horticultural sprays/applications caused expression in B lymphocytes of BOTH CD40 and CD649 except Maneb (CD69 only). PFOS (flame retardant caused no CD marker expression.	Horticultural Spray Application/ Flame Retardant, Stain Repellant		EPA ToxCast data only, 2009
Target Downstream signalling	Chemical disruptor	Exposure route and type Dietary intake	Adverse health effects	Current available evidence: References (includes those from human, animal and aquatic data)
STAT SRC Akt ERK PI3K-mTOR pathway—AKT1, RPS6 and 4EBP1	Bisphenol A	Epoxy resins lining canned foods. Poly-carbonated plastic.	EDC (estrogen mimic) Reproductive and developmental toxin Perturbations Immune system and metabolism. Also see AhR/ER/ Jun/Fos/AP-1 <i>EPA carcinogenicity rating (not a likely carcinogen)</i>	EPA ToxCast data 2009 (161–165)
Target Downstream signalling	Chemical disruptor	Exposure type and route Dietary processing	Adverse health effects	Current available evidence: References (includes those from human, animal and aquatic data)

ErbB2 and downstream signalling such as p-AKT, p-ERK and p-JNK	Edible oil adulterants – Argemone oil, butter yellow.	Exposure: process-induced food contaminant /natural contaminant.	Adverse effects: gall bladder cancer, skin tumour promotion.	(151,166)
ERK	PFOS	Flame retardant/ Stain Repellant	Neuroendocrine and lipid bio-dysregulation. Liver tumours rodents and assoc. with bladder cancer (human). EDC. Bio-accumulates. <i>EPA carcinogenicity rating (not classified)</i>	(164)
ERK	Methoxychlor	Horticultural Spray/Application	Listed above under Growth factors/ Growth Factor Receptors. Also see ER.	(164)
ERK	Cyprodinil	Fungicide (pyrimidine). Used on grapes, almonds, stone fruits. Inhale/ Ingest/skin and mucous membranes (mm)	Listed above under Growth factors/ Growth Factor Receptors. Also see AhR.	(167,168)
<b>Target</b>	<b>Chemical disruptor</b>	<b>Exposure type and route</b>	<b>Adverse health effects</b>	<b>Current available evidence: References (includes those from human, animal and aquatic data)</b>
<b>Aryl hydrocarbon Receptor (AhR)</b>	Cyprodinil	Fungicide (pyrimidine). Used on grapes, almonds, stone fruits. Inhale/ Ingest/skin and mucous membranes (mm)	Pancreatic hyperplasia, liver and renal pathologies, dermal sensitizer (mice and rats) Persists in soil. Also see ERK/ER <i>EPA carcinogenicity rating (not a likely carcinogen).</i>	(168)
<b>AhR</b>	Imazalil (AhR antagonist in human and rat hepatoma cells)	Fungicide (azole) widely used for citrus fruit, bananas. Also used as topical fungicide in veterinary science..	Developmental toxin and teratogen causes - defects in anterior nervous system development - Genotoxicity - Possible Retinoic acid perturbation? - Hepatic toxicity, especially in combination with Carbendazim and Cypermethrin	(169–173)

			- Liver and thyroid adenomas/other carcinomas in mice and rats. Also see PPAR. <i>EPA carcinogenicity rating (likely carcinogen)</i>	
<b>AhR</b>	Lactofen	Herbicide (nitrophenyl-ether). Commercial use on beans, in forestry control of broad leaf weeds. Inhale/ingest/skin/mm/eyes	Hematologic effects, liver and kidney pathologies (hepatomegaly/tumours in mice and rats. Persists in soil, can bio-accumulate. Also see AhR/ER/PPAR <i>EPA carcinogenicity rating (likely carcinogen at higher doses)</i> )	(174)
<b>Target</b>	<b>Chemical disruptor</b>	<b>Exposure type and route</b>	<b>Adverse health effects</b>	<b>Current available evidence: References (includes those from human, animal and aquatic data)</b>
		<b>Horticultural Spray Application</b>		
<b>AhR</b>	Prochloraz	Fungicide (azole). Widely used. Inhale/ingest/skin/mm/eyes	EDC (anti-androgen, anti-estrogen, agonises AhR, potent aromatase inhibitor, inhibits fetal steroidogenesis). Liver adenomas/carcinomas. Also see multiple other targets above and below. <i>EPA carcinogenicity rating (possible carcinogen).</i>	(175–178) (173)
		<b>Dietary intake</b>		
<b>AhR</b>	Phthalates and phthalate esters	Human milk and/or Food contaminant. Plasticisers – in cosmetics, hair sprays, nail polish, medical products, toys, food wrappers, ubiquitous. Inhale/ingest/skin/mm/eyes	EDC male reproductive tract. Teratogen. Cleft palate, skeletal abnormalities, fetal death (animal studies). Also see AR. <i>EPA carcinogenicity rating (possible human carcinogen)</i>	(179–184) EPA <a href="http://www.epa.gov/teach/chem_summ/phthalates_summary.pdf">http://www.epa.gov/teach/chem_summ/phthalates_summary.pdf</a>
<b>AhR</b>	Bisphenol A	Epoxy resins lining canned foods. Poly-carbonated plastic.	EDC (estrogen mimic) Reproductive and developmental toxin Perturbations Immune system and metabolism. Also see multiple other targets above. <i>EPA carcinogenicity rating (not a likely carcinogen)</i>	(185)
<b>Target</b>	<b>Chemical disruptor</b>	<b>Exposure type and route</b>	<b>Adverse health effects</b>	<b>Current available evidence:</b>

