RESEARCH ARTICLE

Pressure regulated basis for gene transcription by delta-cell micro-compliance modeled in silico: Biphenyl, bisphenol and small molecule ligand models of cell contraction-expansion

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Abstract

Molecular diameter, lipophilicity and hydrophilicity exclusion affinity limits exist for small molecule carrier-mediated diffusion or transport through channel pores or interaction with the cell surface glycocalyx. The molecular structure lipophilicity limit for non-specific carrier-mediated transmembrane diffusion through polarity-selective transport channels of the cell membrane is \( L_{\text{external structure}} \cdot H_{\text{polar group}} \leq 1.07 \). The cell membrane channel pore size is \( > 0.752 \) and \( < 0.758 \) nm based on a 3-D ellipsoid model (biphenyl), and within the molecular diameter size range \( 0.744 \) and \( 0.762 \) nm based on a 2-D elliptical model (alkanol). The adjusted van der Waals diameter (vdWD, adj; nm) for the subset of halogenated vapors is predictive of the required MAC for anesthetic potency at an initial \( \Delta \Delta C_{\text{micro}} \) effect. The molecular structure \( L \cdot H_{\text{polar group}} \leq 0.080 \), and the \( L \cdot H_{\text{polar group}} \leq 0.092 \) interval range for the cell surface glycocalyx hydrophilicity barrier interaction is \( 0.101 \) (Saxitoxin, Stx; \( L \cdot H_{\text{polar group}} \leq 0.092 \) (m-xylenediamine, Lxx). Differential effective pressure mapping of gene activation or repression reveals that \( p \)-dioxin exposure results in activation of AhR-Er\( \beta \) (Arnt)/Nrf-2, Ppara\( \delta \), Ery (Lxr\( \alpha \)), Dio3 (Dio2) and Tr\( \beta \) limbs, and due to high affinity Dio2 and Dio3 (OH-TriCDD, Lxx; \( L \cdot H_{\text{polar group}} \leq 1.91–4.31 \)) exothermy-antagonism (\( \Delta \) contraction) with high affinity T\( \delta \)T\( \delta \)-Tr\( \alpha \)-mediated agonism (\( \Delta \) expansion). co-planar PCB metabolite exposure (Lext \cdot H\( ^{-1} \) : 1.95–3.91) results in activation of AhR (Era\( \beta \)/Nrf2, Rev-Erb\( \beta \), Ery, Dio3 (Dio2) and Tr\( \beta \) limbs with a \( \Delta C_{\text{micro}} \) contraction of 0.89 and \( \Delta C_{\text{micro}} \) expansion of 1.05 as compared to \( p \)-dioxin. co-, ortho-planar PCB metabolite exposure results in activation of Car/PxR, Ppara (Srebf1,—Lxr\( \beta \)), Arnt (AhR-Er\( \beta \)), AR, Dio1 (Dio2) and Tr\( \beta \) limbs with a \( \Delta C_{\text{micro}} \) contraction of 0.73 and \( \Delta C_{\text{micro}} \) expansion of 1.18 (as compared to \( p \)-dioxin). Bisphenol A exposure (Lext \cdot H\( ^{-1} \) : 1.08–1.12, BPA–BPE, Ery\( \gamma \), BPAF, Lext \cdot H\( ^{-1} \) : 1.23, CM Era, \( \beta \) results in increased duration at \( P_{\text{eff}} \) for Timm88 (\( P_{\text{eff}} \: 0.247 \)) transcription and in indirect activation of the AhR/Nrf-2 hybrid pathway with decreased duration at \( P_{\text{eff}} \) 0.200 (Nrf1) and increased duration at \( P_{\text{eff}} \) 0.257 (Dffa). The Bpa/Bpaf convergent pathway \( C_{\text{micro}} \) contraction-expansion response increase
in the lower $P_{\text{eff}}$ interval is 0.040; in comparison, small molecule hormone $\Delta C_{\text{micro}}$ contraction-expansion response increases in the lower $P_{\text{eff}}$ intervals for gene expression $\leq 0.168$ (Dex- GR) $\geq 0.156$ (Dht - AR), with grade of duration at $P_{\text{eff}}\ (\text{min-count})$ of $1.33\times10^{5}$ (Dex/ Cort) and $1.8-2.53\times10^{5}$ (Dht/R1881) as compared to the (-) coupled (+) $\Delta C_{\text{micro}} P_{\text{eff}}$ to 0.136 (Wnt5a, Esr2) with applied DES ($1.86\times10^{6}$). The subtype of trans-differentiated cell as a result of an applied toxin or toxicant is predictable by delta-$C_{\text{micro}}$ determined by $P_{\text{eff}}$ mapping. Study findings offer additional perspective on the basis for pressure regulated gene transcription by alterations in cell micro-compliance ($\Delta$ contraction-expansion, $C_{\text{micro}}$), and are applicable for the further predictive modeling of gene to gene transcription interactions, and small molecule modulation of cell effective pressure ($P_{\text{eff}}$) and its potential.

Introduction

The mechanism of detoxification in human cells is induction of the phase I aryl hydrocarbon receptor (AHR)/AhR nuclear translocator (ARNT) pathway by transcriptional activation of 300 monoxygenase system enzyme genes (CYP1A1, CYP1B1) inseries with phase II nuclear respiratory factor-2 (NRF-2, NFE2L2) activation of UDP-glucoronosyl transferases (ie UGT1A6, UGT1A7), glutathione synthesis (GCLC) and NAD(P)H-quinoine acceptor oxidoreductase (NQO1), and glutathione S-transferases (ie GSTA1 -3), within which the constitutive androstane receptor pathway (CAR, NR3C1) also plays a role in phase I/II metabolism (ie CYP3A4, UGT1A1) [4]. $z$, $x$-plane alignment establishes the reading frame for transcriptional factor binding and activation or repression of genes with or without recruitment [5], which results in the differentially-increased activation of CYP1A1 and CYP1B1 genes by co-activator adapter RIP140 recruited to the AhR/ARNT binding affinity xenobiotic response element (XRE) or to the 15mer full-site estrogen response element sequences (ERE) by liganded ERα/β dimers [6–8], transcriptional regulation of SREBF1 by a functional CAR and LXRα or LXRβ interaction [4], or activation of the cell membrane DIO1 gene by SRC-1 co-adapter recruited to T2-ligated TRβ [9].

These pathways are activated by a spectrum of small molecule lipophiles of variable affinity either directly or indirectly, including in response to the classic high-affinity agonists, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at $10^{-12}$ M concentration for activity in vivo [1], as compared to bisphenols such as BPA with bioavailable concentration approaching 2 ng/mL levels in blood for involvement of high- and mid-affinity binding to ERRγ and GPR30 receptors respectively for those well-characterized [10–12]. Furthermore, since such exotoxins have bioaccumulated in the ecosystem, toxicity relative potency factor (REP)-adjusted additive TEF TEQs have been developed on the basis of combinatory data of in vivo dose escalation (ie ED50) and competitive assay studies (EC50, Kd) such as from kinetic in silico models as fractional measures of planar (co-, ortho-) atom structural affinity (TCDD $K_{\text{CALC}} 10^{-10}$, TEF 1) [13, 14]. With serum globulin-binding being high affinity for endogenous ligands, and OH-, MeS(O)PCB metabolites ($\Sigma$) present in the 0.3–30 nM to 0.07–0.7 μM range in local tissue resident adipocytes (ng/g lipid) [15, 16], it can be hypothesized that there is high-affinity pharmacokinetic non-competition at the cell membrane (CM) or subcellular membrane (SCM) enzyme/receptor, and/or nuclear receptor (AhR/ARNT) for exogenous lipophile and metabolite bioaccumulants such as OH-, MeS(O)PCBs, as in prior study it has been noted that dioxin-like co-planar PCB-77 alters membrane fluidity less than ortho-substituted PCB-52 [17].

Polarity-specific transmembrane channels of varying pore sizes exist for facilitated diffusion of water, electrolytes, saccharides and amino acids into eukaryotic cells [18–20], though which
non-polar small molecules will diffuse, both endogenous and exogenous. The permeation thresholds for small molecule hydrophilic micro-molecular permeability across respiratory epithelial (macula occludens, adherens; non-pericytotic) and brain endothelial barriers (zona occludens) are lower than predictable based on molecular diameter of equivalently-sized neutral small molecules due to greater hydrophilicity for size (-Log \( P \)/vdWD, \( nm^{-1} \)), limit interval van der Waals diameters (vdWD) for anionic, neutral and cationic small molecule hydrophiles are 0.50-0.63 nm, between 0.66-0.73/0.81 nm, and at around 0.55 nanometers, respectively [21]. With small molecule hydrophilic plasma half-life and lipophilic tissue biodistribution as determinants, it deserves to be considered that there exist various molecular exclusion and/or philicity affinity limits for exogenous ligands of receptors and channels (ie Saxitoxin, Tetrodotoxin, 1,2-diaminocyclohexane) and small molecule hormones of various classes (ie Cortisol, Aldosterone, E\(_2\), DHT), which include: 1, a structural hydrophilicity for interactions with the epicellular proteoglycan matrix; 2, interval range of electropolarity at channel pore entry zone for endocytic transport; 3, a transition to selective facilitated diffusion and from polarity-selective to non-specific facilitated diffusion, and 4, the limit at which molecular diameter becomes the determinant of transmembrane channel transport subcellularly.

In this study, the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), co-planar and ortho-planar PCB-activated, diethylstilbestrol (DES) and bisphenol (BPA, BPAF) gene regulation pathways are further characterized by differential effective intracellular pressure (\( P_{\text{eff}} \)) mapping of delta-cell micro-compliance in response to exposure in silico, these being model toxin-mediatesed gene activation molecular pathways, as are activation pathways of small molecule lipophiles (ie halogenate ethers), hydrophilic channel substrates or receptor agonists (ie lactate, mannitol; \( m\)-xylenediamine) as compared to those of endogenous steroid axis ligands (ie Estradiol, E\(_2\); Dht). The \( I_{\text{external/external}} \cdot H_{\text{external}}^{-1} \) quotient, isomerism-adjusted \( I_{\text{external/external}} \cdot H_{\text{external}}^{-1} \) quotient for acyclic hydroxylates, and vdWD (nm; sub-Å) are applied as measures to model cellular interactions by affinity and molecular size; correlative differential \( P_{\text{eff}} \) mapping of gene expression in esebsiwaagoT\(_{\text{Q}}\) units is applied to determine the delta (\( \Delta \))-range of \( P_{\text{eff}} \) as a measure of cell micro-compliance (\( C_{\text{micro}} \)); and the \( \Sigma \) \text{min-count} is determined by power regression as a measure of the pressure grade of effect for a subset of molecular size-excluded steroid axis ligands. Therefore, in this study the transcriptional regulation effects will be studied by differential predictive (pred) effective intracellular pressure (\( P_{\text{eff}} \)) mapping of delta (\( \Delta \))-cell micro-compliance to further explore the underlying basis for cell type-specific alterations in gene transcription as it has been determined that \( x\), \( z\)-plane alignment of intergene tropy results in gene transcription in response to applied small molecule inverse agonists over a range of molecular diameter and philicity modeled in silico.

**Methods**

**Selection of small molecules for study and determination of molecular size exclusion and hydrophilicity affinity interaction limits**

Representative classes of small molecules of increasing complexity with non-chiral carbons (2-D elliptical) and/or a chiral carbon (3-D ellipsoid) with halogen-substituted atoms (para-, ortho- and co-/meta-) or functional group charge separation (sufficiently separated in space, SS; insufficiently separated in space, IS) were sampled for the study inclusive of small molecules of sedimentary origin (C\(_1\)-C\(_{13}\) alkanes: methane, ethane, propane, butane), biosynthetic small molecules (C\(_2\)-C\(_{13}\) alcohols: nonalol, decanol, undecanol, dodecanol, tridecanol; saxitoxin (Stx), tetradotoxin (Ttx); trans-retinol, \( \alpha\)-tocopherol; aldosterone (Ald), cortisol (Cort), dexamethasone (Dex), 17\( \beta \)-estradiol E\(_2\), dihydroxytestosterone (Dht), and thyroxine T\(_4\)), and synthetic molecules (tetrathyllead, cyclononalal, acetochlor; diethylstilbestrol (DES),
methyltrienolone; polybrominated diphenyl ether-209; 2,3,7,8-tetrachlorodibenzo-para-dioxin, Tcdd; co-planar polychlorinated biphenyls Pcb-77, Pcb-126; co-planar, ortho-planar Pcb-106, -153, -172, -180; ortho-planar Pcb-54, -95, -132, -153, -172, -180; ortho-planar Pcb-54, -95, -132 and metabolites; bisphenols A, C, E and AF (chiral); branched C2-C4 halogenates: halothane, desflurane, isoflurane, enfurane, sevoflurane; m-xylendiamine; phthalate (mono-, di-n-butyl)). The predicted values of Log P (unitless), molecular weight (Da), van der Waals molecular volume (Å³) and polar surface area (Å²) were applied (www.chemicalize.org) for determinations of molecular diameter (vdWD; nm), and whole or part-molecular lipophilicity or hydrophilicity per diameter (Log P/vdWD; nm⁻¹) inclusive of functional groups as previously reported [21]. Additional parameters were determined inclusive of i) molecular exterior or interior structural lipophilicity per diameter (vdWD, 3-digit sub-Å; L_external (or internal); nm⁻¹) and exterior structural hydrophilicity per diameter (H_external; nm⁻¹) with determinations of ii) polar surface area (psa) Log P/vdWD (nm⁻¹) for intervening single atoms, and iii) the intermediate values of Log P/vdWD for part-molecular structures, as:

\[
\frac{L_{\text{external (internal)}}}{H_{\text{external}}} = \frac{10^{(\text{part})}}{10^{(\text{isophile part})} + 10^{(\text{polar part})}}
\]

When the isophile is an external or intervening ether, the polar part P is 0.3319 (-0.479 nm⁻¹) for mono-oxygen and 1.8197 (0.260 nm⁻¹) for the mono-ether adjustment; and for a 2ary amine, the polar part P is 0.2048 (-0.624 nm⁻¹) for mono-nitrogen with no additional adjustment. The calc L_external/internal * H_external⁻¹ is normalized to methanol as the reference standard, 2.75 (Ch₃oh nl).

**Determination of molecular structure-polar group substituted lipophilicity limit for non-specific transmembrane transport**

The Log P_alkane/vdWD_alkane (L_external structure)]/[Log P_OH/vdWD_OH (H_polar group)] ratio quotient (abs value) was determined for the subset of 1- to 4-C simple alkane hydroxylates (methanol, 1-ethanol, 1-propanol, 1,2-propanol, 1,3-propanediol, 1,2-butandiol, 1,2-ethanediol and 2,3-glycer-1-ol). The unadjusted for isomerism Log P/vdWD was applied for presence of single hydroxyl (OH) group of -1.05 nm⁻¹ (methanol, 1-ethanol), and the adjusted for external isomerism hydrophilic moiety Log P/vdWD was applied for the presence of dual hydroxyl group isomerism, as:

\[
L_{\text{external}} \cdot H_{\text{OH group}}^{-1} (\text{adj}) = \frac{L_{\text{external}}}{-1.05 \text{ nm}^{-1} + (1/i + 1)(0.437)}
\]

\(i + 1\) is the number of carbon bonds in-between the initial hydroxylated position and the subsequent hydroxylated position for a polar group functionalized simple aliphatic. Based on the calc nl L_external/internal * H_external⁻¹ limit for non-specific carrier-mediated diffusion, the interval range limits of molecular hydrophilicity for endocytosis and channel wall domain affinity interactions for the remainder of the molecules of the study sample.

**Determination of the gradient of effect for duration at P_eff for steroid axis ligands at cell membrane receptors**

The minute-receptor counts for corticosteroid axis receptor ligands at GR and MR (Cortisol, Cort; Dexamethasone, Dex; Aldosterone, Ald), estrogen axis receptor ligands at ERα (17β-Estradiol; Diethylstilbestrol, DES), androgen axis receptor ligands (Dihydroxytestosterone, DHT; methyltrienolone, R1881) and macromolecular marker as standard (Insulin-like growth factor II) for negative Δ C_mic shift at lower limit of P_eff. The t1/2 at receptor-receptor count
(min-count) was determined as a product sum of half-lives at receptor and the cell membrane receptor count, and as $\Sigma \text{min-count}$ in case of co-axis receptor system expression (MR, GR). The $t_{1/2}$ at receptor for DES, DHT and R1881 were determined by $x$, $y$-plotting of radiolabeled hormone dissociation constants ($K_D$, $x$-axis) and known $t_{1/2}$ at receptor (min, $y$-axis). The grade of $P_{\text{eff}}$ was stratified by hormone ligand and receptor subtype, positive to negative by min-count, as determined by the semi-exponential power regression, and adjusted for cell receptor count:

$$f(x) = 3.0E - 05 \cdot (K_1)^{0.6784} \cdot n \quad R^2 = 0.955$$

### Selection of genes for study and effective intracellular pressure mapping of pathway genes

Representative genes were selected for effective intracellular pressure ($P_{\text{eff}}$) mapping of cellular pathway regulation by small molecules of the study sample (ie acyclic C$_2$-C$_4$ halogenates; 2,3,7,8-tetrachlorodibenzo-para-dioxin ($p$-dioxin); co-planar PCB-126; co-, ortho-planar PCB-153; bisphenol A, bisphenol AF; biosynthetic, ie tetradotoxin), which includes the following genes, which fall into the following categories:

i. Transcription factor/adapter [AHR, AR, ARNT, ARNTL, ATF3; CEBPD, DDIT3 (CHOP), CREB1, ESR1, ESR2; ESRBG, ESRRa; FOSB, FOS, FOXA1; GTP2IRD1, HNF4A, JUN; NCO1, NCO2; NFE2L2 (NRF-2), NR1D1 (Rev-Erbα), NR1D2 (Rev-Erbβ), NR3C1 (GR), NR3C2 (MR); NR1H3 (LXRα), NR1H2 (LXRβ); NR1I2 (PXR), NR1I3 (CAR), NRFI; PPARA, PPARD, PPARG; PER1, RXRA, RXRB, RARA, RARB, RARG, SIM1, SIN3A, SREBF1, TGF1, THRA, THRb; DBP; HOXA9, HOXA10, HOXA11, HOXA13; KLF4; WNT5A];

ii. Transcription factor co-adapter/co-adapter [PPARGC1A (PGC1α), NRP1, NCOA1 (SRC-1), GADD45A; GADD45B, CIDEA; DFFA];

iii. Cell membrane enzymes/proteins or channels/subunits [ADAM8, EXOC7, NOS1; DIO1, DIO3; MBP; SLC9A1 (NHE-1), SLC2A4 (Glut-4)];

iv. Cell membrane receptor antigen/receptor (CEACAM1, CEACAM5; TSPAN14; TRFC);

v. Cell membrane receptor ligand [DLK1 (PREF-1)];

