Table I – Dose-Response Characterization

Each chemical in the table below was categorized by using one of five possible categories (to determine the relevance and relative strength of the underlying evidence for each of the chemicals being considered) - as follows:

1. LDE (LOW DOSE EFFECT) - The ability of this chemical to exert this particular effect is not well characterized at a range of dose levels, but the evidence suggests that this chemical can exert this effect at low dose levels (i.e., levels that are deemed relevant given the background levels of exposure that exist in the environment and as further defined below).

2. LLDE (Linear Dose-Response with Low Dose Effects) – The ability of this chemical to exert this particular effect is well characterized at a range of dose levels and the evidence suggests that a linear dose-response relationship exists with effects at low dose levels being evident (i.e., levels that are lower than the LOEL/LOAEL or threshold and deemed relevant given the background levels of exposure that exist in the environment).

   Note - a linear dose-response model implies no threshold. Effects at low doses are the same as at higher doses even if at a lesser extent. The effect is directly proportional to the dose.

3. NLDE (Non-linear Dose-Response with Low Dose Effects) – The ability of this chemical to exert this particular effect is well characterized at a range of dose levels and the evidence suggests that a non-linear dose-response relationship exists with exaggerated effects at low dose levels being evident (i.e., levels that are lower than the LOEL/LOAEL or threshold and deemed relevant given the background levels of exposure that exist in the environment)

   Note – a non-linear dose-response with low dose effect implies that the effect does not vary according to the dose of the agent. The effect at low doses may be the same as at the higher doses or different. The non-linear dose-response may have or not have a threshold. It is represented by a sigmoid curve. The non-linear dose-response at low doses may be a non-monotonic dose-response (NMDR)

4. THRESHOLD – The ability of this chemical to exert this particular effect is well characterized at a range of dose levels, and a threshold has been established for this chemical that suggests that this action on this mechanism/pathway does not occur at low dose levels (i.e., levels that are lower than the threshold and deemed relevant given the background levels of exposure that exist in the environment).

5. UNKNOWN – Although the ability of this chemical to exert this particular effect has been shown at higher dose levels, this effect is not well characterized at a range of dose levels, so a LOEL /LOAEL or a threshold has not been determined for this chemical and there is no evidence showing that this chemical exerts this action at low dose levels (i.e., levels that lower than the LOEL/LOAEL or threshold and are deemed relevant given the background levels of exposure that exist in the environment).

A-I = in vivo animal models, A-CL = animal cell lines, A-PC = animal primary cells, H-PC = human primary cells, H-CL = human cell lines, H-E = Human epidemiological studies.

With respect to the human primary cell (H-PC) data from ToxCast[405]: Unknown signifies that the compound was tested across a range of doses and showed statistically significant activity against the specified targets at the lowest test concentrations (~0.01 μM), therefore a threshold could not be established. Threshold in this dataset signifies that there was no activity against the targets at one or more of the lowest concentrations tested.