				References (includes those from human, animal and aquatic data)
<b>AhR</b>	Polybrominated diphenyl ethers (PBDEs) Tetrabromobisphenol (TBBP-A) Hexabromocyclododecane (HBCD)	Human milk and/or food contaminant/ widely used polymers used in textiles, construction, furniture electronics, Inhale/ingest skin/mm. Highly lipophilic.	Endocrine disruption, immunotoxin. Neurotoxin (learning/memory/motor function). Persist in the environment.	(186–192)
<b>Target Steroid Receptors</b>		<b>Horticultural Spray/Application</b>		
<b>ERα</b>	Cyprodinil	Fungicide (pyrimidine). Used on grapes, almonds, stone fruits. Inhale/ Ingest/skin and mucous membranes (mm)	Adverse health effects as listed under AhR/ERK. <i>EPA carcinogenicity rating (not a likely carcinogen).</i>	EPA ToxCast data, 2009
<b>ERα</b> <b>AR</b> <b>ERα</b> <b>AR</b> <b>PGR</b>	Etoazole	Insecticide (miticide and ovicide). Inhale/ingest/skin/mm	Liver toxicity. Genotoxic-chromosomal aberrations. Bioaccumulation potential. EDC potential unknown. Also see Growth Factors/Growth Factor receptors. <i>EPA carcinogenicity rating (not a likely carcinogen)</i>	EPA ToxCast data only, 2009
	<b>HPTE</b>	Metabolite of Methoxychlor insecticide	Decreases progesterone and testosterone production. Modulates ER alpha. Combinational effects of growth factors on HPTE-induced ERE-mediated gene expression. Uterotropic response. OSE <i>EPA carcinogenicity rating (not likely)</i>	(193–195) (153,154)
<b>Target Steroid Receptors</b>	<b>Chemical disruptor</b>	<b>Exposure type and route</b>	<b>Adverse health effects</b>	<b>Current available evidence:</b>
		Horticultural Spray Application		<b>References (includes those from human, animal and aquatic data)</b>
<b>ERα</b> <b>ER</b> <b>PGR</b>	Imazalil	Fungicide. Exposure as listed under AhR.	Adverse effects also listed under AhR PPAR. Teratogen. Anti-androgenic Developmental toxin <i>EPA carcinogenicity rating (likely carcinogen)</i>	(196) (173)

<b>ER<math>\alpha</math></b> <b>AR</b>	Lactofen	Herbicide (nitrophenyl-ether). Commercial use on beans, in forestry control of broad leaf weeds. Inhale/ingest/skin/mm/eyes	Hematologic effects, liver and kidney pathologies, hepatomegaly/tumours in mice and rats. Persists in soil, can bio-accumulate. Also see AhR/PPAR <i>EPA carcinogenicity rating (likely carcinogen at higher doses)</i>	(197)
<b>ER alpha</b> <b>AR</b>	Maneb	Fungicide. Exposure as listed under Growth Factors/Growth Factor receptors.	Adverse health effects also listed under Growth Factors/GFRs Suspected EDC, Repro and developmental toxin. <i>EPA carcinogenicity rating (likely).</i>	(155)
<b>ER alpha (agonist)</b> <b>ER beta (antagonist)</b> <b>AR (antagonist)</b>	Methoxychlor	Insecticide. Exposure as listed under Growth Factors.	Adverse health effects also listed under Growth Factors GFRs/ERK. EDC – reduced fertility. Endocrine disruptor (estrogenic). Reproductive and Developmental toxin (anti-androgenic) Causes cell proliferation and decreased apoptosis in OSE (ovary). Steroid metabolism. <i>EPA carcinogenicity rating (not classified)</i>	(199–202) (161) (153)
<b>Target</b> <b>Steroid Receptors</b>	<b>Chemical disruptor</b>	<b>Exposure type and route</b> <b>Horticultural Spray application</b>	<b>Adverse health effects</b>	<b>Current available evidence:</b> <b>References (includes those from human, animal and aquatic data)</b>
<b>ER alpha</b> <b>AR</b> <b>PGR</b>	Phosalone	Insecticide (OP). Exposure effects as listed under PPAR/Growth Factors.	Potential ground water contaminant. See PPAR. <i>EPA carcinogenicity rating (not likely).</i>	(173)
<b>ER alpha (antagonist)</b> <b>AR (antagonist)</b> <b>PGR</b>	Prochloraz	Azole fungicide. Exposure as listed under AhR.	Adverse effects also listed under AhR. EDC. Inhibits fetal steroidogenesis. Liver adenomas/carcinomas. Inhibits aromatase. Teratogen. Repro and Developmental toxin <i>EPA carcinogenicity rating (possible carcinogen)</i>	(203,204) (175–177)
<b>ER alpha</b>	Pyridaben	Insecticide. Exposure as listed under Growth Factors.	Effects on several metabolic pathways involved in development. <i>EPA carcinogenicity rating (Not a</i>	EPA ToxCast data only, 2009