vi. Cytochrome P450 monooxygenases [CYP1A1, CYP1B1, CYP1A2, CYP2B6, CYP2E1, CYP3A5, CYP3A7; CYP5A, CYP11B1 (11-$\beta$-hydroxylase), CYP11B2 (aldosterone synthase), CYP17A1 (17, 20-lyase)];

vii. Cytosolic/nuclear enzyme, DNA or mRNA adapter [PP1R9B, CUL2, PLEKHG4, RAP-GEFL1; CCND1, CDKN1A; CIDEA; DFFA, CASP3; MEG3, MIAT, MIR132];

viii. Intracellular enzymes [ALAS1, ALAS2; ACSM2A, ALDH3A1, CAT, DAO, DUSP1; FABP4 (aP2), FABP5, FABP6; FASN, GSTM2, ME1, MT1A, NQO1; PCK1, PER1, TIPARP; SCD; SCD5; LGAL1, UGT1A_ locus (UGT1A1, UGT1A6, UGT1A7)];

ix. Mitochondrial membrane-associated (COX6C, COX8C, CYCS; TIMM8B);

x. Mitochondrial-specific protein synthesis/cell cycle regulation (TFB2M);

xi. Rough endoplasmic reticulum enzyme/receptor (DIO2, GPR30, RESP18, OLFM1); and

xii. Secretory peptides/hormones [COL1A1, TFF1 (pS2), SFTPC, PMCH, A2M].
The gene/gene loci positions of protein coding and non-coding genes/gene loci were utilized as previously reported (www.genecards.org; lncipedia.org) for determinations of the episodic sub-episode block sums split-integrated weighted average-averaged gene overexpression entropy quotient as previously reported. The sub-episode block sums and averages were determined for gene loci as categorized by episode and initial SEB structure [5, 22], 1) Episode 3 (≤ 11,864, 7 SEB); 2) Episode 2 (> 11,864 ≤ 265,005, 5 SEB); 3) Episode 4 (> 265,095 < 521,757; 9 SEB); 4) Episode 5 (≥ 521,757 < 784,883; 11 SEB); and 5) Episode 5 (≥ 784,883; 13 SEB). The upstream and downstream part anisotropic sub-episode block sum (uppasebs, dppasebs) and correlate upstream and downstream part anisotropic sub-episode block sum split integrated weighted average (uppasebssiwa, dppasebssiwa) were determined for further calculation of the weighted average upstream and downstream part mesotropic sub-episode block sum split integrated weighted average (uppmsebssiwa, dppmsebssiwa) and the final esebsiwaagoT_O quotient as a measure of effective intracellular pressure (P_{eff}). The increase (plus %; ratio Δ) or decrease (minus %; ratio Δ) in the differential P_{eff} mapping duration response was determined for the subset of marker genes as standards, based on which the placement of additional genes of study sample was determined, as either an increase (or decrease) in duration at P_{eff} as:

\[
\sum_{0}^{n} (uppaseb, dppaseb), \sum_{0}^{m} (uppmseb, dppmseb)
\]

\[
\int_{0}^{h} (dppasebssiwa, dppmsebssiwa) \, dt
\]

\[
\int_{0}^{d} (uppasebssiwa, uppmsebssiwa) \, dt
\]

\[
esebsiwaagoT_O,
\]

\[
\%\text{inc, dec} (+, -\Delta \text{ ratio}), \geq 2-x \text{ P for std marker mRNA}
\]

**Determination of range of cell micro-compliance response by correlative differential gene expression P_{eff} mapping**

Representative gene overexpression range of cell micro-compliance P_{eff} mapping upper and lower bounds were determined for applied TCDD, co-planar PCB (ie OH-PCB-77; OH-PCB-126), and ortho-, co-, ortho-planar (ie OH-PCB-54; OH-PCB-95; OH-PCB-153) in silico, as follows:

C_{micro} = \frac{k}{P_{eff \ TCDD\ upper} - P_{eff \ TCDD\ lower}}

The P_{eff} for activation of gene marker standards (std) in addition to predicted differential P_{eff} gene expression of exposure-modeled cell(s) was determined on the basis of intracellular esebsiwaagoT_O pressure units (P_{eff}). The upper and lower bounds of the expansion response were determined as subtractive residuals of the upper direction maxima from the lower direction contraction responses from the respective minima in each direction of the PCB-95 or...
PCB-153 exposed normal cell modeled in silico. The contraction-expansion response range of cell micro-compliance ($C_{\text{micro}}$) was then determined as the difference between max and min bounds of range (BoK) in $C_{\text{micro}}$ $P_{\text{eff}}$ range units. Pairwise delta ($\Delta$) micro-compliance ($C_{\text{micro}}$) comparisons between the range of the cellular contraction-expansion response to p-dioxin exposure (TCDD, std; bracket 1), and co-planar PCB-126 (bracket 2 vs 1) and co-, ortho-planar PCB-95/-153 (bracket 3 vs 1) were performed [$\Delta$, ratio expansion; a.u.].

Results

van der Waals diameter and external structural lipophilicity per polar group hydrophilicity of small molecule hydroxylates that are polarity-specific transport channel substrates

Methane (CH$_4$) has a Log $P$ of 1.08, and a vdWD of 0.373 nm with a Log $P$/vdWD of 2.89 nm$^{-1}$. Methanol (CH$_3$OH) has a $I_{\text{external structure}}/H_{\text{polar group}}$ ratio of 2.75 (reference, 0 or 1) (Table 1).

Ethane (C$_2$H$_6$) has a Log $P$ of 1.35, and a vdWD of 0.437 nm with a Log $P$/vdWD of 3.09 nm$^{-1}$. Ethan-1-ol (C$_2$H$_6$OH) has a $I_{\text{external structure}}/H_{\text{polar group}}$ ratio of 2.94, calc $\Delta$ $I_{\text{external structure}}$/H$_{\text{polar group}}$ of 0.19, and a nl calc $I_{\text{external structure}}/H_{\text{polar group}}$ quotient of 1.069. 2-ethan-1-ol (C$_3$H$_7$O) has a $I_{\text{external structure}}/H_{\text{polar group}}$ ratio of 1.47, calc $\Delta$ $I_{\text{external structure}}$/H$_{\text{polar group}}$ of 1.28, and a nl calc $I_{\text{external structure}}/H_{\text{polar group}}$ quotient of 0.535 (Table 1).

Propane (C$_3$H$_8$) has a Log $P$ of 1.80, and a vdWD of 0.485 nm with a Log $P$/vdWD of 3.71 nm$^{-1}$. Propan-1-ol (C$_3$H$_7$OH) has a $I_{\text{external structure}}/H_{\text{polar group}}$ ratio of 3.53, calc $\Delta I_{\text{external structure}}$/H$_{\text{polar group}}$ of 0.78, and a nl calc ratio $I_{\text{external structure}}$/H$_{\text{polar group}}$ quotient of 1.280. Propan-1,2-diol (C$_3$H$_6$O$_2$) has a $I_{\text{external structure}}/H_{\text{polar group}}$ ratio of 2.90, calc $\Delta$ $I_{\text{external structure}}$/H$_{\text{polar group}}$ of 0.13, and a nl calc $I_{\text{external structure}}$/H$_{\text{polar group}}$ quotient of 1.047. Propan-1,3-diol (C$_3$H$_8$O$_2$) has a $I_{\text{external structure}}$/H$_{\text{polar group}}$ ratio of 3.08, calc $\Delta$ $I_{\text{external structure}}$/H$_{\text{polar group}}$ of 0.31, and a nl calc $I_{\text{internal}}$/H$_{\text{polar group}}$ quotient of 1.113. 2,3-glycer-1-ol (C$_6$H$_12$O$_3$) has a $I_{\text{external structure}}$/H$_{\text{polar group}}$ ratio of 1.18, calc $\Delta$ $I_{\text{external structure}}$/H$_{\text{polar group}}$ of 1.57, and a nl calc $I_{\text{external}}$/H$_{\text{polar group}}$ quotient of 0.428. Mannitol (C$_{6}$H$_{12}$O$_{6}$) has a $I_{\text{internal structure}}$/H$_{\text{polar group}}$ ratio of 0.838, calc $\Delta$ $I_{\text{internal structure}}$/H$_{\text{polar group}}$ of 1.91, and a nl calc $I_{\text{internal}}$/H$_{\text{polar group}}$ quotient of 0.304 (Table 1).

Table 1. Molecule structural hydrophilicity limit for non-specific diffusion into cells through polarity-specific transmembrane transport channels.

| Hydroxylate external structure | Formula | Log $P$ | Molecular weight (Da) | Size ($\text{Å}^3$) | vdWD (nm) | Log $P$/vdWD (nm$^{-1}$) | $I_{\text{external structure}}/H_{\text{polar group}}$ $\Delta$ $/\text{calc, calc}_i$ $\Delta$/ref$^i$ |
|-------------------------------|---------|---------|-----------------------|---------------------|-----------|-------------------------|-----------------------------------------------|
| Hexane                        | C$_2$H$_6$ | 3.13    | 86.1                   | 113.2               | 0.593     | 5.28                    | Mannitol (0.838, 1.91; 0.304) |
| Butane                        | C$_2$H$_6$ | 2.24    | 58                     | 79.1                | 0.526     | 4.26                    | 1,2-butanediol (3.34, 0.57; 1.21) |
| Propane                       | C$_3$H$_8$ | 1.80    | 44                     | 62.2                | 0.485     | 3.71                    | 1-propanediol [3.53, 0.78; 1.28] |
|                              |         |         |                       |                     |           |                         | 1,3-propanediol [3.08, 0.31; 1.11] |
|                              |         |         |                       |                     |           |                         | 1,2-propanediol [2.90, 0.13; 1.05] |
|                              |         |         |                       |                     |           |                         | 2,3-glycer-1-ol [1.18, 1.57; 0.428] |
| Ethane                        | C$_2$H$_6$ | 1.35    | 30                     | 45.2                | 0.437     | 3.09                    | 1-ethanol [2.94, 0.19; 1.07] |
|                              |         |         |                       |                     |           |                         | 1,2-ethanediol [3.09, 1.28; 0.535] |
| Methane                       | CH$_4$  | 1.08    | 16                     | 28.3                | 0.373     | 2.89                    | Methanol [ref$^a$] |

$^a$ hydroxyl group hydrophilicity is Log $P$/vdWD of · 1.05 nm$^{-1}$ (Log $P$: -0.33; vdWD: 0.316 nm)

$^b$ dual hydroxylate isomerism adjustment for 1,2-propanediol, 1,3-propanediol and 1,2-butanediol is Log $P$/vdWD$^{-1}$/[1.05 + (1/i + 1)(0.437)], where i = no. of C bonds in-between the initial OH position and the subsequent hydroxylate for a simple aliphatic or cycloaliphatic

$^\Delta$, calc -ref; nl calc, calc — ref/ref when calc > ref, and 1 — (calc - ref/ref) when ref > calc Note(s): Polarity-specific transport occurs at a nl calc ratio < 1.07 (1,2-propanediol, 1,2-ethanediol and 2,3-glycer-1-ol)

$^\Delta$, calc -ref; nl calc, calc — ref/ref when calc > ref, and 1 — (calc - ref/ref) when ref > calc Note(s): Polarity-specific transport occurs at a nl calc ratio < 1.07

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Lactate (C₃H₅O₃) has a Log P of -0.47 (Log D, -3.7), and a vdWD of 0.526 nm with a Log P/vdWD of -0.893 nm⁻¹ (Log D/vdWD, -7.04 nm⁻¹). Lactate (lactic acid) has a calc Iᵦbulk / H_polar group of 0.309 (0.901), calc ΔIᵦbulk / H_polar group of 1.85 (2.44), and a nl calc Iᵦbulk / H_polar group quotient of 0.112 (0.328) (Table 1).

Butane (C₄H₁₀) has a Log P of 2.24, and a vdWD of 0.526 nm with a Log P/vdWD of 4.26 nm⁻¹. 1,2-butanediol (C₆H₁₄O₂) has a calc Iᵦbulk / H_polar group of 3.54, calc ΔIᵦbulk / H_polar group of 0.57, and a nl calc Iᵦbulk / H_polar group quotient of 1.207 (Table 1).

van der Waals diameter and external structural lipophilicity per polar group hydrophilicity parameters of small molecule halogenates that are non-specific transport channel substrates

Halothane (C₂HBrClF₃) has a Log P of 2.12, and a vdWD of 0.554 nm with a Log P/vdWD of 3.82 nm⁻¹ (Table 2).

Desflurane (C₃H₂F₅O) has a Log P of 2.40, and a vdWD of 0.571 nm with a Log P/vdWD of 4.21 nm⁻¹. Part-halogenate 1,1,1-trifluoro-2-fluoroethane (C₂H₂F₃) has a Log P of 1.33, and a vdWD of 0.493 nm with a Log P/vdWD of 2.70 nm⁻¹. Part-halogenate fluoromethane (CH₂F) has a Log P of 0.370, and a vdWD of 0.394 nm with a Log P/vdWD of 0.939 nm⁻¹. Desflurane has a calc Iᵦbulk / H_polar group ratio of 9.62, and a nl calc Iᵦbulk / H_polar group quotient of 3.50 (Table 2).

Isoflurane (C₃H₂ClF₃O) has a Log P of 2.84, and a vdWD of 0.588 nm with a Log P/vdWD of 4.83 nm⁻¹. Part-halogenate 1,1,1-trifluoro-2-chloroethane (C₂H₂ClF₃) has a Log P of 1.79, and a vdWD of 0.515 nm with a Log P/vdWD of 3.48 nm⁻¹. Part-halogenate difluoromethane (CH₂F₂) has a Log P of 0.677 (calc), and a vdWD of 0.413 nm with a Log P/vdWD of 1.65 nm⁻¹. Isoflurane has a calc Iᵦbulk / H_polar group ratio of 11.25, and a nl calc Iᵦbulk / H_polar group quotient of 4.09 (Table 2).

Enflurane (C₃H₂ClF₅) has a Log P of 2.80, and a vdWD of 0.588 nm with a Log P/vdWD of 4.77 nm⁻¹. Part-halogenate 1-chloro-1,2,2-trifluoroethane (C₂H₂ClF₃) has a Log P of 1.54, and a vdWD of 0.515 nm with a Log P/vdWD of 2.99 nm⁻¹. Part-halogenate difluoromethane

### Table 2. Small molecule halogenates with affinity interactions at inner mitochondrial membrane P450 cytochromes.

| Halogenate/Part-halogenate | Formula | Log P | Molecular Weight (Da) | Size (Å²) | vdWD (nm) | Polar SA (Å²) | Log P/vdWD (nm⁻¹) | Iᵦbulk / H_polar group | H_polar group quotient |
|---------------------------|---------|-------|-----------------------|----------|----------|--------------|-------------------|-----------------------|------------------------|
| Halothane                 | C₂HBrClF₃ | 2.12  | 196                   | 92.6     | 0.554    | -            | 3.82; n/a          |                      |                       |
| Desflurane                | C₃H₂F₅O   | 2.40  | 168                   | 101      | 0.571    | 9            | 4.21; 3.50         |                      |                       |
| 1,1,1-trifluoro-2-fluoroethane | C₂H₂F₃  | 1.33  | 102                   | 65       | 0.493    | -            | 2.70; n/a          |                      |                       |
| Isoflurane                | C₃H₂ClF₃O | 2.84  | 184                   | 110      | 0.588    | 9            | 4.83; 4.09         |                      |                       |
| 1,1,1-trifluoro-2-chloroethane | C₂H₂ClF₃ | 1.79  | 118                   | 74.2     | 0.515    | -            | 3.48; n/a          |                      |                       |
| Enflurane                 | C₃H₂ClF₅  | 2.80  | 184                   | 110      | 0.588    | 9            | 4.77; 3.72         |                      |                       |
| 1-chloro-1,2,2-trifluoroethane | C₂H₂ClF₃ | 1.54  | 118                   | 74.2     | 0.515    | -            | 2.99; n/a          |                      |                       |
| Sevoflurane               | C₂H₂F₅O   | 2.27  | 200                   | 123      | 0.610    | 9            | 3.72; 3.83         |                      |                       |
| 1,1,1,3,3,3-hexafluoropropane | C₃H₂F₆  | 2.13  | 152                   | 92.05    | 0.553    | -            | 3.85; n/a          |                      |                       |

^ The molecular diameter (vdWD, nm) is predictive of end-tidal minimum alveolar concentration (MAC, vol %), \( y = 10.41x - 4.707 \) (\( R^2 = 0.73 \)) in comparison to molecular weight (Da), \( y = 0.0081x - 0.214 \) (\( R^2 = 0.29 \)), when trichloromethane (0.72%, 0.505 nm), halothane (0.75%), enflurane (1.17%), sevoflurane (1.80%) are x, y-plotted; and \(^\wedge\) lower non-polar part-structural lipophilicity Log P/vdWD is predictive of deviation from measured minimum alveolar concentration (MAC) \(^\dagger\) Difluoromethane (C₂H₂F₂), common part-structure moiety to Isoflurane, Enflurane and Desflurane (Log P 0.677, vdWD 0.413 nm, 1.65 nm⁻¹; \( y = 16.154x - 5.995, R^2 = 1 \)); and Fluoromethane (CH₂F), part-structure moiety of Sevoflurane (Log P 0.37, vdWD 0.394 nm, 0.939 nm⁻¹).
(CH$_2$F$_2$) has a Log $P$ of 0.677 (calc), and a vdWD of 0.413 nm with a Log $P$/vdWD of 1.65 nm$^{-1}$. Enflurane has a calc $L_{\text{external structure}}$/$L_{\text{polar group}}$ ratio of 10.23, and a nl calc $L_{\text{external structure}}$/$L_{\text{polar group}}$ quotient of 3.72 (Table 2).

Sevoflurane (C$_3$H$_5$F$_2$) has a Log $P$ of 2.27, and a vdWD of 0.610 nm with a Log $P$/vdWD of 3.72 nm$^{-1}$. Part-halogenate 1,1,1,3,3,3-hexafluoropropane (C$_3$H$_2$F$_3$) has a Log $P$ of 2.13, and a vdWD of 0.553 nm with a Log $P$/vdWD of 3.85 nm$^{-1}$. Sevoflurane has a calc $L_{\text{external structure}}$/$L_{\text{polar group}}$ ratio of 10.54, and a nl calc $L_{\text{external structure}}$/$L_{\text{polar group}}$ quotient of 3.83 (Table 2).

### Gene expression effective pressure mapping for small molecule halogenates that are outer mitochondrial transmembrane channel substrates

CYP2E1 is a 2 A 2 q terminal final SEB gene at $x$, $y$-vertical axis angulation 48.4°. CYP2E1 has an uppsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.6445E + 04, 7.3717E + 04, 2.7927E + 04 and 5.5415E + 04 intergene bases. CYP2E1 has an uppsebssiwa and dppsebssiwa of 2.2186E + 04 and 6.4566E + 04 intergene bases with a $P_{\text{eff}}$ of 0.344 esebsiwaago$T_Q$ units (Table 3).