Review Team	Chemical Name	Disruptive Action on Key Mechanism/Pathway	Low Dose Effect (LDE, LLDE, NLDE, Threshold, Unknown)
Angiogenesis	Diniconazole	Vascular Cell Adhesion Molecule and Cytokine Signaling	Threshold (H-PC)[405]
Angiogenesis	Ziram	Vascular Cell Adhesion Molecule and Cytokine Signaling	Threshold (H-PC)[405,406]
Angiogenesis	Chlorothalonil	Thrombomodulin, Vascular Proliferation and Cytokine Signaling	Unknown (H-PC)[405] NLDE (A-*in vivo*)[407]
Angiogenesis	Biphenyl	Angiogenic Cytokine Signaling	Unknown (H-PC)[405]
Angiogenesis	Tributyltin chloride	Vascular Cell Proliferation and Adhesion Molecule Signaling	Unknown (H-PC)[405]
Angiogenesis	Methylene bis(thiocyanate)	Plasminogen Activating System and Cytokine Signaling	Unknown (H-PC)[405]
Angiogenesis	HPTE	Vascular Cell Adhesion Molecule and Cytokine Signaling	Unknown (H-PC)[405] Threshold (A-I*)[286] LDE (A-I*)[408] *Extrapolated from in vivo data on the parent compound, Methoxychlor
Angiogenesis	PFOS	Angiogenic Cytokine Signaling	Threshold (H-PC)[405] LDE (H-CL)(287)
Angiogenesis	Bisphenol AF	Matrix Metalloproteinase Expression and Estrogen Receptor Signaling	Unknown (H-PC)[405]
Angiogenesis	C.I. solvent yellow 14	Aryl-Hydrocarbon Receptor and Hypoxic Signaling	Unknown (H-PC)[405]
Deregulated Metabolism	Cypermethrin	AR and ER expression, Reduction of ATP and Mitochondrial Enzymes, Mitochondrial Membrane Potential	LLDE (A-I)[409] NLDE (A-I)[409] NLDE (H-CL)[405,410,411]
Deregulated Metabolism	Acrolein	p53 Activation, DNA Repair Inhibition, PERK Phosphorylation, Mitochondrial Dysfunction, Cell Survival	LLDE (A-I, A-CL, H-PC, H-CL)[412-417] NLDE[416] Threshold[413]
Deregulated Metabolism	Rotenone	Cell Cycle, DNA Damage Response, Proliferation, Differentiation, Mitochondria	LLDE (H-CL)[265,418,419] NLDE (H-CL)[265,419] Unknown (H-CL,H-PC)[405]
Deregulated Metabolism	Copper	p53 Activation, p21 Upregulation, Cell Viability	LLDE (H-CL)[420-422]
Deregulated Metabolism	Nickel	Neutrophil Apoptosis, E-Cadherin Regulation, MMP Production	LLDE (H-CL)[312] NLDE (H-CL)[423] Threshold (H-CL)[423]
Deregulated Metabolism	Cadmium	p53-dependent Apoptosis, Cell Proliferation	LLDE (H-CL)[424], Threshold (H-CL)[425]
Deregulated Metabolism	Diazinon	AChE Activity, Neuronal Cytotoxicity	Unknown (A-PC)[426] LLDE (H-CL)[427] Threshold (H-CL)[405]
Deregulated Metabolism	Iron	KRAS Mutations	LLDE (A-I)[428]
Deregulated Metabolism	Malathion	Lymphocyte Mutations, Cytotoxicity	Unknown (H-PC, H-E)[405,429]
Tissue Invasion and Metastasis	Bisphenol A	MMP-2 and MMP-9 Expression, Increased Migration, Invasion, EMT, Oxidative Stress, ER Signaling	LDE (H-CL)[430,431], Threshold (H-CL, H-PC)[405]
Tissue Invasion and Metastasis	Hexacholorobenzene	Activation of c-Src, HER1, STAT5b and ERK1/2 signaling	LLDE (H-CL, A-I)[432]
Tissue Invasion and Metastasis	Sulfur dioxide	MMP-9 Expression	Unknown (A-PC)[433]

Tissue Invasion and Metastasis	Phthalates	MMP-2 and MMP-9 Expression	LDE (H-CL)[431], Unknown (H-CL, H-PC)[405]
Tissue Invasion and Metastasis	Iron	ROI Generation, NFkB Activation, uPA Expression	Unknown (H-CL)[434]
Tissue Invasion and Metastasis	Biorhythms/Melatonin	GSK3β Activation, EMT Regulation	Unknown (H-CL, H-E)[435,436]
Resistance to Cell Death	Bisphenol A (BPA)	Inhibition of GJIC, Activation of mTOR pathway, downregulation of p53, p21 and BAX, binding to ER-alpha, weakly binds to TH receptor and AR, activation of ERK1/2 and p38	NLDE(H-CL, A-CL)[437-439] Threshold (H-CL, H-PC)[405]
Resistance to Cell Death	Dibutyl phthalate (DBP)	Activation of PPAR-alpha, inhibition of GJIC, expression of cyclin D and cdk-4, activation of AhR/HDAC6/c-Myc pathway	NLDE (H-CL)[440] Unknown (H-CL, H-PC)[405]
Resistance to Cell Death	Chlorothalonil	Upregulation of ErbB-2 tyrosine kinase and MAP kinase, aromatase inhibitor	Threshold-based (i.e. non-linear) (A-I)[441] Unknown (H-PC)[405] Threshold (H-CL)[405]
Resistance to Cell Death	Lindane	Induction of MAPK/ERK pathways	Threshold-based (i.e. non-linear) (A-I)[442] Threshold (H-CL)[405]
Resistance to Cell Death	Dichlorvos	Expression of p16, Bcl-2 and c-myc	LLDE (A-I)[443] Threshold (H-CL)[405]
Resistance to Cell Death	Methoxychlor	Binding to ER-alpha receptor, upregulation of cyclin D1, downregulation of p21	LLDE (H-CL, A-CL)[440,444] Unknown (H-PC)[405] Threshold (H-CL)[405]
Resistance to Cell Death	Oxyfluorfen	Expression of *Cyp2b10* and *Cyp4a10* transcripts (markers of PPAR-alpha activation)	Threshold (A-I)[445], Unknown (H-CL, H-PC)[405]
Resistance to Cell Death	Diethylhexyl phthalate (DEHP)	Activation of PPAR-alpha, inhibition of GJIC	Threshold-based (i.e. non-linear) (A-I)[446]
Resistance to Cell Death	Linuron	Hypersecretion of LH, inhibition of GJIC	Unknown (H-CL)[447]
Replicative Immortality	Nickel-derived compounds, (e.g. Nickel chloride)	Epigenetic silencing of p16	LLDE (H-CL, A-PC) [209]
Replicative Immortality	Diethylstilbestrol	Allelic loss and point mutation in ETRG-1 gene	LLDE (A-I) [448]
Replicative Immortality	Reserpine	Epigenetic modifications	Unknown (A-PC) [449] Threshold (H-CL)[405]
Replicative Immortality	Phenobarbital	Reduces expression of the CDKN1A product p21, CAR Activation	LLDE (A-I) [215,450]
Replicative Immortality	Acetaminophen	Cellular energy loss, mitochondrial damage, Telomerase activation	LDE (H-CL, A-I, A-CL)[219-222,451]
Replicative Immortality	Cotinine	Telomerase activation	LLDE (H-PC) [452]
Replicative Immortality	Nitric oxide	p53 inactivation	LLDE (H-PC, H-CL, A-CL, A-I) [453]
Replicative Immortality	Na-selenite	p53 promoter methylation	LLDE (A-CL, A-I) [454,455]
Replicative Immortality	Lead	p53 inactivation	LLDE (H-PC, H-CL, A-CL, A-I) [453]
Sustained	Bisphenol A	Estrogen receptor activation, Cell	LLDE (A-I, H-CL, H-E) [12,456]