			<i>likely carcinogen)</i>	
		<b>Dietary intake</b>		
<b>Steroid Receptor AR Target Steroid Receptor AR GPR30 ER alpha (agonist) ER beta (low affinity) mER and ERRy AR (anatanagonist) PGR-A Aromatase</b>	Phthalates	Exposure – ubiquitous as listed under AhR/PPAR	EDC male reproductive tract Teratogen. Adverse effects also listed under AhR. <i>EPA carcinogenicity rating (possible human carcinogen)</i>	(205,206)
	<b>Chemical disruptor</b>	<b>Exposure type and route</b>	<b>Adverse health effects</b>	<b>Current available evidence: References (includes those from human, animal and aquatic data</b>
	Trenbolone acetate Hormone growth promoters	Synthetic anabolic steroid. Used to promote growth in beef cattle. Muscle gain supplement for human bodybuilding.	EDC – androgenic. Found in surface waters, run off causes endocrine disruption in fish. <i>EPA carcinogenicity rating(?)</i>	(207–214)
	Bisphenol A	Exposure –ubiquitous as listed above.	As listed above. <i>EPA carcinogenicity rating (not a likely carcinogen)</i>	(215–217) (161) (163)
<b>ER (agonist)</b>	<b>PFOS</b>	<b>Flame Retardant</b>	Lipid bio-dysregulation. Liver tumours rodents and assoc. with bladder cancer (human). EDC. Bio-accumulates. <i>EPA carcinogenicity rating (not classified)</i>	(189)
<b>Target Peroxisome Proliferator Activated Receptor (PPAR)</b>	Perfluorooctane-sulfonic acid (PFOS)	Fluorosurfactant. Stain repellent classified as a POP (persistent in environment). Inhale/ingest. Can bio-accumulate.	EDC. Neuroendocrine and lipid bio-dysregulation. Liver tumours rodents and assoc. with bladder cancer (human), EPA 2006. <i>EPA carcinogenicity rating (not classified).</i>	(224) (190) (225,226)
		<b>Dietary Intake</b>		
	Phthalates	Exposure – ubiquitous as listed under ER/ AhR/PPAR	Adverse Health effects as listed under AhR/ER	(227)
	<b>HPTE</b>	<b>Horticultural Spray/application</b>	<i>EPA carcinogenicity (not able to be classified).</i>	(228)
		Metabolite of Methoxychlor		

PPAR	Imazalil	Exposure as listed under AhR Fungicide (azole)	Adverse health effects as listed under AhR. Imazalil activates PPAR alpha transcription <i>in vitro</i> . EPA carcinogenicity rating (likely carcinogen)	(229) (173)
	Lactofen	Herbicide (nitro-phenyl ether) Exposure as listed under AhR/ER	Adverse health effects as listed under AhR/ER. EPA carcinogenicity rating (likely carcinogen at higher doses)	(230,231) (174)
PPAR	Phosalone	Insecticide (OP). Inhale/ingest/skin/mm/eyes.	ACH inhibitor, neurotoxin with CNS and G.I tract effects. Potential ground water contaminant. EPA carcinogenicity rating (not likely).	(232)
	Prochloraz	Fungicide (azole). Exposure as listed under AhR	Adverse health effects as listed under AhR. EPA carcinogenicity rating (possible carcinogen)	(173)
Target	Chemical disruptor	Exposure type and route Dietary intake	Adverse health effects	Current available evidence: References (includes those from human, animal and aquatic data)
Jun/Fos/AP-1 RPS6 4EBP1	Bisphenol A	As listed above	Listed above	(165) (178) (232)
Target Cell Cycle Regulators	Maneb <i>S phase (CDK2)</i> Methoxychlor <i>G1-S (decreases in p21)</i> <i>Increases CDK4, cyclin D2</i> HPTE <i>Increases CDK4, cyclin D2</i>	Horticultural Spray/application	Listed above	EPA ToxCast data only, 2009
	PFOS G1 phase	Flame retardant/ Stain Repellant	Listed above	EPA ToxCast data only, 2009
	Bisphenol A <i>G1-S (in vitro) – increases in cyclin D1</i>	Dietary intake	Listed above	EPA ToxCast data only, 2009