CYP2B6 is a 2 M 5 initial and final SEB gene at $x$, $y$-vertical axis angulation of 50.9°. CYP2B6 has an uppsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.4887E + 04, 3.2241E + 04, 3.224E + 03, 2.3693E + 04 intergene bases. CYP2B6 has an uppsebssiwa and dppsebssiwa of 2.7170E + 04 and 3.1800E + 04 intergene bases with a $P_{\text{eff}}$ of 0.324 esebsiwaago$T_Q$ units (Table 3).

JUN is a 3 M 5 NCA ACM final SEB gene at $x$, $y$-vertical axis angulation 57.8°. JUN has an uppsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 6.8635E + 04, 1.32597E + 05, 1.5679E + 04 and 1.83485E + 05 intergene bases. JUN has an uppsebssiwa and dppsebssiwa of 4.2157E + 04 and 1.58041E + 05 intergene bases with a $P_{\text{eff}}$ of 0.267 esebsiwaago$T_Q$ units (Table 3).

TFB2M is a 2 A 5 initial and final SEB gene at $x$, $y$-vertical axis angulation 57.8°. TFB2M has an uppsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.4509E + 04, 1.64443E + 05, 6.7711E + 04 and 1.43918E + 05 intergene bases. TFB2M has an uppsebssiwa.
and dppesebssiwa of 4.110E + 03 and 1.54180E + 05 intergene bases with a P_{eff} of 0.267 esebsiwaagoT_{Q} units (Table 3).

SFTPC is a 3 A 7 initial and final SEB gene at x-, y-vertical axis angulation 59.0°. SFTPC has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.7644E + 04, 1.79499E + 05, 3.9387E + 04 and 8.1734E + 04 intergene bases. SFTPC has an uppesebssiwa and dpepsebssiwa of 3.3516E + 04 and 1.30616E + 05 intergene bases with a P_{eff} of 0.257 esebsiwaagoT_{Q} units (Table 3).

FOSB is a 3 A 8 ACM final SEB gene at x-, y-vertical axis angulation 65.6°. FOSB has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.2564E + 04, 2.9210E + 04, 3.621E + 03 and 5.4102E + 04 intergene bases. FOSB has an uppesebssiwa and dpepsebssiwa of 8.092E + 03 and 4.1656E + 04 intergene bases with a P_{eff} of 0.194 esebsiwaagoT_{Q} units (Table 3).

CREB1 is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 71.4°. CREB1 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.5030E + 04, 4.03885E + 05, 5.2441E + 04 and 9.8597E + 05 intergene bases. CREB1 has an uppesebssiwa and dpepsebssiwa of 3.8736E + 04 and 2.51241E + 05 intergene bases with a P_{eff} of 0.154 esebsiwaagoT_{Q} units (Table 3).

HMOX1 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 71.5°. HMOX1 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.3974E + 04, 3.8608E + 04, 4.636E + 03 and 8.2968E + 04 intergene bases. HMOX1 has an uppesebssiwa and dpepsebssiwa of 9.305E + 03 and 6.078E + 04 intergene bases with a P_{eff} of 0.153 esebsiwaagoT_{Q} units (Table 3).

van der Waals diameter and structural lipophilicity parameters of small molecules within the channel molecular size-inclusion range

Biphenyl (C_{12}H_{10}) has a Log P of 3.62, a vdWD of 0.655 nm and a Log P/vdWD of 5.53 nm\(^{-1}\) (Table 4).

Cyclononalol (C_{19}H_{18}O) has a Log P of 2.61, a vdWD of 0.688 nm and a Log P/vdWD of 3.91 nm\(^{-1}\) (Table 4).

Nonal-1-ol (C_{20}H_{20}O) has a Log P of 3.06, a vdWD of 0.682 nm and a Log P/vdWD of 4.48 nm\(^{-1}\) (Table 4).

Tetraethyllead (C_{28}H_{36}Pb\(^{6+}\)) has a Log P of 1.94, a vdWD of 0.700 nm and a Log P/vdWD of 2.77 nm\(^{-1}\) (Table 4).

Bisphenol E (BPE; C_{14}H_{14}O\(_2\)) has a Log P of 3.74, a vdWD of 0.727 nm and a Log P/vdWD of 5.14 nm\(^{-1}\). Part-BPE 1,1-diphenylethane (C_{14}H_{14}) has a Log P of 4.35, a vdWD of 0.701 nm and a Log P/vdWD of 6.21 nm\(^{-1}\). Bisphenol E has a calc I_{external structure}/H_{polar group} ratio of 2.10, and a nl calc I_{external structure}/H_{polar group} quotient of 1.08 (Table 4).

Decan-1-ol (C_{19}H_{22}O) has a Log P of 3.47, a vdWD of 0.704 nm and a Log P/vdWD of 4.93 nm\(^{-1}\) (Table 4).

Bisphenol A (BPA; C_{15}H_{16}O\(_2\)) has a Log P of 4.04, a vdWD of 0.742 nm and a Log P/vdWD of 5.44 nm\(^{-1}\). Part-BPA 2-phenylpropan-2-yl benzene (C_{15}H_{16}) has a Log P of 4.65, a vdWD of 0.722 nm and a Log P/vdWD of 6.44 nm\(^{-1}\). Bisphenol A has a calc I_{external structure}/H_{polar group} ratio of 3.07, and a nl calc I_{external structure}/H_{polar group} quotient of 1.12 (Table 4).

Undecan-1-ol (C_{11}H_{22}O) has a Log P of 3.92, a vdWD of 0.724 nm and a Log P/vdWD of 5.41 nm\(^{-1}\) (Table 4).

Mono-n-butylphthalate (BP, MBP; C_{12}H_{14}O\(_4\)) has a Log P (D) of 2.96 (-0.55), a vdWD of 0.724 nm and a Log P (D)/vdWD of 4.09 (-0.76) nm\(^{-1}\) (Table 4). MBP has a calc I_{external structure}/H_{polar group} ratio of 0.886, and a nl calc I_{external structure}/H_{polar group} quotient of 0.322.
Table 4. Small molecules with intracellular effects at inner mitochondrial membrane ETS cytochromes, rough endoplasmic reticulum deiodinase or at orphan nuclear receptors.

| Small molecule 1,2 | Formula | Log P/D | Molecular Weight (Da) | Size (Å²) | vdWD (nm) 3 | Polar SA (Å²) | Log P/vdWD (nm⁻¹) 4 |
|-------------------|---------|---------|----------------------|-----------|-------------|--------------|----------------------|
| Biphenyl          | C₈H₁₀   | 3.62    | 154                  | 153       | 0.655       | -            | 5.53                 |
| Cyclononalal      | C₈H₆O   | 2.61    | 142                  | 162       | 0.668       | 20           | 3.91                 |
| Nonaol            | C₈H₆O   | 3.06    | 144                  | 173       | 0.682       | 20           | 4.48                 |
| Tetraethyllead    | C₈H₆Pb⁴⁺| 1.94    | 324                  | 186       | 0.700       | -            | 2.77                 |
| 1,1-diphenylethane| C₁₀H₁₄   | 4.35    | 182                  | 187       | 0.701       | -            | 6.21                 |
| Decanol           | C₁₀H₁₂O | 3.47    | 158                  | 190       | 0.704       | 20           | 4.93                 |
| 2-phenylpropan-2-yl benzene | C₆H₁₃   | 4.65    | 196                  | 204       | 0.722       | -            | 6.44                 |
| Undecanol         | C₁₀H₂₂O | 3.92    | 172                  | 207       | 0.724       | 20           | 5.41                 |
| Mono-α,β-buty1phthalate | C₁₂H₁₀O₄ | 2.96 (-0.55) | 222          | 206       | 0.724       | 64           | 4.09 (-0.76)         |
| Bisphenol E       | C₁₄H₁₄O₂ | 3.74    | 214                  | 209       | 0.727       | 40           | 5.14                 |
| 2,2-dichloro-1-phenylethyl benzene | C₆H₆Cl₂ | 4.90    | 248                  | 209       | 0.727       | -            | 6.74                 |
| ortho-planar PCB-54 | C₁₂H₄Cl₂ | 5.84    | 290                  | 209       | 0.727       | -            | 8.04                 |
| 2,3,7,8-tetrachlorodibenzo-p-dioxin | C₁₂H₆Cl₂O₂ | 5.42 | 320                  | 216       | 0.735       | 18           | 7.38                 |
| ortho-planar PCB-95 | C₁₂H₆Cl₂ | 6.76  | 326                  | 218       | 0.737       | -            | 9.17                 |
| Bisphenol A       | C₁₃H₁₈O₂ | 4.04    | 228                  | 222       | 0.742       | 40           | 5.44                 |
| Dodecanol         | C₁₂H₂₂O | 4.36    | 186                  | 224       | 0.744⁴      | 20           | 5.86                 |
| Bisphenol C       | C₁₆H₁₄Cl₂O₂ | 4.29 | 280                  | 224       | 0.744       | 40           | 5.77                 |
| Idothryoxine      | C₁₂H₁₁NO₄ | 3.73 | 777                  | 225⁵      | 0.745⁵      | 93           | 5.00⁶                |
| co-planar PCB-126 | C₁₂H₁₂Cl₂ | 6.69 ⁵ | 324                  | 228       | 0.749       | -            | 8.94                 |
| 4'-OH-2,3,3',4,5-PCB-106 | C₁₂H₁₂Cl₂O | 6.34 | 343                  | 231       | 0.752⁵      | 20           | 8.43                 |

1) 1,1-diphenylethane (6.21 nm⁻¹), 2-phenylpropan-2-yl benzene (6.44 nm⁻¹) and 2,2-dichloro-1-phenylethyl benzene (6.74 nm⁻¹) are the respective internal molecular structures of bisphenol E (BPE, 5.14 nm⁻¹; EREα, EREγ), bisphenol A (BPA, 5.44 nm⁻¹; EREα, EREγ) and bisphenol C (BPC, 5.77 nm⁻¹; EREα, EREβ) 2) lower limit of range for molecular size-inclusion at the transmembrane channel pore as determined by elliptical molecules, vdWD = 0.744 nm; and 3) lower limit of range for molecular size-inclusion at the cell membrane channel pore as determined by ellipsoid (chiral carbon) small molecules, vdWD = 0.752 nm; and 4) lower limit of external structure - H polar group ⁴ for biphenyl metabolites is 1.92 (4-OH-biphenyl). ⁵ Log P values for ortho-planar PCB-95 and co-planar PCB-126, calculated weighted average (chemicalize, ACID/Labs or EPI suite at chemspider and PubChem databases) ⁶ Thyroxine (T₄), vdWD is adjusted for x, y-dimensional molecular aspect, b = (T₄ unadjusted vdWD) (0.760 nm) · (c⁻¹), where c = 0.874.

Bisphenol C (BPC; C₁₂H₁₀Cl₂O₂) has a Log P of 4.29, a vdWD of 0.744 nm and a Log P/vdWD of 5.77 nm⁻¹. Part-BPC 2,2-dichloro-1-phenylethyl benzene (C₁₂H₁₀Cl₂) has a Log P of 4.90, a vdWD of 0.727 nm and a Log P/vdWD of 6.74 nm⁻¹. Bisphenol C has a calc I external structure/H polar group ratio of 3.21, and a nl calc I external structure/H polar group quotient of 1.15 (Table 4). 2',2',6',6'-ortho-planar PCB-54 (C₁₂H₆Cl₂) has a Log P of 5.84, a vdWD of 0.727 nm and a Log P/vdWD of 8.04 nm⁻¹ (Table 4). 2,3,7,8-tetrachlorodibenzo-p-dioxin (C₁₀H₆Cl₂O₂; p-dioxin, TCDD) has a Log P of 5.42, a vdWD of 0.735 nm and a Log P/vdWD of 7.38 nm⁻¹ (Table 4), p-dioxin has a calc I external structure/H polar group ratio of 11.86, and a nl calc I external structure/H polar group quotient of 4.31. 8-OH-2,3,7,8-TriCDD has a calc I external structure/H polar group ratio of 5.25, and a nl calc I external structure/H polar group quotient of 1.91. 8-O-glucuronide;2,3,7,8-TriCDD has a calc I external structure/H polar group ratio of 1.15, and a nl calc I external structure/H polar group quotient of 0.419. 2',5',5',6'-ortho-planar PCB-95 (C₁₂H₅Cl₅) has a Log P of 6.76, a vdWD of 0.737 nm and a Log P/vdWD of 9.17 nm⁻¹ (Table 4). 3,4',5',5'- co-planar PCB-126 (C₁₂H₅Cl₅) has a Log P of 6.69, a vdWD of 0.749 nm and a Log P/vdWD of 8.94 nm⁻¹ (Table 4).
Dodecan-1-ol (C\textsubscript{12}H\textsubscript{26}O) has a Log P of 4.36, a vDW of 0.744 nm and a Log P/vdWD of 5.86 nm\textsuperscript{-1} (Table 4).

Dodecan-1-ol (C\textsubscript{12}H\textsubscript{26}O) has a Log P of 4.36, a vDW of 0.744 nm and a Log P/vdWD of 5.86 nm\textsuperscript{-1} (Table 4).

3,5,3’,5’-Iodothyroxine (C\textsubscript{13}H\textsubscript{11}I\textsubscript{4}NO\textsubscript{4}) has a Log P of 3.73, a vDW of 0.745 nm and a Log P/vdWD of 5.00 nm\textsuperscript{-1} (Table 4). Iodothyroxine has a calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ ratio of 1.625, and a nl calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ quotient of 0.591. (4’-hydroxy-3’,5’-diiodophe-noxy)-1-ethyl-3,5-diiodophenyl (non-zwitterion part $T_D$) has a calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ ratio of 8.92, and a nl calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ quotient of 3.24.

4’-OH-2,3,3’,4,5-PCB-106 (C\textsubscript{12}H\textsubscript{32}O) has a Log P of 6.34, a vDW of 0.752 nm and a Log P/vdWD of 8.43 nm\textsuperscript{-1} (Table 4).

van der Waals diameter and structural lipophilicity parameters of small molecules in the molecular size-exclusion range

2’,3,4,4’,5,6-PCB-153 (C\textsubscript{12}H\textsubscript{32}O) has a Log P of 7.24, a vDW of 0.758 nm and a Log P/vdWD of 9.55 nm\textsuperscript{-1} (Table 5).

Tridecan-1-ol (C\textsubscript{13}H\textsubscript{28}O) has a Log P of 4.81, a vDW of 0.762 nm and a Log P/vdWD of 6.31 nm\textsuperscript{-1} (Table 5).

4’-OH-3,3’,4,5,5’,6-ortho-planar PCB-136 (C\textsubscript{12}H\textsubscript{32}O) has a Log P of 7.04, a vDW of 0.767 nm and a Log P/vdWD of 9.18 nm\textsuperscript{-1} (Table 5).

Bisphenol AF (BFAF, C\textsubscript{15}H\textsubscript{10}F\textsubscript{14}O\textsubscript{2}) has a Log P of 4.77, a vDW of 0.774 nm and a Log P/vdWD of 6.17 nm\textsuperscript{-1}. 1,1,3,3,3-hexafluoro-2-phenylpropan-2-yl (C\textsubscript{15}H\textsubscript{10}F\textsubscript{6}) has a Log P of 5.38, a vDW of 0.756 nm and a Log P/vdWD of 7.12 nm\textsuperscript{-1}. Bisphenol AF has a calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ ratio of 3.39, and a nl calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ quotient of 1.23 (Table 5).

Table 5. Small molecules in the molecular size-exclusion range at the cell membrane channel pore with extracellular effects on nuclear pathways via transmembrane receptor or protein affinity interactions.

| Small molecule | Formula | Log P | Molecular Weight (Da) | Size (Ang\textsuperscript{-1}) | vDW (nm) | Polar SA (Ang\textsuperscript{-1}) | Log P/vdWD (nm\textsuperscript{-1}) |
|----------------|---------|-------|-----------------------|-------------------------------|---------|----------------------------|-------------------------------|
| 2’,3,4,4’,5,6-PCB-153 | C\textsubscript{12}H\textsubscript{32}O | 7.24 | 358 | 236 | 0.758\textsuperscript{b} | - | 9.55 |
| Tridecan-1-ol | C\textsubscript{13}H\textsubscript{28}O | 4.81 | 200 | 241 | 0.762\textsuperscript{a} | 20 | 6.31 |
| 4’-OH-ortho-planar PCB-136 | C\textsubscript{12}H\textsubscript{32}O | 7.04\textsuperscript{c} | 376 | 245 | 0.767 | 20 | 9.18 |
| Bisphenol AF | C\textsubscript{15}H\textsubscript{10}F\textsubscript{14}O\textsubscript{2} | 4.77 | 336 | 252 | 0.774 | 40 | 6.17 |
| 2,2’,4,4’,6-PBDE-100 | C\textsubscript{12}H\textsubscript{32}Br\textsubscript{5} | 7.32 | 560 | 271 | 0.775 | 9 | 9.44 |
| Acetochlor | C\textsubscript{12}H\textsubscript{29}Cl\textsubscript{2}NO\textsubscript{2} | 3.50 | 269 | 256 | 0.778 | 30 | 4.50 |
| 4’-OH-2,3,3’,4,5,5’,6-PCB-172 | C\textsubscript{12}H\textsubscript{32}Cl\textsubscript{2}O | 7.55 | 421 | 259 | 0.781 | 20 | 9.92 |
| Di-\textit{n}-butyl phthalate | C\textsubscript{12}H\textsubscript{23}O\textsubscript{4} | 4.63 | 278 | 275 | 0.797 | 53 | 5.81 |
| 4’-CH\textsubscript{3}-SO\textsubscript{2}-ortho-planar PCB-132 | C\textsubscript{13}H\textsubscript{32}Cl\textsubscript{2}O\textsubscript{2} | 6.09 | 436 | 290 | 0.811 | 34 | 7.51 |
| \textit{trans}-retin-1-ol | C\textsubscript{20}H\textsubscript{30}O | 4.69 | 286 | 310 | 0.829 | 20 | 5.66 |
| $\alpha$-tocopherol | C\textsubscript{29}H\textsubscript{48}O\textsubscript{2} | 10.51 | 430 | 481 | 0.960 | 18 | 10.95 |

\textsuperscript{1} Bisphenol AF (BFAF) external structure is 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-yl within the nl calc $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ quotient range of 1.17 (BPC)–1.23 (BPAF) for mid-to-high binding to ER\textsubscript{α}/ER\textsubscript{β} (Acetochlor, L–H \textsuperscript{-1} 1.16).