Proliferative Signalling		cycle/senescence	NLDE (A-I)[457,458] Threshold (H-CL)[405]
Sustained Proliferative Signalling	Cyprodinil	Increased proliferation signaling, Aryl hydrocarbon receptor activation	Unknown (H-PC, H-CL)[140,405,459] Threshold (H-CL)[405]
Sustained Proliferative Signalling	Imazalil	AR signaling	NLDE (A-I)[122,460] Threshold (H-CL, H-PC)[405]
Sustained Proliferative Signalling	Maneb	Nitric Oxide Signaling	Unknown (A-CL, H-CL, H-PC) [405,461,462]
Sustained Proliferative Signalling	Methoxyclor	ER signaling	Threshold (H-CL)[405] LDE (A-I)[463,464] NLDE (A-I)[465]
Sustained Proliferative Signalling	PFOS	Nuclear hormone receptors	Threshold (H-CL)[405] LLDE (A-I) [148,466]
Sustained Proliferative Signalling	Phthalates	CAR, ER signaling	Unknown (H-CL)[405] LDE (A-I)[467-469]
Sustained Proliferative Signalling	Phosalone	Increased proliferation, PXR signaling	Unknown (H-PC, H-CL) [405,470,471]
Sustained Proliferative Signalling	Polybrominated diphenylethers (PBDEs)	ER signaling	LDE (A-I)[472,473]
Sustained Proliferative Signalling	Prochloraz	ER signaling	LDE (A-I)[474,475]
Sustained Proliferative Signalling	Trenbolone acetate	Insulin-like growth hormone-1 and AR signaling	Unknown, LDE (A-I, H-CL, H-E)[158,476]
Tumor Promoting Inflammation	Bisphenol A	immune cell proliferation, pro-inflammatory cytokine induction	Threshold (H-PC)[405] LDE (A-I, H-CL, H-E)[88,477-480]
Tumor Promoting Inflammation	Phthalates	Immunomodulation of macrophages, lymphocytes, eosinophils, and neutrophils	Unknown (H-PC, H-CL, H-E)[405,481]
Tumor Promoting Inflammation	PBDEs	Induction of pro-inflammatory cytokines (IL6, IL8 and CRP), Inhibition of anti-inflammatory cytokines (IL10)	Threshold (H-PC, H-CL)[104,482-484]
Tumor Promoting Inflammation	Atrazine	Immunomodulation of T cell and B cells, Pro-inflammatory cytokines	Unknown (H-PC, A-I)[92,405,485]
Tumor Promoting Inflammation	Vinclozolin	Pro-inflammatory cytokine induction, NFkB activation	Unknown (H-PC, A-I)[105,106,405,486]
Tumor Promoting Inflammation	4-Nonylphenol	Pro-inflammatory cytokine induction, NFkB activation, iNOS induction	Unknown (A-CL, H-CL, H-PC)[108,109,405]
Immune System Evasion	Pyridaben	Chemokine signaling, TGF-b, FAK, HIF-1a, IL-1a pathways	Unknown (H-CL, H-PC, A-CL)[333,405,487] Threshold (A-I)[488]
Immune System Evasion	Triclosan	Chemokine signaling, TGF-b, FAK, IL-1a pathways	Threshold (H-CL, H-PC, A-I)[405,489-491] LDE (A-I, H-CL)[355,492]
Immune System Evasion	Pyraclostrobin	Chemokine signaling, TGF-b, IL-1a pathways	Unknown (H-CL, H-PC)[405]
Immune System Evasion	Fluoxastrobin	Chemokine signaling, EGR, HIF-1a, IL-1a pathways	Unknown (H-CL, H-PC)[405]