\textsuperscript{2} \textit{trans}-retin-1-ol with a van der Waals diameter (vDW) at 0.829 nm is a specific substrate for the cell membrane STRA6 transporter; and

\textsuperscript{3} lower limit of range for molecular size-exclusion at the transmembrane channel pore as determined by elliptical small molecules, range 0.742–0.762 nm, and \textsuperscript{b}

\textsuperscript{4} upper limit of range for molecular size-exclusion at the cell membrane channel pore as determined by ellipsoid small molecules, range 0.752–0.758 nm; and \textsuperscript{b}

\textsuperscript{5} the upper limit of $\text{I}_{\text{external structure}}/\text{H}_{\text{polar group}}$ for PCB metabolites is 3.91 (4’-OH-2,2’,3,3’,4,5,5’,6-PCB-208), UL \textsuperscript{a} Log P values for 4’-OH-ortho-planar PCB-136 (isomer, 2’-OH-co-planar PCB-169), calculated weighted average determined from ACD/Labs, EPI suite, chemicalize and/or PubChem databases as applicable; PBDE, polybrominated diphenyl ether BDE-100.

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2,2′,4,4′,6-PBDE-100 (C₁₂H₁₀Br₃) has a Log P of 7.32, a vdWD of 0.775 nm and a Log P/vdWD of 9.44 nm⁻¹ (Table 5).

Acetochlor (C₁₂H₂₀Cl₃NO₂) has a Log P of 3.50, a vdWD of 0.778 nm and a Log P/vdWD of 4.50 nm⁻¹. n-(1-chloroethyl)-n-(2-ethoxymethyl)-2-methyl-6-ethylaniline has a Log P of 4.18, a vdWD of 0.758 nm and a Log P/vdWD of 5.43 nm⁻¹. Acetochlor has a calc I_{external structure}/P_{polar group} ratio of 3.20, and a nl calc I_{external structure}/P_{polar group} quotient of 1.16 (Table 5).

4'-OH-2,3,3',4,5,5',6'-PCB-172 (C₁₂H₂Cl₃O) has a Log P of 7.55, a vdWD of 0.781 nm and a Log P/vdWD of 9.92 nm⁻¹ (Table 5).

Di-n-butyl phthalate (DBP; C₁₄H₂₂O₄) has a Log P of 4.63, a vdWD of 0.797 nm and a Log P/vdWD of 5.81 nm⁻¹ (Table 5). DBP has a calc I_{external structure}/P_{polar group} ratio of 4.099, and a nl calc I_{external structure}/P_{polar group} quotient of 1.491.

4'-CH₃-SO₂-ortho-planar PCB-132 (C₁₃H₆Cl₆O₂S) has a Log P of 6.09, a vdWD of 0.811 nm and a Log P/vdWD of 7.51 nm⁻¹ (Table 5).

trans-retin-1-ol (C₂₀H₃₀O) has a Log P of 4.69, a vdWD of 0.829 nm and a Log P/vdWD of 5.66 nm⁻¹ (Table 5). trans-retin-1-ol has a calc I_{external structure}/P_{polar group} ratio of 6.914, and a nl calc I_{external structure}/P_{polar group} quotient of 2.54. trans-retinoic acid has a calc I_{external structure}/P_{polar group} ratio of 9.913, and a nl calc I_{external structure}/P_{polar group} quotient of 3.32.

α-tocopherol (C₂₀H₃₀O₂) has a Log P of 10.51, a vdWD of 0.960 nm and a Log P/vdWD of 10.95 nm⁻¹ (Table 5). α-tocopherol has a calc I_{external structure}/P_{polar group} ratio of 8.018, and a nl calc I_{external structure}/P_{polar group} quotient of 2.92. 13'-O-glucuronide-α-tocopherol (C₁₆H₂₂O₄) has a calc I_{external structure}/P_{polar group} ratio of 1.26, and a nl calc I_{external structure}/P_{polar group} quotient of 0.459.

Gene expression effective pressure mapping for small molecule chlorinates that are cell membrane, rough endoplasmic membrane enzyme or orphan nuclear receptor substrates

2,3,7,8-tetrachlorodibenzop-p-dioxin (Tcdd). AHR is a 5 A 9 ACM final SEB gene at x-, y-vertical axis angulation 42.3°. AHR has an uppassebssiwaa, dppassebssiwaa, uppmsesebsi with dppmsebsiwi of 7.173E + 03, 7.2908E + 04, 1.71804E ± 05 and 3.79987E ± 05 intergene bases. AHR has an uppasebssiwaa and dppesebssiwaa of 8.9488E + 04 and 2.26448E ± 05 intergene bases with a P_{eff} of 0.395 ebsesiwaagoTₐ units (Table 6).

COX8C is a 4 M 9 initial and final SEB gene at x-, y-vertical axis angulation 44.0°. COX8C has an uppassebssiwaa, dppassebssiwaa, uppmsesebsi with dppmsebsiwi of 9.8211E ± 04, 1.71795E ± 05, 7.786E ± 03 and 1.06511E ± 05 intergene bases. COX8C has an uppasebssiwaa and dppesebssiwaa of 5.2998E ± 04 and 1.39153E ± 05 intergene bases with a P_{eff} of 0.381 ebsesiwaagoTₐ units (Table 6).

CEACAM1 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 44.2° (act). CEACAM1 has an uppassebssiwaa, dppassebssiwaa, uppmsesebsi with dppmsebsiwi of 6.3333E ± 04, 1.31731E ± 05, 1.4468E ± 04, 7.3384E ± 04 intergene bases (act). CEACAM1 has an uppasebssiwaa and dppesebssiwaa of 3.8900E ± 04 and 1.02558E ± 05 intergene bases with a P_{eff} of 0.379 ebsesiwaagoTₐ units (act) (Table 6).

SLC2A4 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 44.6°. SLC2A4 has an uppassebssiwaa, dppassebssiwaa, uppmsesebsi with dppmsebsiwi of 1.5426E ± 04, 2.7907E ± 04, 917 and 1.5607E ± 04 intergene bases. SLC2A4 has an uppasebssiwaa and dppesebssiwaa of 8.172E ± 04 and 2.1757E ± 04 intergene bases with a P_{eff} of 0.376 ebsesiwaagoTₐ units (Table 6).

RXRA is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 44.8°. RXRA has an uppassebssiwaa, dppassebssiwaa, uppmsesebsi with dppmsebsiwi of 3.7754E ± 04, 7.2478E ± 04
Table 6. Effective intracellular pressure mapping of gene activation by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) via the AhR-Erf (Arnt); Nrf-2: Pparδ, Errγ (LxRα): Dio3/Dio2 (Tru) pathway.

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppesebsiwaun, uppesebsiwaun (Pabar, fract) | Pabar range effect fract (Δ%) |
|---------------------------------------------|-------------------------|-----------|-----------------------------------------------|------------------------------------------|-------------------------------|
| AHR, aryl hydrocarbon receptor (429,794; 550,898) | 7p21.1 (+) | 42.3 | 5 A 9 stIMIM, acm (5 A 11) | 8.9488E + 04, 2.26448E + 05 (0.395) | (+) |
| COX8C, cytochrome C oxidase subunit 8C (1,166; 374,660) | 14q22.12 (+) | 44.0 | 4 M 9 (-) | 5.2998E + 04, 1.39153E + 05 (0.381) | (+10.2) |
| CEACAM1, carcinoembryonic antigen related cell adhesion molecule 1 (53,931; 54,447) | 19q13.2 (–) | 44.2 | 2 M 5 (-) | 3.890OE + 04, 1.02558E + 05 (0.379) | (+20.3) |
| SLC2A4 (Glut-4), solute carrier family 2 member 4 (6,540; n/a) | 17p13.1 (+) | 44.6 | 3 M 7 (-) | 8.172E + 03, 2.1757E + 04 (0.376) | (+) |
| RXRA, retinoid X receptor alpha (123,489; n/a) | 9q34.3 (+) | 44.8 | 2 M 5 (-) | 2.2689E + 04, 6.0662E + 04 (0.374) | (+) |
| NR1D1, nuclear receptor subfamily 1 group D member 1 (7,942; n/a) | 17q21.2 (-) | 44.9 | 3 M 7 ext (-) | 1.7961E + 04, 4.8106E + 04 (0.373) | (+0.16) |
| DAO, d-α-amino acid oxidase | 12q24.11 (+) | 48.9 | 2 M 5 (-) | 3.0313E + 04, 8.6996E + 04 (0.348) | (-) |
| PPARD, peroxisome proliferator-activated receptor delta (85,634; n/a) | 6p21.31 (+) | 49.0 | 2 M 5 (-) | 1.7924E + 04, 5.2800E + 04 (0.339) | (+) |
| GADD45B, growth arrest and DNA damage inducible beta (275,458; n/a) | 19p13.3 (+) | 49.9 | 4 M 5 stIMia acm, nca acm (4 M 9) | 2.0045E + 04, 6.0366E + 04 (0.332) | (+) |
| ALAS1, 5-α-methylolulinate synthase 1 (16,245;18,054) | 3p21.2 (+) | 50.9 | 2 A 5 (-) | 1.5772E + 04, 4.8734E + 04 (0.324) | (-) |
| DBP, D-box binding PAR EZIP transcription factor (7,521; n/a) | 19q13.33 (-) | 55.8 | 3 A 7 (-) | 1.3046E + 04, 4.6054E + 04 (0.283) | (+0.3) |
| SCD, stearoyl-coenzyme A desaturase (17,817; 107,029) | 10q24.2 (+) | 56.0 | 2 M 5 (-) | 2.6206E + 04, 9.3046E + 04 [0.282 (0.2816)] | (+0.16) |
| RXRB, retinoic acid receptor B (7,269; 328,916) | 6p21.8 (-) | 56.0 | 4 A 7 acm (4 A 9) | 2.3576E + 04, 8.3743E + 04 [0.282 (0.2815)] | (+) |
| PPARGC1A, PPARG coactivator alpha (829,563; n/a) | 4p15.2 (-) | 56.3 | 6 M 13 (-) | 1.20545E + 05, 4.32277E + 05 (0.279) | -- |
| MTJ1A, metallothionein 1A (1,422; n/a) | 16q13 (+) | 57.0 | 3 M 7 (-) | 1.0479E + 04, 3.8405E + 04 (0.273) | (+0.07) |
| SREBF1, sterol regulatory element binding transcription factor 1 (6,219; n/a) | 17p11.2 (-) | 61.4 | 2 M 5 (-) | 1.2714E + 04, 5.3646E + 04 (0.237) | -- |
| DIO1, dehydrogenase I (21,520; 19,848) | 1p32.3 (+) | 61.5 | 2 A 4 nca (2 A 5) | 1.8591E + 04, 7.8810E + 04 (0.236) | .CM |
| FABP5, fatty acid binding protein 5 (4,295; n/a) | 8q21.13 (-) | 63.0 | 3 M 7 (-) | 3.2236E + 04, 1.44208E + 05 (0.224) | (+0.07) |
| TIPARP, TCDD inducible poly(ADP-ribose) polymerase (33,556; n/a) | 3q25.31 (+) | 63.1 | 2 A 4 nca stIMIM (2 A 5) | 1.9209E + 04, 8.6191E + 04 [0.223 (0.2233)] | (+) |
| SIN3A, SIN3 transcription regulator family member A (86,484; n/a) | 15q24.1 (-) | 63.0 | 2 M 7 acm (2 M 5) | 1.3371E + 04, 5.9872E + 04 [0.223 (0.2229)] | (+) |
| PPARG, peroxisome proliferator-activated receptor gamma (268,877; n/a) | 3p25.2 (+) | 63.2 | 2 M 5 (-) | 2.6689E + 04, 1.20354E + 05 (0.222) | -- ** |
| RARB, retinoic acid receptor B (423, 601; n/a) | 3p24.2 (+) | 63.2 | 4 A 9 (-) | 3.6064E + 04, 1.62543E + 05 (0.222) | (+) |
| CYP1A1, cytochrome P450, family 1, subfamily A, polypeptide 1 (6,069; n/a) | 15q24.1 (-) | 63.9 | 3 A 7 (-) | 1.0633E + 04, 4.9247E + 04 (0.216) | (+33.5) |
| NRIHI3, nuclear receptor subfamily 1 group H member 3 (20,734; n/a) | 11p11.12 (+) | 64.7 | 2 M 7 acm (2 M 5) | 1.0224E + 04, 4.8803E + 04 [0.209 (0.2095)] | (+) |
| ESRRG, estrogen related receptor gamma (634,510; n/a) | 1q11 (-) | 64.7 | 5 A 9 acm (5 A 11) | 4.6694E + 04, 2.23137E + 05 [0.209 (0.2093)] | (±0.5) |
| CYP1A2, cytochrome P450, family 1, subfamily A2 (7,765; n/a) | 15q24.1 (+) | 65.7 | 3 A 9 acm (3 A 7) | 1.5646E + 04, 7.7758E + 04 (0.201) | (+0.10) |
| NRF1, nuclear respiratory factor 1 (145,381; n/a) | 7q32.2 (+) | 65.8 | 2 A 5 (-) | 2.0850E + 04, 1.04212E + 05 (0.200) | (-) |
| ESRRα, estrogen related receptor alpha (11,220; n/a) | 11q13.1 (+) | 66.8 | 3 M 9 acm (3 M 7) | 7.796E + 03, 3.9699E + 04 (0.196) | (±0.7) |

(Continued)
### Table 6. (Continued)

| Gene | Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppsebssiwana, dppebssiwana (Peff, fract) | Peff range effect fract (Δ %) |
|------|---------------------------------------------|-------------------------|----------|-----------------------------------------------|------------------------------------------|--------------------------------|
| ARNTL, ARNT like factor (111,160; n/a) | 11p15.3 (+) | 66.9 | 2 M 5 (-) | 1.5097E + 04, 7.8855E + 04 (0.192) | (+) |
| EXOC7, exocyst complex component 7 (40,584; 51,507) | 17q25.1 (-) | 67.1 | 3 M 9 (3 M 7) | 3.692E + 03, 1.947E + 04 (0.190) | (+1.05) |
| ESR1, estrogen receptor alpha (472,929; n/a) | 6q25.1 (+) | 68.0 | 4 A 9 acm nca (4 A 9) | 5.0063E + 04, 2.7263E + 05 (0.184) | (-) |
| DIO2, iodothyronine deiodinase 2 (190,233; n/a) | 14q24.2 (-) | 68.5 | 4 M 9 (-) | 1.5758E + 04, 8.6969E + 04 (0.178) | (+) |
| RARA, retinoic acid receptor, alpha (48,473; n/a) | 17q21.2 (+) | 68.4 | 2 M 5 (-) | 1.9801E + 04, 1.0935E + 05 (0.173) | (+) |
| NCOR2, nuclear receptor corepressor 2 (243,179; 355,292) | 17q24.2 (-) | 68.5 | 4 M 9 (-) | 1.5557E + 04, 8.7918E + 04 (0.177) | (+) |
| NRIP1, Nuclear receptor interacting protein 1 (104,702; 248,423) | 21q11.2 (-) | 69.1 | 2 M 7 acm (2 M 5) | 1.41470E + 05, 8.15738E + 05 (0.173) | (+) |
| CYP1B1, cytochrome P450, family 3, subfamily A, polypeptide 1 (42,930; 565,830) | 2p22.2 (-) | 69.6 | 5 M 11 (-) | 6.1304E + 04, 3.63307E + 05 (0.169) | (+24.3) |
| ALDH3A1, aldehyde dehydrogenase family, polypeptide A6 (10,960; n/a) | 17p12.1 (-) | 69.7 | 2 A 7 (-) | 1.0360E + 04, 6.1604E + 04 (0.168) | (+1.9) |
| ACSM2A, acyl-CoA synthetase medium chain family member 2A (36,209; n/a) | 16p12.3 (+) | 70.9 | 2 A 5 (-) | 1.5522E + 04, 6.6500E + 04 (0.158) | (-) |
| HMOX1 | [0.153 (0.1331)] | (+) |
| NQO1, NAD(P)H dehydrogenase quinone 1 (19,673; n/a) | 16q22.11 (-) | 72.2 | 2 A 5 (-) | 1.8473E + 04, 1.2530E + 05 (0.147) | (+0.65) |
| ESR2, estrogen receptor beta (254,319; 254,368) | 14q23.2-q23.3 (-) | 73.6 | 2 A 5 (-) | 1.3835E + 04, 1.0162E + 05 (0.136) | (+) |
| MEI, malic enzyme 1 (221,353; n/a) | 6q14.2 (-) | 73.7 | 2 M 5 (-) | 3.9550E + 04, 2.9230E + 05 (0.135) | (+0.10) |
| CYP3A7, cytochrome P450, family 3, subfamily A, polypeptide 1 (50,244; 50,522) | 7q22.1 (-) | 76.6 | 2 M 5 (-) | 2.1824E + 04, 1.9724E + 05 (0.112) | (-) |
| UGT1A7, UDP glucuronosyltransferase family member A7 (81,699; 187,867) | 2q31.1 (+) | 77.2 | 2 M 5 ext (2 M 5) | 2.9540E + 04, 2.7760E + 05 (0.106) | (+2.8) |
| DIO3, deiodinase type 3 (2,102; n/a) | 14q32.3 (+) | 78.4 | 2 A 5 (-) | 3.504E + 04, 3.638E + 04 (0.096) | (+) |
| IGGM, immunoglobulin heavy chain M (4,511; n/a) | 14q32.3 (-) | - | - | (-0.088) | (--) |
| ARNT,aryl hydrocarbon receptor nuclear translocator (67,064; n/a) | 1q21.3 (+) | 82.4 | 2 A 5 | 4.287E + 04, 6.7882E + 04 (0.063) | -- |
| TPAN14, tetraspan 14 (79,316; n/a) | 10q23.1 (+) | 83.1 | 2 A 8 acm acm (2 A 5) | 1.4992E + 04, 2.6365E + 05 (0.057) | -- |

* % dec in effect genes include DA0I, -4.1; ALAS1, - 0.54; ACSM2A, -7.0; CYP3A7, -37.6; and DIO2, -0.54 (2-fold change threshold)
* CEACAM1, SCD, COX8A and CYP3A7 are respective orthologs (pred) of rodent CEACAM10, SCD2, COX8H and CYP3A13
* actual
* **ESRRG initial under-activation during EXOC7 protein expression phase, while ESRRG overactivation**
* □ Baseline decrease at Peff duration during acute applied exposure (hours) *in vitro*
* "**NcoR2 and PPARγ interaction**" **RARA and ERRγ interaction** *NFIB repression of PCK1 transcription factor decreases (as cited)
* Activation of MEI gene at TRx response element (TRE) increases, as does DBP gene activation containing both TRE and ERRα/E RE (not determined, n.d.)
* "**RIP140 (NRIP1) as co-activator for AHR-ERRα/β and ERR transcription factors; and ** PPARGCIα (PGC1α) as co-activator for PPARG and SREBF1 transcription factors Note(s): 1) Gene loci sub-episode block structure (SEB) variations include: non-contributory anisotropy (NCA), anisotropy converted to mesotropy (ACM), 0.5-factor adjusted stabilizing mesotropy or anisotropy converted to stabilizing isotropy for anisotropy or mesotropy (stIAM, stIMA or stIMM), and/or extended block (ext) SEB; and 2) gene(s) with previously reported episode and sub-episode block structure include CEACAM1 (unadj), NFE2L2 (NRF-2), NRF1 [22] and IGGM [38].
04, 7.624E + 03 an 4.8816E + 04 intergene bases. RXRA has an uppesebssiwa and dppebssiwa of 2.2689E + 04 and 6.0662E + 04 intergene bases with a $P_{\text{eff}}$ of 0.374 esebsiwaagoT$Q$ units (Table 6).

NR1D1 is a 3 M 7 ext final SEB gene at $x$-, $y$-vertical axis angulation 44.9°. NR1D1 has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 3.2742E + 04, 6.6932E+ 04, 3.181E + 03 and 2.9279E + 04 intergene bases. NR1D1 has an uppesebssiwa and dppebssiwa of 1.7961E + 04 and 4.8106E + 04 intergene bases with a $P_{\text{eff}}$ of 0.373 esebsiwaagoT$Q$ units (Table 6).

DAO is a 2 M 5 initial and final SEB gene at $x$-, $y$-vertical axis angulation 47.9°. DAO has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 6.0186E +04, 1.15409E + 05, 440 and 6.0583E + 04 intergene bases. DAO has an uppesebssiwa and dppebssiwa of 3.0313E + 04 and 8.6996E + 04 intergene bases with a $P_{\text{eff}}$ of 0.348 esebsiwaagoT$Q$ units (Table 6).

PPARD is a 2 M 5 initial and final SEB gene at $x$-, $y$-vertical axis angulation 49.0°. PPARD has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 3.3902E + 04, 7.5097E + 04, 1.946E + 03 and 3.0504E + 04 intergene bases. PPARD has an uppesebssiwa and dppebssiwa of 1.7924E + 04 and 5.2800E + 04 intergene bases with a $P_{\text{eff}}$ of 0.339 esebsiwaagoT$Q$ units (Table 6).

GADD45B is a 4 M 5 stIMfa, ACM, NCA ACM final SEB gene at $x$-, $y$-vertical axis angulation 49.9°. GADD45B has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 3.8061E + 04, 9.8594E + 04, 2.029E + 03 and 2.2138E + 04 intergene bases. GADD45B has an uppesebssiwa and dppebssiwa of 2.0045E + 04 and 6.0366E + 04 intergene bases with a $P_{\text{eff}}$ of 0.332 esebsiwaagoT$Q$ units (Table 6).

ALAS1 is a 2 A 5 initial and final SEB gene at $x$-, $y$-vertical axis angulation 50.9°. ALAS1 has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 3.9292E + 03, 2.9633E + 04, 2.7615E + 04 and 6.7836E + 04 intergene bases. ALAS1 has an uppesebssiwa and dppebssiwa of 1.5772E + 04 and 4.8734E + 04 intergene bases with a $P_{\text{eff}}$ of 0.324 esebsiwaagoT$Q$ units (Table 6).

DBP is a 3 A 7 initial and final SEB gene at $x$-, $y$-vertical axis angulation 55.8°. DBP has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 2.499E + 03, 4.4612E + 04, 2.3594E + 04 and 4.7496E + 04 intergene bases. DBP has an uppesebssiwa and dppebssiwa of 1.3046E + 04 and 4.6054E + 04 intergene bases with a $P_{\text{eff}}$ of 0.283 esebsiwaagoT$Q$ units (Table 6).

RXRB is a 4 A 7 final SEB gene at $x$-, $y$-vertical axis angulation 56.0°. RXRB has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 8.075E + 03, 8.3710E + 04, 3.9078E + 04 and 8.3775E + 04 intergene bases. RXRB has an uppesebssiwa and dppebssiwa of 2.3576E + 04 and 8.3743E + 04 intergene bases with a $P_{\text{eff}}$ of 0.282 esebsiwaagoT$Q$ units (Table 6).

PPARGC1A is a 6 M 13 initial and final SEB gene at $x$-, $y$-vertical axis angulation 56.3°. PPARGC1A has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 1.98293E + 05, 4.43060E + 05, 4.21495E + 05 intergene bases. PPARGC1A has an uppesebssiwa and dppebssiwa of 1.20545E + 05 and 4.32277E + 05 intergene bases with a $P_{\text{eff}}$ of 0.279 esebsiwaagoT$Q$ units (Table 6).

SCD is a 2 M 5 initial and final SEB gene at $x$-, $y$-vertical axis angulation 56.9°. SCD has an uppasebssiwa, dppebssiwa, uppmsebssiwa and dppmsebssiwa of 4.0705E + 04, 7.4127E + 04, 1.1708E + 04 and 1.11966E + 05 intergene bases. SCD has an uppesebssiwa and dppebssiwa of 2.6206E + 04 and 9.3046E + 04 intergene bases with a $P_{\text{eff}}$ of 0.282 esebsiwaagoT$Q$ units (Table 6).
MT1A is a 3 M 7 initial and final SEB gene at x-, y-vertical axis angulation 57.0°. MT1A has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.9593E + 04, 4.5208E + 04, 1.365E + 03 and 3.1603E + 04 intergene bases. MT1A has an uppasebssiwaa and dppsebssiwaa of 1.0479E + 04 and 3.8405E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.223 esebsisiwaago\( T_Q \) units (Table 6).

SREPF1 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 61.4°. SREPF1 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.6701E + 04, 4.6217E + 04, 8.727E + 03 and 6.1076E + 04 intergene bases. SREPF1 has an uppasebssiwaa and dppsebssiwaa of 1.2714E + 04 and 5.3646E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.237 esebsisiwaago\( T_Q \) units (Table 6).

DIO1 is a 2 A 4 NCA final SEB gene at x-, y-vertical axis angulation 60.7°. DIO1 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 3.0841E + 04, 8.6335E + 04, 6.342E + 03 and 7.1284E + 04 intergene bases. DIO1 has an uppasebssiwaa and dppsebssiwaa of 1.8591E + 04 and 7.8810E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.236 esebsisiwaago\( T_Q \) units (Table 6).

FABP5 is a 3 M 7 initial and final SEB gene at x-, y-vertical axis angulation 63.9°. FABP5 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 5.2075E + 04, 1.38023E + 05, 1.2397E + 04 and 1.50392E + 05 intergene bases. FABP5 has an uppasebssiwaa and dppsebssiwaa of 3.2236E + 04 and 4.5892E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.224 esebsisiwaago\( T_Q \) units (Table 6).

TIPARP is a 2 A 4 NCA stIMfM final SEB gene at x-, y-vertical axis angulation 63.1°. TIPARP has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 2.8072E + 04, 1.44556E + 05, 1.7547E + 04 and 2.7819E + 04 intergene bases. TIPARP has an uppasebssiwaa and dppsebssiwaa of 1.9209E + 04 and 8.6191E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.223 esebsisiwaago\( T_Q \) units (Table 6).

SIN3A is a 2 M 7 NCA final SEB gene at x-, y-vertical axis angulation 63.0°. SIN3A has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 2.2660E + 04, 5.6611E + 04, 4.082E + 03 and 6.3132E + 04 intergene bases. SIN3A has an uppasebssiwaa and dppsebssiwaa of 1.3371E + 04 and 5.9872E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.223 esebsisiwaago\( T_Q \) units (Table 6).

PPARG is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 63.2°. PPARG has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 5.1238E + 04, 9.3514E + 04, 2.140E + 03 and 1.4719E + 05 intergene bases. PPARG has an uppasebssiwaa and dppsebssiwaa of 2.6689E + 04 and 1.20354E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.222 esebsisiwaago\( T_Q \) units (Table 6).

RARB is a 4 A 9 initial and final SEB gene at x-, y-vertical axis angulation 63.2°. RARB has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 2.6685E + 04, 2.28760E + 04, 4.5444E + 04 and 9.6325E + 04 intergene bases. RARB has an uppasebssiwaa and dppsebssiwaa of 3.6064E + 04 and 1.62543E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.222 esebsisiwaago\( T_Q \) units (Table 6).

CYP1A1 is a 3 A 7 initial and final SEB gene at x-, y-vertical axis angulation 63.9°. CYP1A1 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.620E + 03, 5.2602E + 04, 1.9646E + 04 and 4.5892E + 04 intergene bases. CYP1A1 has an uppasebssiwaa and dppsebssiwaa of 1.0633E + 04 and 4.9247E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.216 esebsisiwaago\( T_Q \) units (Table 6).

CYP1A2 is a 3 A 9 ACM final SEB gene at x-, y-vertical axis angulation 65.7°. CYP1A2 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.1688E + 04, 1.11934E + 05, 1.9604E + 04 and 4.3582E + 04 intergene bases. CYP1A2 has an uppasebssiwaa and
of 3.692E + 03 and 1.9475E + 04 intergene bases with a P_{eff} of 0.209 esebssiwaagoT_{Q} units (Table 6).

NR1H3 is a 2 M 7 ACM final SEB gene at x-, y-vertical axis angulation 64.7°. NR1H3 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 8.803E + 03, 9.694E + 04, 3.1126E + 04 and 4.10031E + 05 intergene bases. NR1H3 has an uppasebssiwa and dppasebssiwa of 1.0224E + 04 and 4.8803E + 04 intergene bases with a P_{eff} of 0.209 esebssiwaagoT_{Q} units (Table 6).

NRF1 is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 65.8°. NRF1 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 8.3287E + 04, 3.11479E + 05 intergene bases. NRF1 has an uppasebssiwa and dppasebssiwa of 2.0850E + 04 and 1.04212E + 05 intergene bases with a P_{eff} of 0.200 esebssiwaagoT_{Q} units (Table 6).

ESR1 is a 2 M 7 ACM final SEB gene at x-, y-vertical axis angulation 64.7°. ESR1 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 8.038E + 04, 2.3346E + 04, 8.567E + 03 and 7.4260E + 04 intergene bases. ESR1 has an uppasebssiwa and dppasebssiwa of 1.9801E + 04 and 1.09351E + 05 intergene bases with a P_{eff} of 0.209 esebssiwaagoT_{Q} units (Table 6).

EXOC7 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 67.1°. EXOC7 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 5.265E + 03, 9.381E + 03, 2.119E + 03 and 2.9570E + 04 intergene bases. EXOC7 has an uppasebssiwa and dppasebssiwa of 3.692E + 03 and 1.9475E + 04 intergene bases with a P_{eff} of 0.190 esebssiwaagoT_{Q} units (Table 6).

ESRRA is a 3 M 9 ACM final SEB gene at x-, y-vertical axis angulation 64.7°. ESRRA has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 9.619E + 03, 2.5863E + 04, 5.972E + 03 and 5.3354E + 04 intergene bases. ESRRA has an uppasebssiwa and dppasebssiwa of 3.9699E + 04 and 3.9699E + 04 intergene bases with a P_{eff} of 0.196 esebssiwaagoT_{Q} units (Table 6).

ARNTL is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 66.9°. ARNTL has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.7408E + 04, 4.4697E + 04, 1.2785E + 04 and 1.13014E + 05 intergene bases. ARNTL has an uppasebssiwa and dppasebssiwa of 1.5097E + 04 and 7.8855E + 05 intergene bases with a P_{eff} of 0.191 esebssiwaagoT_{Q} units (Table 6).

EXOC7 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 67.1°. EXOC7 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 8.038E + 04, 9.694E + 04, 2.119E + 03 and 3.26647E + 05 intergene bases. EXOC7 has an uppasebssiwa and dppasebssiwa of 3.9699E + 04 and 9.6944E + 04 intergene bases with a P_{eff} of 0.191 esebssiwaagoT_{Q} units (Table 6).

ESR1 is a 4 A 9 ACM (-2) NCA (+2) final SEB gene at x-, y-vertical axis angulation 67.8°. ESR1 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.4317E + 04, 3.26647E + 05, 7.5809E + 04 and 2.18623E + 05 intergene bases. ESR1 has an uppasebssiwa and dppasebssiwa of 5.0063E + 04 and 2.72635E + 05 intergene bases with a P_{eff} of 0.184 esebssiwaagoT_{Q} units (Table 6).

DIO2 is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 67.9°. DIO2 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 3.1126E + 04, 4.10031E + 05, 6.5612E + 04 and 1.19045E + 05 intergene bases. DIO2 has an uppasebssiwa and dppasebssiwa of 4.8369E + 04 and 2.64538E + 05 intergene bases with a P_{eff} of 0.183 esebssiwaagoT_{Q} units (Table 6).

RARA is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 68.1°. RARA has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.0934E + 04, 1.76592E + 05, 1.8669E + 04 and 4.2109E + 04 intergene bases. RARA has an uppasebssiwa and dppasebssiwa of 1.9801E + 04 and 1.09351E + 05 intergene bases with a P_{eff} of 0.181 esebssiwaagoT_{Q} units (Table 6).

NCOR2 is a 4 M 9 initial and final SEB gene at x-, y-vertical axis angulation 68.5°. NCOR2 has an uppasebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.6316E + 04, 3.4858E + 04 and 7.7758E + 04 intergene bases with a P_{eff} of 0.210 esebssiwaagoT_{Q} units (Table 6).
+ 04, 1.52E + 04 and 1.42541E + 05 intergene bases. *NCOR2* has an *uppesebsiwa* and *dppe-sebsiwa* of 1.5758E + 04 and 8.8699E + 04 intergene bases with a $P_{\text{eff}}$ of 0.178 *esebsiwaagoT_Q* units (Table 6).

*THRA* is a 2 M 7 ACM final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 68.6°. *THRA* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 2.1732E + 04, 4.7912E + 04, 9.383E + 03 and 1.27923E + 05 intergene bases. *THRA* has an *uppesebsiwa* and *dppebsiwa* of 1.5557E + 04 and 8.7918E + 04 intergene bases with a $P_{\text{eff}}$ of 0.177 *esebsiwaagoT_Q* units (Table 6).

*NRIPI* is a 2 M 7 ACM final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 69.1°. *NRIPI* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 2.36743E + 05, 5.72072E + 05, 4.6198E + 04 and 1.059404E + 06 intergene bases. *NRIPI* has an *uppesebsiwa* and *dppebsiwa* of 1.41470E + 05 and 8.15738E + 05 intergene bases with a $P_{\text{eff}}$ of 0.173 *esebsiwaagoT_Q* units (Table 6).

*CYP1B1* is a 5 M 11 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 69.6°. *CYP1B1* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 6.4259E + 04, 1.90422E + 05, 5.8349E + 04 and 5.36193E + 05 intergene bases. *CYP1B1* has an *uppesebsiwa* and *dppebsiwa* of 6.1304E + 04 and 3.63307E + 04 intergene bases with a $P_{\text{eff}}$ of 0.169 *esebsiwaagoT_Q* units (Table 6).

*ALDH3A1* is a 3 A 7 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 69.7°. *ALDH3A1* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 7.446E + 03, 9.0420E + 04, 1.3274E + 04 and 3.2789E + 04 intergene bases. *ALDH3A1* has an *uppesebsiwa* and *dppebsiwa* of 1.0360E + 04 and 6.1604E + 04 intergene bases with a $P_{\text{eff}}$ of 0.168 *esebsiwaagoT_Q* units (Table 6).

*ACSM2A* is a 2 A 5 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 70.9°. *ACSM2A* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 8.452E + 03, 1.14103E + 05, 1.2592E + 04 and 1.8897E + 04 intergene bases. *ACSM2A* has an *uppesebsiwa* and *dppebsiwa* of 1.052E + 04 and 6.6500E + 04 intergene bases with a $P_{\text{eff}}$ of 0.158 *esebsiwaagoT_Q* units (Table 6).

*NQO1* is a 2 A 5 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 72.2°. *NQO1* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 8.720E + 03, 1.85367E + 05, 2.8226E + 04 and 6.5249E + 04 intergene bases. *NQO1* has an *uppesebsiwa* and *dppebsiwa* of 1.8473E + 04 and 1.25308E + 05 intergene bases with a $P_{\text{eff}}$ of 0.147 *esebsiwaagoT_Q* units (Table 6).

*ESR2* is a 2 A 5 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 73.6°. *ESR2* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 1.810E + 03, 1.26875E + 05, 2.5861E + 04 and 7.6369E + 04 intergene bases. *ESR2* has an *uppesebsiwa* and *dppebsiwa* of 1.3835E + 04 and 1.01622E + 05 intergene bases with a $P_{\text{eff}}$ of 0.136 *esebsiwaagoT_Q* units (Table 6).

*ME1* is a 2 M 5 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 73.7°. *ME1* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 5.2685E + 04, 1.58850E + 05, 2.6415E + 04 and 4.27755E + 05 intergene bases. *ME1* has an *uppesebsiwa* and *dppebsiwa* of 3.9550E + 04 and 2.92302E + 05 intergene bases with a $P_{\text{eff}}$ of 0.135 *esebsiwaagoT_Q* units (Table 6).

*CYP3A7* is a 2 M 5 initial and final SEB gene at $x\text{-}_{\text{y}}$, $y$-vertical axis angulation 76.6°. *CYP3A7* has an *uppasebsiwa, dpappebsiwa, uppmsebsiwa* and *dppmsebsiwa* of 1.9558E + 04, 5.2160E + 04, 2.4091E + 04 and 3.42328E + 05 intergene bases. *CYP3A7* has an *uppesebsiwa* and *dppebsiwa* of 2.1824E + 04 and 1.97244E + 05 intergene bases with a $P_{\text{eff}}$ of 0.111 *esebsiwaagoT_Q* units (Table 6).
UGT1A7 is a 2 M 5 ACM final extended SEB gene at x-, y-vertical axis angulation 77.2°. UGT1A7 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.4610E + 04, 3.4472E + 04, 4.4440E + 04 and 5.20736E + 05 intergene bases. UGT1A7 has an uppasebsiwiwa and dppesebsiwiwa of 2.9540E + 04 and 2.77604E + 05 intergene bases with a $P_{eff}$ of 0.106 esebsiwaagoTQ units (Table 6).

DIO3 is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 78.4°. DIO3 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 4.463E + 03, 6.6352E + 04, 2.545E +03 and 6.385E + 03 intergene bases. DIO3 has an uppasebsiwiwa and dppesebsiwiwa of 3.504E + 03 and 3.6368E + 04 intergene bases with a $P_{eff}$ of 0.096 esebsiwaagoTQ units (Table 6).

ARNT is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 82.4°. ARNT has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 3.424E + 03, 1.23406E + 05, 5.151E +03 and 1.2359E + 04 intergene bases. ARNT has an uppasebsiwiwa and dppesebsiwiwa of 4.287E +03 and 6.7882E + 04 intergene bases with a $P_{eff}$ of 0.063 esebsiwaagoTQ units (Table 6).

TSPAN14 is a 2 A 8 ACM ACM final SEB gene at x-, y-vertical axis angulation 83.1°. TSPAN14 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.5608E + 04, 4.94044E + 05, 1.4376E + 04 and 3.3255E + 04 intergene bases. TSPAN14 has an uppasebsiwiwa and dppesebsiwiwa of 1.4992E + 04 and 2.63650E + 05 intergene bases with a $P_{eff}$ of 0.057 esebsiwaagoTQ units (Table 6).