Immune System Evasion	Bisphenol A	Chemokine signaling, TGF-b pathway	Threshold (H-PC)[405] LDE (A-I)[12] NLDE (H-CL)[493] NLDE (A-CL),[494-497] NLDE (A-I)[498-501]
Immune System Evasion	Maneb	PI3K/Akt signaling, Chemokine signaling, TGF-b, FAK, IGF-1, IL-6, IL-1a pathways	Unknown (H-CL, H-PC)[405,502-504] LDE (A-I)[505] Threshold (A-I)[333,506] Threshold (A-CL, A-I)[507]
Evasion of Anti-Growth Signalling	DDT	Induces MDM2, cyclin D1, E2F1 expression, disrupts gap junctions	NLDE (A-I, H-CL, A-CL)[173-175]
Evasion of Anti-Growth Signalling	chlorpyrifos	Increases proliferation	LDE (H-CL, H-PC)[508,509]
Evasion of Anti-Growth Signalling	folpet	Disrupts G1-S checkpoint kinases, downregulates p53, promotes proliferation	LDE(A-C)[176]
Evasion of Anti-Growth Signalling	atrazine	Induces estrogen production and proliferation	LDE(H-CL, A-I)[510-512]
Evasion of Anti-Growth Signalling	Bisphenol A	Reduced p53, reduced connexin 43 expression, increased proliferation	NLDE (H-CL, A-I)[171,194,513,514]
Tumor Microenvironment	Nickel	reactive oxygen species and cellular stress	NLDE (A-I)[515]
Tumor Microenvironment	BPA	IL-6 expression, improper dendritic cell maturation and polarization, ROS production	LLDE (A-I)[516] NLDE (A-I)[516]
Tumor Microenvironment	Butyltins (such as TBT)	Natural Killer cell inhibition	LDE (A-I)[517]
Tumor Microenvironment	methylmercury	Chronic oxidative stress	LDE (H-PC, H-CL)[518,519]
Tumor Microenvironment	Paraquat	Chronic ROS production, cellular stress	Unknown (A-I)[520]
Genome Instability	Lead	Dysfunctional DNA repair, defect in telomere maintenance	Unknown (A-CL)[57,521,522], Threshold (H-CL, H-E)[60,523]
Genome Instability	Acrylamide	Inactivation of DNA repair proteins/enzymes	Unknown (A-CL, A-I, H-CL)[67,524]
Genome Instability	Quinones	Affect free cysteine residues in catalytic center of DNA methyltransferases (DNMT)	Unknown (A-CL)[77]
Genome Instability	Nickel	Affect enzymes that modulate post-translational histone modification	LDE (H-E)[58,525] LDE (A-CL, H-CL)[59]
Genome Instability	Bisphenol A	Epigenetic changes via interactions with miRN	Threshold (H-PC)[68]
Genome Instability	Alloy particles (tungsten/nickel/cobalt)	Disruption of DNA damage/redox signaling involving Nrf, NFKB, Egr, etc.	LDE (A-I)[63]
Genome Instability	Titanium dioxide NPs	Decreased NADH levels and impaired mitochondrial membrane potential and mitochondrial respiration, ROS generation	Unknown (A-PC)[64]
Genome Instability	Benomyl	Spindle defects leading to formation of micronuclei	Threshold (A-CL)[526,527]
Genome Instability	Carbon nanotubes	Spindle defects leading to formation of micronuclei	LLDE (A-CL)[83,528] Unknown (A-I)[528]