**co-planar polychlorinated biphenyl.** HNF4A is a 2 A 5 NCA ACM final SEB gene at x-, y-vertical axis angulation 38.4°. HNF4A has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.0705E + 04, 1.08134E + 05, 1.47071E + 05 and 2.61534E + 04 intergene bases. HNF4A has an uppasebsiwiwa and dppesebsiwiwa of 7.8888E + 04 and 1.84834E + 05 intergene bases with a $P_{eff}$ of 0.427 esebsiwaagoTQ units (Table 6).

PCK1 is a 3 M 7 ACM ACM final SEB gene at x-, y-vertical axis angulation 49.5°. PCK1 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.04153E + 05, 2.22857E + 05, 1.2995E + 04 and 1.29275E + 05 intergene bases. PCK1 has an uppasebsiwiwa and dppesebsiwiwa of 5.8574E + 04 and 1.76066E + 05 intergene bases with a $P_{eff}$ of 0.333 esebsiwaagoTQ units (Table 7).

RESP18 is a 3 M 5 ACM q term final SEB gene at x-, y-vertical axis angulation 50.5°. RESP18 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 4.9633E + 04, 1.16462E + 05, 3.1333E + 05 and 4.4955 + 05 intergene bases. RESP18 has an uppasebsiwiwa and dppesebsiwiwa of 2.6383E + 04 and 8.0709E + 04 intergene bases with a $P_{eff}$ of 0.327 esebsiwaagoTQ units (Table 7).

CYP5A is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 52.6°. CYP5A has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 4.1825E + 04, 3.21263E + 05, 1.14755E + 05 and 1.84810E + 05 intergene bases. CYP5A has an uppasebsiwiwa and dppesebsiwiwa of 7.8290E + 04 and 2.53036E + 05 intergene bases with a $P_{eff}$ of 0.309 esebsiwaagoTQ units (Table 7).

RARG is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 52.7°. RARG has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 3.847E + 03, 4.4654E + 04, 2.5927E + 04 and 5.1723E + 04 intergene bases. RARG has an uppasebsiwiwa and dppesebsiwiwa of 1.4887E + 04 and 4.8189E + 04 intergene bases with a $P_{eff}$ of 0.309 esebsiwaagoTQ units (Table 7).

CYCS is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 54.1°. CYCS has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.04197E + 04, 2.02726E + 05, 1.3747E + 04 and 8.5931E + 04 intergene bases. CYCS has an uppasebsiwiwa and
Table 7. Effective intracellular pressure mapping of gene activation by co-planar polychlorinated biphenyl via the AhR-Era/β (Arnt): Nrf-2ζ: Rev-Erb β, Erreα: Dio3/Dio2 (Troc) pathway*.

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppesbssiwaa, dppesbssiwaa (Peff, fract) | Peff range effect fract (Δ%; Δ fract) |
|---------------------------------------------|-------------------------|-----------|-----------------------------------------------|------------------------------------------|--------------------------------------|
| HNF4A, hepatocyte nuclear factor 4A (79,067; n/a) | 10q26.3 (+) 38.4 2 A 4 nca acm (2 A 5) | 7.8888E + 04, 1.84834E + 04 (0.427) | (-)K |
| AHR | (0.395) (+) |
| COX6C | (0.381) (+2.5; 0.24) |
| CEACAM1 | (0.379) (+13.9; 0.68) |
| SLC2A4 | (0.376) (--) |
| RXRA | (0.374) (+) |
| PCK1, phosphoenolpyruvate carboxykinase 1 (7,042; n/a) | 20q13.31 (+) 49.8 3 A 7 acm acm ext^ (3 A 7) | 5.8574E + 04, 1.76066E + 05 (0.427) | (-)K |
| GADD45B | (0.332) (+) |
| NFE2L2 | (0.331) (+0.08; 1.14) |
| RESP18, regulated endocrine-specific protein 18 homolog (9,377; n/a) | 2q35 (-) 50.5 3 M 5 acm q term (3 M 7) | 2.6383E + 04, 1.76066E + 05 (0.427) | (-)K |
| ALAS1 | (0.324) (--) |
| CYP5A, cytochrome P450, family 5, subfamily A (49,988; n/a) | 18q22.3 (-) 52.6 2 A 5 (-) | 1.48887E + 04, 4.8189E + 04 (0.309) | (+2.2) |
| RXRB | (0.324) (--) |
| CYCS, cytochrome C, somatic (62,499; n/a) | 7p15.3 (-) 54.1 2 M 5 (-) | 4.2867E + 04, 1.44328E + 04 (0.297) | (+0.30) |
| DBP | (0.283) (--) |
| SCD | (0.282) (--) |
| PPARC1A | (0.279) (--) |
| FASN, fatty acid synthase (19,962; n/a) | 7q25.3 (-) 56.4 2 M 5 (-) | 8.785E + 03, 3.1543E +04 (0.278) | (-)K |
| MT1 | (0.273) (+0.11; 1.57) |
| NOS1, nitric oxide synthase 1 (244,082; n/a) | 12q24.22 (-) 58.4 2 A 7 acm (2 A 5) | 1.0595E + 04, 4.0449E + 04 (0.262) | (+) |
| GADD45A, growth arrest and DNA damage inducible alpha (3,162; n/a) | 1p31.3 (+) 60.4 3 M 7 ext (+) | 2.4941E + 04, 1.01955E + 05 (0.245) | (+0.34) |
| NRID2, nuclear receptor subfamily 1 group D member 2 (35,359; n/a) | 17p13.3 (+) 64.5 2 M 5 (-) | 6.2412E + 04, 2.58343E + 05 (0.242) | (+) |
| COL1A1, collagen type I alpha 1 chain (18,360; n/a) | 17q21.33 (-) - - - | - | (-0.241) (--) |
| SREBF1 (26,619; n/a) | (0.237) (-)K |
| DIO1 | (0.236) (-)K |
| TIPARP | (0.223) (-) |
| SIN3A | (0.223 (0.2229) (-) |
| PPARG | (0.222) (-) |
| RARB | (0.222) (-) |
| CAT, catalase (33,138) | 11p13 (+) 63.4 2 M 5 (-) | 1.7938E + 04, 8.1622E + 04 (0.220) | (+0.87) |
| CYP1A1 | (0.216) (+42.9; 1.28) |
| COX6C, cytochrome C oxidase subunit 6C (20,815; 20,863) | 5q22.1 (+) 64.5 2 A 4 acm (2 A 5) | 3.3414E + 04, 1.58072E + 05 (0.211) | (+0.34) |
| ESRRG | (0.209) (--) |
| CYP1A2 | (0.201) (+0.26; 2.60) |
| NRF1 | (0.200) (-) |

(Continued)
Table 7. (Continued)

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppsesbssiwa, dppsesbssiwa (Peff, fract) | Peff range effect fract (Δ%Δ fract) |
|---------------------------------------------|-------------------------|-----------|-----------------------------------------------|----------------------------------------|-------------------------------------|
| ESRR[A | 1p13.3 (+) | 69.6 | 2 M 6 nca acm (2 A 5) | 1.4017E + 04, 8.3148E + 04 | (+6.6) |
| ALDH3A1 | 14q32.33 (-) | - | - | -0.131 | (-) |
| ACSM2A | 22q13.1 (+) | 74.2 | 3 A 7 (-) | 6.856E + 03, 5.2584E + 04 | (+0.90) |
| LGAL1, galectin 1 (4,201; n/a) | 1p13.3 (+) | 69.6 | 2 M 6 nca acm (2 A 5) | 1.4017E + 04, 8.3148E + 04 | (+6.6) |
| UGT1A7 | 1p13.3 (+) | 69.6 | 2 M 6 nca acm (2 A 5) | 1.4017E + 04, 8.3148E + 04 | (+6.6) |
| ARNT | 22q13.1 (+) | 74.2 | 3 A 7 (-) | 6.856E + 03, 5.2584E + 04 | (+0.90) |
| TSPAN14 | 1p13.3 (+) | 69.6 | 2 M 6 nca acm (2 A 5) | 1.4017E + 04, 8.3148E + 04 | (+6.6) |

* % Peff duration of effect increases or decreases from Table 6; Δ ratio, ratio from % change in comparison to TCDD Peff duration of effect
* % dec in effect genes include RESP18, IGHA1, - 0.84; FASN, -0.72; PCK1, ACSM2A - 0.36; and HNF4A, ALAS1, DIO2, SREBF1, - 0.24 (2-fold change threshold)
* SLC2A4, SREBF1 binding response element(s) * ESRR[A over-activation during EXOC7 protein expression phase
* NFIA/-B, PCK1 required transcription factor decrease, as does antagonist NFIX (as cited)
^ activation of ME1 gene with TRα/β response element (TRE) increases only; and
* RIP140 (NRIPI) as co-activator for AhR and ERRα transcription factors Note(s): 1) Gene loci sub-episode block structure (SEB) variations include non-contributory anisotropy (NCA), anisotropy converted to mesotropy (ACM), 0.5-factor adjusted stabilizing mesotropy or anisotropy converted to stabilizing isotropy for anisotropy or mesotropy (stIAM, stIMA or stIMIM), and/or extended block (ext) SEB, ^ ie PCK1 is a 2 M 5 (-2) acm (+2) acm extended SEB gene; and ^2 gene(s) with previously reported episode and sub-episode block structure include ^2 COL1A1 [22] and IGHA1 [38].

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dppsesbssiwa of 4.2867E + 04 and 1.44328E + 05 intergene bases with a Peff of 0.297 esebssiwaagotQ units (Table 7).

FASN is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 56.4°. FASN has an uppasesbssiwa, dppapesbssiwa, uppmasesbssiwa and dpppmasesbssiwa of 1.6097E + 04, 5.0211E + 04, 1.472E + 04 or 1.2875E + 04 intergene bases. FASN has an uppasesbssiwa and dppapesbssiwa of 8.785E + 03 and 3.1543E + 04 intergene bases with a Peff of 0.278 esebssiwaagotQ units (Table 7).

NOS1 is a 3 A 7 ACM final SEB gene at x-, y-vertical axis angulation 58.4°. NOS1 has an uppasesbssiwa, dppapesbssiwa, uppmasesbssiwa and dpppmasesbssiwa of 2.496E + 03, 3.6292E + 04, 1.8694E + 04 and 4.4605E + 04 intergene bases. NOS1 has an uppasesbssiwa and dppapesbssiwa
of 1.0595E + 04 and 4.0449E + 04 intergene bases with a $P_{ef}$ of 0.262 $esebssiwaagoT_Q$ units (Table 7).

GADD45A is a 3 M 7 ext final SEB gene at $x$, $y$-vertical axis angulation 60.4°. GADD45A has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $3.4312E + 04$, $8.5949E + 04$, $6.470E + 03$ and $1.17960E + 05$ intergene bases. GADD45A has an $uppsebssiwa$ and $dppebssiwaa$ of $2.4941E + 04$ and $1.01955E + 05$ intergene bases with a $P_{ef}$ of 0.245 $esebssiwaagoT_Q$ units (Table 7).

NRID2 is a 2 A 6 ext final SEB gene at $x$, $y$-vertical axis angulation 60.8°. NRID2 has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $3.6660E + 04$, $3.30263E + 05$, $8.8163E + 03$ and $1.86423E + 05$ intergene bases. NRID2 has an $uppsebssiwa$ and $dppebssiwaa$ of $6.2412E + 04$ and $2.58343E + 05$ intergene bases with a $P_{ef}$ of 0.242 $esebssiwaagoT_Q$ units (Table 7).

CAT is a 2 M 5 initial and final SEB gene at $x$, $y$-vertical axis angulation 63.4°. CAT has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $3.0584E + 04$, $7.9950E + 04$, $5.293E + 03$ and $8.3295E + 04$ intergene bases. CAT has an $uppsebssiwa$ and $dppebssiwaa$ of $1.7938E + 04$ and $8.1622E + 04$ intergene bases with a $P_{ef}$ of 0.220 $esebssiwaagoT_Q$ units (Table 7).

COX6C is a 2 A 4 ACM final SEB gene at $x$, $y$-vertical axis angulation 64.5°. COX6C has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $5.3278E + 04$, $1.13133E + 05$, $1.3550E + 04$ and $2.73011E + 05$ intergene bases. COX6C has an $uppsebssiwa$ and $dppebssiwaa$ of $3.3414E + 04$ and $1.58072E + 05$ intergene bases with a $P_{ef}$ of 0.169 $esebssiwaagoT_Q$ units (Table 7).

GSTM2 is a 2 M 5 NCA ACM final SEB gene at $x$, $y$-vertical axis angulation 59.6°. GSTM2 has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $2.2001E + 04$, $4.1822E + 04$, $6.033E + 03$ and $1.24474E + 05$ intergene bases. GSTM2 has an $uppsebssiwa$ and $dppebssiwaa$ of $1.4017E + 04$ and $8.3148E + 04$ intergene bases with a $P_{ef}$ of 0.169 $esebssiwaagoT_Q$ units (Table 7).

LGALS1 is a 3 A 7 initial and final SEB gene at $x$, $y$-vertical axis angulation 74.2°. LGALS1 has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $6.039E + 03$, $8.6386E + 04$, $7.672E + 03$ and $1.8783E + 04$ intergene bases. LGALS1 has an $uppsebssiwa$ and $dppebssiwaa$ of $6.856E + 03$ and $5.2584E + 04$ intergene bases with a $P_{ef}$ of 0.130 $esebssiwaagoT_Q$ units (Table 7).

**orthog-planar intracellular, ortho-co-planar extracellular polychlorinated biphenyl.**

DCAKD is a 2 M 5 acm final SEB gene at $x$, $y$-vertical axis angulation 72.1°. DCAKD has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $6.7286E + 04$, $1.07727E + 05$, $3.77E + 02$ and $5.3956E + 04$ intergene bases. DCAKD has an $uppsebssiwa$ and $dppebssiwaa$ of $5.2432E + 04$, $1.23677E + 05$, $2.116E + 03$ and $1.8633E + 04$ intergene bases. DCAKD has an $uppsebssiwa$ and $dppebssiwaa$ of $5.7120E + 04$, $1.23677E + 05$, $2.116E + 03$ and $1.8633E + 04$ intergene bases. DCAKD has an $uppsebssiwa$ and $dppebssiwaa$ of $2.9618E + 04$ and $7.1155E + 04$ intergene bases with a $P_{ef}$ of 0.418 $esebssiwaagoT_Q$ units (Table 8).

PPARA is a 2 A 4 NCA final SEB gene at $x$, $y$-vertical axis angulation 39.7°. PPARA has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $5.7120E + 04$, $1.23677E + 05$, $2.116E + 03$ and $1.8633E + 04$ intergene bases. PPARA has an $uppsebssiwa$ and $dppebssiwaa$ of $2.9618E + 04$ and $7.1155E + 04$ intergene bases with a $P_{ef}$ of 0.416 $esebssiwaagoT_Q$ units (Table 8).

DDIT3 is a 3 M 5 NCA ACM final SEB gene at $x$, $y$-vertical axis angulation 40.97°. DDIT3 has an $uppasebssiwa$, $dppebssiwa$, $uppmsbssiwa$ and $dpmpsesbssiwa$ of $5.2432E + 04$, $1.09617E + 05$, $6.288E + 03$ and $3.5032E + 04$ intergene bases. DDIT3 has an $uppsebssiwa$ and $dppebssiwaa$ of $2.9360E + 04$ and $7.2324E + 04$ intergene bases with a $P_{ef}$ of 0.406 $esebssiwaagoT_Q$ units (Table 8).
Table 8. Effective intracellular pressure mapping of gene activation by (co-) ortho-planar polychlorinated biphenyls and metabolites via the Car/PXR, Rarγ; Ppara/γ, Rxrβ (Srebfl1, -Lxrγβ): Arnt (AhR-Er) pathway.

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | $\text{eppepsebiswaa}$, $\text{eppepsebiswaa}$ ($P_{\text{eff}}$ frac) | $P_{\text{eff}}$ range effect fraction (% inc) |
|---------------------------------------------|------------------------|-----------|-----------------------------------------------|-------------------------------|-------------------------------------|
| **DCARD**, dephospho-CoA kinase domain containing (37,804) | 17q21.13 (-) | 72.1 | 2 M 3 acm (2 M 5) | 3.3832E + 04, 8.0842E + 04 (0.418) | (+1.0) |
| **PPARA**, peroxisome proliferator activated receptor alpha (93,236, 237,141) | 22q13.31 (+) | 39.7 | 2 A 4 nca (2 A 5) | 2.9618E + 04, 7.1155E + 04 (0.416) | (+) |
| **DDIT3**, DNA damage inducible transcript 3 (5,150; n/a) | 12q13.3 (-) | 41 | 3 M 5 nca acm (3 M 7) | 2.9360E + 04, 7.2324E + 04 (0.406) | (+) |
| **AHR**, nuclear receptor subfamily 1 group I member 3 (8,933; n/a) | 17q25.3 (-) | 59.6 | 2 M 5 (-) | 1.1026E + 04, 4.3832E + 04 | (+) |
| **CYP3A4**, cytochrome P450, family 3, subfamily A4 (27,306; n/a) | 2q37.13 (+) | 57.2 | 3 M 9 stMf a nca acm (3 M 7) | 4.3171E + 04, 1.33165E + 05 | (+) |
| **NR1I3**, nuclear receptor subfamily 1 group I member 3 (8,933; n/a) | 19q13.2 (+) | 52.3 | 3 A 5 acm (3 A 7) | 5.5470E + 04, 1.44398E + 05 | (+0.7) |
| **CARLE1**, carcinoembryonic antigen related cell adhesion molecule 1 (23,806; n/a) | 18q11.13 (-) | 48.7 | 2 A 7 acm (2 A 5) | 2.5366E + 04, 7.4138E + 04 | (+) |
| **CEACAM5**, carcinoembryonic antigen related cell adhesion molecule 1 (21,849; 63,627) | 17p13.3 (-) | 55.6 | 3 A 7 (-) | 8.318E + 03, 2.9199E + 04 | (+) |
| **SCD**, stearoyl-coenzyme A desaturase 5 (169,321; n/a) | 3q26.11 (-) | 62.5 | 2 M 3 acm (2 M 5) | 7.567E + 03, 2.6969E + 04 | (+0.3) |
| **CDO1**, 5'-aminolevulinate synthase 2 (22,010; n/a) | 3p14.21 (-) | 62.9 | 2 A 3 q term (2 A 5) | 5.7628E + 04, 2.5702E + 05 | (+) |
| **MYBP**, myelin basic protein (154,882; 235,160) | 1q12.13 (-) | 41 | 3 M 5 nca acm (3 M 7) | 2.9360E + 04, 7.2324E + 04 (0.406) | (+) |

(Continued)
**Table 8.** (Continued)

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | upppessebssiwaa, dppessebssiwaa (Peff, fract) | Peff range effect fract (% inc) |
|---------------------------------------------|------------------------|----------|-----------------------------------------------|------------------------------------------|-------------------------------|
| PPARG                                        |                        |          |                                               | (0.222)                                  | (+)                           |
| CYP1A1                                       |                        |          |                                               | (0.216)                                  | (+)                           |
| ESRGG                                        |                        |          |                                               | (0.209)                                  | (+)                           |
| NR1H3                                        |                        |          |                                               | (0.209)                                  | (+)                           |
| ESRRA                                        |                        |          |                                               | (0.196)                                  | (-)                           |
| ARNTL                                        |                        |          |                                               | (0.191)                                  | (+)                           |
| EXOC7                                        |                        |          |                                               | (0.190)                                  | (+)                           |
| ESRI                                         |                        |          |                                               | (0.184)                                  | (-)                           |
| DIO2                                         |                        |          |                                               | (0.183)                                  | □ (-)R                       |
| NCOR1, nuclear receptor corepressor 1 (189,029; n/a) | 17p11.2 (-) | 70.6     | 2 A 5 (-)                                    | 1.1215E+04 + 04, 6.9779E+04 (0.161)       | (+)                           |
| CASP3, caspase 3 (21,824; n/a)               | 4q35.1 (-)             | 70.7     | 2 M 5 (-)                                    | 2.0709E+04 + 04, 1.2948E+05 (0.160)       | (+)                           |
| CES2, carboxylesterase 2 (10,653; 40.706)    | 1q621 (+)              | 70.8     | 2 A 4 acm (2 A 5)                            | 1.5814E+04 + 04, 9.9445E+04 (0.159)       | (+1.3)                       |
| CYP3A45, cytochrome P450, family 3, subfamily A5 (31,838: n/a) | 7q22.1 (-) | 71.05    | 3 M 5 nca2 acm (3 M 7)                       | 1.0477E+04 + 04, 6.6776E+04 (0.157)       | (+44.7)                      |
| AR, androgen receptor (186,599; n/a)         | Xp12 (+)               | 71.1     | 2 A 5 (-)                                    | 3.7729E+04 + 04, 2.4127E+05 (0.156)       | (+)                           |
| CYP4A11, cytochrome P450, family 4, subfamily A11 (12,326; n/a) | 1p33 (-) | 72.0     | 2 M 5 (-)                                    | 1.3322E+04 + 04, 8.9325E+04 (0.149)       | (+)                           |
| GTF2IRD1, general transcription factor II I repeat domain-containing (148,816; n/a) | 7q11.23 (+) | 73.1     | 2 M 7 acm (2 M 5)                            | 1.5928E+04 + 04, 1.1406E+05 (0.140)       | (-)B                         |
| ES2                                          |                        |          |                                               | [0.136 (0.1361)]                         | (+)                           |
| PPP1R9B, protein phosphatase 1 regulatory subunit 9B (17,288; n/a) | 17q21.33 (-) | 74.4     | 2 M 5 (-)                                    | 3.9081E+04 + 04, 3.0386E+05 (0.129)       | (+)                           |
| FABP3, fatty acid binding protein 3 (24,436; n/a) | 1p35.2 (-) | 74.5     | 2 A 2 (2 A 5)                                | 1.1053E+04 + 04, 8.6640E+04 (0.128)       | (+)                           |
| UGT1A1                                       |                        |          |                                               | [0.106 (0.1064)]                         | (+)                           |
| FABP6, fatty acid binding protein 6 (51,369; 98,133) | 5q33.3 (+) | 78.3     | 2 M 4 (2 A 5)                                | 3.9038E+04 + 04, 4.0472E+05 (0.1096)       | (+1.0)                       |
| DIO3                                         |                        |          |                                               | [0.096 (0.0963)]                         | (+)                           |
| ARNT                                         |                        |          |                                               | (0.063)                                  | (+)                           |
| TSPAN14                                      |                        |          |                                               | (0.057)                                  | (+2.0)                       |

* % Peff duration of effect increases or decreases from baseline

*% Peff duration of effect decrease genes include GTF2IRD1, -14.3; PCK1, DUSP1–10.7; DIO2, -7.1; and NF1A, Peff n.d. (2-fold change threshold)

© MIR132, MBP and PPP1R9B Peff duration of effect from sub-acute exposure to ortho-PCB-95 (intracellular) or ortho-PCB-136 (extracellular) and substituent metabolities (-OH, Ch3-SO2-) as cited

^CYP3A44 is a PPARα-activated gene in the pathway

^4-digit esebssiwatoTQ genes include CYP2B6, 0.3238 (ALAS1, 0.3236) and FABP6, 0.0965 (DIO3, 0.0963); • CYP2B6 and CYP3A5 are orthologs (pred) of rodent CYP2B2 and CYP2B15/-12; and *PGC1α (PPARGC1A) as co-activator for PPARα, SREBP1 and ERRx transcription factors Note(s): Gene loci sub-episode block structure (SEB) variations include non-contributory anisotropy (NCA), anisotropy converted to mesotropy (ACM), 0.5-factor adjusted stabilizing mesotropy or anisotropy converted to stabilizing anisotropy for anisotropy or mesotropy (stIAM, stIMIA or stIMIM), and/or extended block (ext) SEB.

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NR1I3 is a 3 M 5 ACM final SEB gene at x-, y-vertical axis angle 43.2°. NR1I3 has an upppessebssiwaa, dppessebssiwaa, uppmsebssiwaa and dpppmsebssiwaa of 6.3252E+04, 1.04908E+05, 2.9155E+04 and 1.33970E+05 intergene bases. NR1I3 has an uppessebssiwaa and dppessebssiwaa of 4.6203E+04 and 1.19293E+05 intergene bases with a Peff of 0.387 esebssiwatoTQ units (Table 8).

FOXA1 is a 3 M 7 ACMx2 final SEB gene at x-, y-vertical axis angle 43.6°. FOXA1 has an upppessebssiwaa, dppessebssiwaa, uppmsebssiwaa and dpppmsebssiwaa of 8.365E+03, 5.8310E+04,
1.02576E + 05 and 2.30487E + 05 intergene bases. FOXA1 has an uppsebsiwiwa and dppebsiwiwa of 5.5470E + 04 and 1.44398E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.384 (0.3841) esebsiwaagoTQ units (Table 8).

FKBP5 is a 2 A 7 ACM final SEB gene at \( x \), \( y \)-vertical axis angulation 48.7°. FKB5 has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 9.472E + 03, 6.3245E + 04, 4.1261E + 04 and 8.5032E + 04 intergene bases. FKB5 has an uppsebsiwiwa and dppebsiwiwa of 2.5366E + 04 and 7.4138E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.342 esebsiwaagoTQ units (Table 8).

NCOA1 is a 3 M 7 stlMfa NCA ACM final SEB gene at \( x \), \( y \)-vertical axis angulation 50.8°. NCOA1 has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 7.5277E + 04, 1.69917E + 05, 1.1065E + 04 and 9.6413E + 04 intergene bases. NCOA1 has an uppsebsiwiwa and dppebsiwiwa of 4.3171E + 04 and 1.33165E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.324 esebsiwaagoTQ units (Table 8).

CYP2B6 is a 2 M 5 initial and final SEB gene at \( x \), \( y \)-vertical axis angulation 50.9°. CYP2B6 has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.4887E + 04, 3.2241E + 04, 3.224E + 03 and 2.3693E + 04 intergene bases. CYP2B6 has an uppsebsiwiwa and dppebsiwiwa of 9.056E + 03 and 2.7967E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.324 esebsiwaagoTQ units (Table 8).

NR1I2 is a 2 A 5 initial and final SEB gene at \( x \), \( y \)-vertical axis angulation 52.3°. NR1I2 has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.0367E + 04, 1.00223E + 05, 4.4883E + 04, 7.6998E + 04 intergene bases. NR1I2 has an uppsebsiwiwa and dppebsiwiwa of 2.7625E + 04 and 8.8611E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.312 esebsiwaagoTQ units (Table 8).

CIDEA is a 2 A 3 stlMfa final SEB gene at \( x \), \( y \)-vertical axis angulation 54.7°. CIDEA has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 4.9350E + 04, 2.09403E + 05, 2.1519E + 04 and 3.4977E + 04 intergene bases. CIDEA has an uppsebsiwiwa and dppebsiwiwa of 3.5735E + 04 and 1.22190E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.292 esebsiwaagoTQ units (Table 8).

THRB is a 3 A 9 stlMfa final SEB gene at \( x \), \( y \)-vertical axis angulation 55.2°. THRB has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.9549E + 04, 2.47380E + 05, 1.08453E + 05 and 1.96893E + 05 intergene bases. THRB has an uppsebsiwiwa and dppebsiwiwa of 6.4001E + 04 and 2.22137E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.288 esebsiwaagoTQ units (Table 8).

MBP is a 2 A 3 NCA ACM q term final SEB gene at \( x \), \( y \)-vertical axis angulation 62.9°. MBP has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 3.8325E + 04, 2.97769E + 05, 7.6708E + 04 and 2.16048E + 05 intergene bases. MBP has an uppsebsiwiwa and dppebsiwiwa of 5.7628E + 04 and 2.5702E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.224 esebsiwaagoTQ units (Table 8).

CYP3A4 is a 2 A 3 ACM final SEB gene at \( x \), \( y \)-vertical axis angulation 56.1°. CYP3A4 has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.3755E + 04, 3.8086E + 04, 1.379E + 03 and 1.5851E + 04 intergene bases. CYP3A4 has an uppsebsiwiwa and dppebsiwiwa of 7.567E + 03 and 2.6969E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.281 esebsiwaagoTQ units (Table 8).

NR1H2 is a 2 M 5 final SEB gene at \( x \), \( y \)-vertical axis angulation 57.3°. NR1H2 has an uppsebsiwiwa, dppebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 2.4733E + 04, 6.2238E + 04, 1.1164E + 04 and 7.0526E + 04 intergene bases. NR1H2 has an uppsebsiwiwa and dppebsiwiwa of 1.7949E + 04 and 6.6382E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.270 esebsiwaagoTQ units (Table 8).
CEACAM5 is a 2 A 4 stIMfA final SEB gene at x-, y-vertical axis angulation 59.5°. CEACAM5 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 2.1447E + 04, 5.6869E + 04, 6.140E + 03 and 5.2392E + 04 intergene bases. CEACAM5 has an uppasebsiwiwa and dppasebsiwiwa of 1.3795E + 04 and 5.4631E + 04 intergene bases with a P_{eff} of 0.252 esebsiwaago\textsubscript{TQ} (Table 8).

MAFG is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 59.6°. MAFG has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 7.819E + 03, 5.4643E + 04, 1.4233E + 04 and 3.3022E + 04 intergene bases. MAFG has an uppasebsiwiwa and dppasebsiwiwa of 1.1026E + 04 and 4.3832E + 04 intergene bases with a P_{eff} of 0.252 esebsiwaago\textsubscript{TQ} units (Table 8).

SCD5 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 59.6°. SCD5 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 7.7158E + 04, 1.60532E + 05, 4.3087E + 04 and 3.17760E + 05 intergene bases. SCD5 has an uppasebsiwiwa and dppasebsiwiwa of 6.0123E + 04 and 2.39146E + 05 intergene bases with a P_{eff} of 0.251 esebsiwaago\textsubscript{TQ} units (Table 8).

MBP is a 2 A 4 ACM q term final SEB gene at x-, y-vertical axis angulation 60.5°. MBP has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.9347E + 04, 1.76854E + 05, 7.6708E + 04 and 2.16048E + 05 intergene bases. MBP has an uppasebsiwiwa and dppasebsiwiwa of 4.8027E + 04 and 1.96451E + 05 intergene bases with a P_{eff} of 0.244 esebsiwaago\textsubscript{TQ} units (Table 8).

CUL2 is a 2 A 3 NCA ACM final SEB gene at x-, y-vertical axis angulation 56.4°. CUL2 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.8848E + 04, 2.74921E + 05, 2.08721E + 05, 5.41134E + 05 intergene bases. CUL2 has an uppasebsiwiwa and dppasebsiwiwa of 1.13635E + 05 and 4.08028E + 05 intergene bases with a P_{eff} of 0.278 esebsiwaago\textsubscript{TQ} units (Table 8).

ALAS2 is a 2 A 3 p term final SEB gene at x-, y-vertical axis angulation 62.55°. ALAS2 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 2.0152E + 04, 2.56510E + 05, 6.1069E + 04 and 1.00950E + 05 intergene bases. ALAS2 has an uppasebsiwiwa and dppasebsiwiwa of 4.0611E + 04 and 1.78730E + 05 intergene bases with a P_{eff} of 0.227 esebsiwaago\textsubscript{TQ} units (Table 8).

NCOR1 is a 2 A 5 NCAx3 final SEB gene at x-, y-vertical axis angulation 70.6°. NCOR1 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.2911E + 04, 2.4777E + 04, 9.52E + 03 and 1.14781E + 05 intergene bases. NCOR1 has an uppasebsiwiwa and dppasebsiwiwa of 1.1215E + 04 and 6.9779E + 04 intergene bases with a P_{eff} of 0.161 esebsiwaago\textsubscript{TQ} units (Table 8).

CASP3 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 70.7°. CASP3 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 2.2777E + 04, 4.4665E + 04, 1.8640E + 04 and 2.14308E + 05 intergene bases. CASP3 has an uppasebsiwiwa and dppasebsiwiwa of 2.0790E + 04 and 1.29486E + 05 intergene bases with a P_{eff} of 0.160 esebsiwaago\textsubscript{TQ} units (Table 8).

CES2 is a 2 A 4 ACM final SEB gene at x-, y-vertical axis angulation 70.8°. CES2 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 3.0860E + 04, 9.0630E + 04, 7.68E + 02 and 1.08260E + 05 intergene bases. CES2 has an uppasebsiwiwa and dppasebsiwiwa of 1.5772E + 04 and 9.9445E + 04 intergene bases with a P_{eff} of 0.159 esebsiwaago\textsubscript{TQ} units (Table 8).

CYP3A5 is a 3 M 5 NCAx2 ACM final SEB gene at x-, y-vertical axis angulation 71.05°. CYP3A5 has an uppasebsiwiwa, dppasebsiwiwa, uppmsebsiwiwa and dppmsebsiwiwa of 1.3739E + 04, 3.3986E + 04, 7.215E + 03 and 9.9566E + 04 intergene bases. CYP3A5 has an uppasebsiwiwa
and $dppsebssiwaa$ of $1.0477E + 04$ and $6.6776E + 04$ intergene bases with a $P_{\text{eff}}$ of $0.157$ $esebssiwaagoT_Q$ units (Table 8).

AR is a 2 A 5 initial and final SEB gene at $x, y$-vertical axis angulation $71.1^\circ$. AR has an $uppasebssiwaa$, $dppasebssiwaa$, $uppmsebssiwaa$ and $dpppmsebssiwaa$ of $1.9384E + 04$, $3.8080E + 05$, $5.6075E + 04$ and $1.01739E + 05$ intergene bases. AR has an $uppesebssiwaa$ and $dpppesebssiwaa$ of $3.7729E + 04$ and $2.41270E + 05$ intergene bases with a $P_{\text{eff}}$ of $0.156$ $esebssiwaagoT_Q$ units (Table 8).

$CYP4A11$ is a 2 M 5 initial and final SEB gene at $x, y$-vertical axis angulation $72.0^\circ$. $CYP4A11$ has an $uppasebssiwaa$, $dppasebssiwaa$, $uppmsebssiwaa$ and $dpppmsebssiwaa$ of $2.9160E + 04$, $5.2809E + 04$, $2.697E + 03$ and $1.75310E + 05$ intergene bases. $GTF2IRD1$ has an $uppasebssiwaa$ and $dpppesebssiwaa$ of $1.3322E + 04$ and $8.9254E + 04$ intergene bases with a $P_{\text{eff}}$ of $0.149$ $esebssiwaagoT_Q$ units (Table 8).

$PPP1R9B$ is a 2 M 5 initial and final SEB gene at $x, y$-vertical axis angulation $74.4^\circ$. $PPP1R9B$ has an $uppasebssiwaa$, $dppasebssiwaa$, $uppmsebssiwaa$ and $dpppmsebssiwaa$ of $4.2770E + 04$, $1.02872E + 05$, $3.5391E + 04$ and $5.04863E + 05$ intergene bases. $PPP1R9B$ has an $uppesebssiwaa$ and $dppesebssiwaa$ of $3.9081E + 04$ and $3.03867E + 05$ intergene bases with a $P_{\text{eff}}$ of $0.129$ $esebssiwaagoT_Q$ units (Table 8).

$FABP3$ is a 2 A 5 initial and final SEB gene at $x, y$-vertical axis angulation $74.5^\circ$. $FABP3$ has an $uppasebssiwaa$, $dppasebssiwaa$, $uppmsebssiwaa$ and $dpppmsebssiwaa$ of $1.2880E + 04$, $1.56459E + 05$, $9.227E + 03$ and $1.6822E + 04$ intergene bases. $FABP3$ has an $uppesebssiwaa$ and $dppesebssiwaa$ of $1.1053E + 04$ and $8.6640E + 04$ intergene bases with a $P_{\text{eff}}$ of $0.128$ $esebssiwaagoT_Q$ units (Table 8).

$FABP6$ is a 2 M 4 final SEB gene at $x, y$-vertical axis angulation $78.3^\circ$. $FABP6$ has an $uppasebssiwaa$, $dppasebssiwaa$, $uppmsebssiwaa$ and $dpppmsebssiwaa$ of $5.8309E + 04$, $7.63245E + 05$, $1.9768E + 04$ and $4.6206E + 04$ intergene bases. $FABP6$ has an $uppesebssiwaa$ and $dppesebssiwaa$ of $3.9038E + 04$ and $4.04726E + 05$ intergene bases with a $P_{\text{eff}}$ of $0.096$ $esebssiwaagoT_Q$ units (Table 8).

van der Waals diameter, structural lipophilicity and pressure regulation
grade half-life parameters for small molecules with exterior structural lipophilicity

Aldosterone ($C_{21}H_{28}O_3$) has a Log $P$ of $1.06$, a $vdWD$ of $0.856$ nm and a Log $P/vdWD$ of $1.23$ $nm^{-1}$. Aldosterone has a calc $L_{\text{external structure}}/H_{\text{polar group}}$ ratio of $1.31$, and a nl calc $L_{\text{external structure}}/H_{\text{polar group}}$ quotient of $0.478$. The $t_{1/2}$ at receptor-receptor count ($t_{1/2R_{\text{count}}}$) for aldosterone at MR is $2.366E + 04$ min-count, at GR is $6.610E + 03$ min-count, and the $\Sigma$ min-count is $3.0270E + 04$ (Table 9).

Cortisol ($C_{21}H_{29}O_2$) has a Log $P$ of $1.28$, a $vdWD$ of $0.861$ nm and a Log $P/vdWD$ of $1.49$ $nm^{-1}$. Cortisol has a calc $L_{\text{external structure}}/H_{\text{polar group}}$ ratio of $1.36$, and a nl calc $L_{\text{external structure}}/H_{\text{polar group}}$ quotient of $0.495$. The $t_{1/2}$ at receptor-receptor count ($t_{1/2R_{\text{count}}}$) for cortisol at MR is $7.605E + 03$ min-count, at GR is $6.610E + 03$ min-count, and the $\Sigma$ min-count is $1.42E + 04$ (Table 9).

Dexamethasone (DEX; $C_{21}H_{29}FO_3$) has a Log $P$ of $1.68$, a $vdWD$ of $0.873$ nm and a Log $P/vdWD$ of $1.92$ $nm^{-1}$. Corticosterone (Cort; $C_{21}H_{29}O_4$) has a Log $P$ of $2.02$, a $vdWD$ of $0.854$...
Table 9. Effective intracellular pressure grade of effect for molecular size-excluded steroid axis small molecule ligands at cell membrane receptors.

| Small molecule1 | Formula     | Log P | Molecular Weight (Da) | Size (Å^2) | vdWD (nm) | Polar SA (Å^2) | L_{external structure}/H_{polar group} (Ch,Oh ml); Log P/vdWD (nm)^2 | t_{1/2} \text{R}_{\text{count}} (min-count)^2 | \Sigma \text{min-count} |
|-----------------|-------------|-------|-----------------------|------------|-----------|---------------|------------------------------------------------|---------------------------|---------------------|
| Aldosterone     | C_{21}H_{29}O_{5} | 1.06  | 360                   | 341        | 0.856     | 92            | 0.478 (1.23)                                         | 2.366E+04 (MR), 6.61E+03 (GR) | 3.027E+04   |
| Cortisol        | C_{21}H_{30}O_{5} | 1.28  | 362                   | 347        | 0.861     | 95            | 0.495 (1.49)                                         | 7.60E+03 (MR), 6.61E+03 (GR) | 1.421E+04   |
| Dexamethasone   | C_{21}H_{30}O_{5} | 1.68  | 392                   | 362        | 0.873     | 95            | 0.461 (1.92)                                         | 1.183E+03 (MR), 1.322E+05 (GR) | 1.333E+05   |
| Diethylstilbestrol (DES) | C_{18}H_{20}O_{12} | 5.19  | 268                   | 263        | 0.786     | 40            | 1.31 (6.6)                                             | 1.863745E+06 (ERα) - | -                   |
| 17β-estradiol   | C_{18}H_{18}O_{2} | 3.75  | 272                   | 270        | 0.792     | 37            | 1.14 (4.73)                                           | 1.2E+06 (ERα) - | -                   |
| Dihydroxytestosterone (Dht) | C_{19}H_{20}O_{2} | 3.41  | 290                   | 301        | 0.822     | 37            | 1.15 (4.15)                                           | 1.7981E+05 (AR) - | -                   |
| Methyltrienolone (R1881) | C_{19}H_{20}O_{2} | 2.53  | 284                   | 278        | 0.800     | 37            | 0.932 (3.16)                                          | 2.4734E+05 (AR) - | -                   |
| Insulin-like growth factor II5 | -          | -     | -                     | -          | -         | -             | -                                                        | 1.943502E+06 (IGFII) - | -                   |

5 Macromolecular standard for negative ΔC_{micro} shift at lower limit of P_{eff}

1) half-lives at receptor (t_{1/2}) for DES at ERα (t_{1/2} = 663), DHT—R1881 at AR (t_{1/2} = 38.3–52.6 min) and IGFIIR at IGRIIR/M6P (t_{1/2} = 55.5) are determined by semi-exponential power regression x, y-plotting of radiolabeled hormone dissociation constants (K_{D}, x-axis) and values of t_{1/2} at receptor (min, y-axis), y = 3E - 05*x^{0.6784}, R^2 = 0.955 (y = 1E-08x + b = 45.50, R^2 = 0.999)

2) the rank order for the steroid axis hormone t_{1/2}; R_{\text{count}} (Σ \text{min-count} P_{eff} regulation effect is cortisol, aldosterone, DEX/corticosterone (Cort), DHT/R1881 (positive) and E2, DES (negative); and

3) the rank order of steroid axis hormone ligands for receptor subtypes (L_{external structure}/H_{polar group} quotient) is 0.461–0.495 (corticosteroid), 0.932–1.15 (androgen) and 1.18–1.31 (estrogen).

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Gene expression effective pressure mapping for small molecule hormones and bisphenol as ligands of cell membrane steroid axis receptors (in pharmacokinetic non-competition)

GCLC is a 2 A 3 ACM final SEB gene at x-, y-vertical axis angulation 32.4°. GCLC has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 2.128E + 04, 3.8969E + 04, 1.39792E + 05 and 2.58868E + 05 intergene bases. GCLC has an uppsebsiwaaa and dppebsiwaaa of 7.0960E + 04 and 1.48918E + 05 intergene bases with a $P_{\text{eff}}$ of 0.477 esebsiwaago$T_Q$ units (Table 10).

PER1 is a 2 A 6 ACM final SEB gene at x-, y-vertical axis angulation 42.4°. PER1 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 3.3824E + 04, 1.27508E + 04, 2.173E + 03 and 1.8993E + 04 intergene bases. PER1 has an uppsebsiwaaa and dppebsiwaaa of 1.7998E + 04 and 4.5728E + 04 intergene bases with a $P_{\text{eff}}$ of 0.394 esebsiwaago$T_Q$ units (Table 10).

PMCH is a 3 M 5 ACM final SEB gene at x-, y-vertical axis angulation 43.3°. PMCH has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 6.5883E + 04, 1.27508E + 04, 1.1105E + 04 and 7.1788E + 04 intergene bases. PMCH has an uppsebsiwaaa and dppebsiwaaa of 3.8494E + 04 and 9.848E + 04 intergene bases with a $P_{\text{eff}}$ of 0.386 esebsiwaago$T_Q$ units (Table 10).

NR3C1 is a 2 A 3 ACM final SEB gene at x-, y-vertical axis angulation 44.5°. NR3C1 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 1.2643E + 04, 2.26184E + 05, 2.10238E + 05, 3.65899E + 05 intergene bases. NR3C1 has an uppsebsiwaaa and dppebsiwaaa of 1.11440E + 05 and 2.96042E + 05 intergene bases with a $P_{\text{eff}}$ of 0.376 esebsiwaago$T_Q$ units (Table 10).

GPER1 is a 3 A 7 initial and final SEB gene at x-, y-vertical axis angulation 44.6°. NR3C1 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 4.697E + 03, 3.4332E + 04, 5.6825E + 04 and 1.29323E + 05 intergene bases. NR3C1 has an uppsebsiwaaa and dppebsiwaaa of 3.0761E + 04 and 8.1827E + 04 intergene bases with a $P_{\text{eff}}$ of 0.376 esebsiwaago$T_Q$ units (Table 10).

INSL3 is a 3 A 7 initial and final SEB gene at x-, y-vertical axis angulation 47.9° (act). INSL3 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 6.248E + 03, 5.8905E + 04, 3.7545E + 04 and 6.6648E + 04 intergene bases (act). INSL3 has an uppsebsiwaaa and dppebsiwaaa of 2.1896E + 04 and 6.2777E + 04 intergene bases with a $P_{\text{eff}}$ of 0.349 esebsiwaago$T_Q$ units (act) (Table 10).

DLK1 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 48.3°. DLK1 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 7.2336E + 04, 1.62011E + 05, 3.088E + 03 and 5.6714E + 04 intergene bases. DLK1 has an uppsebsiwaaa and dppebsiwaaa of 3.7712E + 04 and 1.69362E + 05 intergene bases with a $P_{\text{eff}}$ of 0.345 esebsiwaago$T_Q$ units (Table 10).

OLFM1 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 50.5°. OLFM1 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 2.7728E + 04, 6.0118E + 04, 9.980E + 03 and 5.7711E + 04 intergene bases. OLFM1 has an uppsebsiwaaa and dppebsiwaaa of 1.8854E + 04 and 5.7711E + 04 intergene bases with a $P_{\text{eff}}$ of 0.327 esebsiwaago$T_Q$ units (Table 10).

ADAM8 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 52.8°. ADAM8 has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 3.0415E + 04, 6.0950E + 04, 9.529E + 03 and 6.8596E + 04 intergene bases. ADAM8 has an uppsebsiwaaa and dppebsiwaaa of 1.9972E + 04 and 6.4773E + 04 intergene bases with a $P_{\text{eff}}$ of 0.308 esebsiwaago$T_Q$ units (Table 10).
Table 10. Effective intracellular pressure mapping of gene activation by molecular size-excluded small molecule hormones via cell membrane Gr, Mr, Er/β and AR receptor pathways as compared to bisphenol A.

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppesebiswia, dppesebiswia (Pπ, fract) | CM receptor ligand | Cell type |
|-----------------------------------------------|-------------------------|-----------|-----------------------------------------------|----------------------------------------|-------------------|-----------|
| GABPA (37,891; n/a)                           | 21q21.3 (+)              | -         | -                                             | -                                     | (0.694)           | Dec (PC12) |
| GCLC, glutamate-cysteine ligase catalytic subunit (119, 630; n/a) | 6p12.1 (-)              | 32.4      | 2 A 3 acm (2 A 5)                              | 7.096E06 + 04, 1.48918E + 05           | (0.477)           | Bpa [HCC] |
| PER1, period circadian protein homolog 1 (24,299; n/a) | 17p13.1 (-)             | 42.4      | 2 A 6 acm (2 A 5)                              | 1.7998E06 + 04, 4.5728E + 04           | (0.394)           | Dex [PC12] |
| PMCH, pro-melanin concentrating hormone (1,378; n/a) | 12q23.2 (-)             | 43.3      | 3 M 5 acm (3 M 7)                              | 3.8494E06 + 04, 9.9848E + 04           | (0.386)           | Dht [Bpa (dec)] |
| NR3C1, nuclear receptor subfamily 3 group C member 1 (157,582; n/a) | 5q31.3 (-)              | 44.5      | 2 A 3 acm (2 A 5)                              | 1.1144E05 + 05, 2.96042E + 05          | [0.3764 (0.376)]  | Dex (dec) |
| GPER1, G protein-coupled estrogen receptor 1 (11, 608; n/a) | 7p22.3 (+)              | 44.6      | 3 A 7 (-)                                      | 3.0761E04 + 04, 8.1827E + 04           | [0.3759 (0.376)]  | Ald [Dex (dec)] |
| INSL3, insulin like 3 (5,063; n/a)ext         | 19p13.11 (-)             | 47.9      | 3 A 7 (-)                                      | 2.1896E04 + 06, 6.2777E + 04           | (0.349)           | Bpa |
| DLK1, delta like non-canonical notch ligand 1 (12,520; n/a) | 14q32.31 (+)             | 48.3      | 2 M 5 (-)                                      | 3.7712E06 + 04, 1.69362E + 05          | [0.345]           | Bpa |
| FKBP5                                         |                         |           |                                                |                                       | (0.342)           | Dex (Dex + Dht) |
| OLFM1, olfactomedin 1 (45,942; n/a)           | 9q34.3 (+)               | 50.5      | 2 M 5 (-)                                      | 1.8854E04 + 04, 5.7711E + 04           | (0.327)           | E2 |
| ADAM8, ADAM metallopeptidase domain 8 (14,468; n/a) | 10q26.3 (-)             | 52.8      | 2 M 5 (-)                                      | 1.9972E04 + 04, 6.4773E + 04           | (0.308)           | Bpa |
| SIM1, single-minded homolog 1 (79,921; n/a)   | 6q16.3 (-)               | 55.0      | 2 A 5 (-)                                      | 3.1171E04 + 04, 1.02794E + 05          | (0.303)           | Bpa |
| CCND1, cyclin D1 (13,888; n/a)                | 11q13.3 (+)              | 55.0      | 2 A 5 (-)                                      | 2.5646E04 + 04, 8.8315E + 04           | (0.290)           | E2 [Bpa (dec)] |
| RAPGFI1, link guanine nucleotide exchange factor II (182,670; n/a) | 17q21.2 (+)             | 55.9      | 2 A 5 (-)                                      | 9.904E04 + 03, 3.5054E + 04           | (0.283)           | E2 |
| CYP3A4                                        |                         |           |                                                |                                       | (0.281)           | Dex (inc); E2 (dec) |
| CDKNIA, Cyclin-dependent kinase inhibitor 1A (p21, 10,880; n/a) | 6p21.2 (+)              | 56.7      | 3 A 5 acm slIMMα (3 A 7)                       | 2.3343E04 + 04, 8.4664E + 04           | (0.276)           | Bfap [HCC] |
| DUSP1                                         |                         |           |                                                |                                       | (0.272)           | Dex |
| JUN                                           |                         |           |                                                |                                       | (0.267)           | Bpa |
| FABP4, fatty acid binding protein 4 (4,845; n/a) | 8q21.13 (-)             | 58.1      | 3 A 7 (-)                                      | 5.8408E04 + 04, 2.21498E + 05          | (0.264)           | Bpa (+ Dex) |
| NR3C2, nuclear receptor subfamily 3, group C, member 2 (366,517; n/a) | 4q31.23 (-)             | 58.4      | 4 A 9 (-)                                      | 5.1635E04 + 04, 1.97691E + 05          | (0.261)           | Dex (Ald) |
| MEG3, maternally expressed 3 (259,450; 81,622) | 14q32.31 (+)             | 58.9      | 2 A 2 acm acm ext (2 A 5)                      | 5.5514E04 + 04, 2.5541E + 05           | (0.258)           | -- |
| DFFA, DNA fragmentation factor subunit alpha (16,015; n/a) | 1p36.22 (-)             | 58.9      | 2 A 5 (-)                                      | 3.7047E04 + 04, 1.43906E + 05          | (0.257)           | Bpa |
| FOS, fos proto-oncogene, AP-1 transcription factor subunit (3,461; n/a) | 14q24.3 (+)             | 59.1      | 3 M 9 acm (3 M 7)                              | 4.4895E04 + 04, 9.5063E + 04           | (0.256)           | Bpa |
| TIMM8B, translocase of inner mitochondrial membrane 8 homolog 8 (1,999; n/a) | 11q23.2 (-)             | 60.2      | 3 A 8 acm acm ext (3 A 7)                      | 3.9647E04 + 04, 1.60497E + 05          | (0.247)           | Bpa |
| GADD45A                                       |                         |           |                                                |                                       | (0.245)           | Bfap [HCC] |
| CYP1A1                                        |                         |           |                                                |                                       | (0.216)           | Bpa [HCC], Bfap [HCC] |
| ESRRG                                         |                         |           |                                                |                                       | (0.209)           | Bpa |
| MIAT, myocardial infarction associated transcript (30,068; n/a) | 22q12.1 (+)             | 65.2      | 2 M 6 acm (2 A 5)                              | 6.444E03 + 03, 3.1409E + 04           | (0.205)           | Bpa |
| NRF1                                          |                         |           |                                                |                                       | [0.200 (0.2001)] | Bpa |
| CYP17A1, cytochrome P450 family 17 subfamily A member 1 (7,003; n/a) | 10q24.32 (-)             | 65.8      | 3 A 5 nca acm (3 A 7)                         | 2.8621E04 + 04, 1.43391E + 05          | [0.200 (0.1996)] | Dht (Continued) |
**Table 10. (Continued)**

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppesebsiwa, dppsebsiwa 
\( P_{\text{eff}} \) fract | CM receptor ligand
\(^\text{Cell type}\) 
\(^\text{(dec)}\) decrease, dec |
|---|---|---|---|---|---|
| **ESRRA** | | | 0.196 | -- |
| **FOSB** | | | 0.194 (0.1943) | Dex (dec) |
| **PLEKHG4**, pleckstrin homology and RhoGEF containing G4 (11,991; n/a) | 16q21 (+) | 66.6 | 2 A 8 acm acm ext (2 A 5) | 9.490E + 03, 4.8961E + 04 \[0.194 (0.1938)\] | Bpa |
| **ESR1** | | | 0.184 (0.1836) | E\(_2\) |
| **FLNA**, filamin A (26,115; n/a) | Xq28 (-) | 67.8 | 2 A 5 | 1.1217E + 04, 6.1000E + 04 \[0.184 (0.1839)\] | E\(_2\) |
| **SLC9A1**, solute carrier family 9 member A1 (68,173; n/a) | 1p36.11 (-) | 68.8 | 2 M 5 (-) | 1.8447E + 04, 1.10234E + 05 \[0.167\] | Ald |
| **AR** | | | (0.156) | Dht |
| **HMOX1** | | | 0.153 (0.1531) | Bpa (inc, m) |
| **TFF1**, trefoil factor 1 (4,313; n/a) | 21q22.3 (-) | 72.2 | 3 M 7 (-) | 2.3119E + 04, 1.57237E + 04 \[0.147\] | E\(_2\) |
| **ESR2** | | | [0.136 (0.1361)] | E\(_2\) (dec) | [Bpa (s.s; inc, m) + agonist] |
| **CYP11B2**, cytochrome P450 family 11 subfamily B member 2 (7,305; 36,731) | 8q24.3 (-) | 76.5 | 2 A 5 (-) | 1.6007E + 04, 1.43026E + 05 \[0.112\] | E\(_2\) + \(\chi^{HCC}\) (Ald) |
| **UGT1A1** | | | (0.106) | Bpa \(\text{HCC}\) |
| **CYP11B1**, cytochrome P450 family 11 subfamily B member 1 (7,498; n/a) | 8q24.3 (-) | 78.1 | 3 M 7 (-) | 1.4197E + 04, 1.43639E + 05 \[0.099\] | Dex (dec) |
| **TGF1**, TGFβ induced factor homeobox 1 (194,834; 48,371) | 18p11.31 (+) | 80.3 | 2 A 5 (-) | 1.9246E + 04, 2.4060E + 04, 4.2285E + 04 and 1.05247E + 05 intergene bases. |

**BPA**, intracellular ligand, ERR\(_{\gamma}\); BPAF, extracellular ligand, ER\(_{\beta}\); cell type, if transformed (ie PC12, HCC); Dht, dihydroxytestosterone; Ald, aldosterone; X, CM receptor inverse agonist(s)/antagonist; \(^a\), actual; s-s, sex specific

\(^b\)\( P_{\text{eff}}\) at duration for expression of AhR gene reporter plasmid; SLC9A1, NHE-1; SLC9A1, NHE-1;\(\gamma\); CYP11B1, 11-beta-hydroxylase; CYP11B2, aldosterone synthase; \(^c\) FOS, JUN, ESR1 and ESR2, ERE containing genes

\(^d\) AhR, CAR & GR response element-containing genes, UGT1A1; CYP11A1, Ahr (Arnt) recruitment of ER to XRE; and GSTA1, JUN recruitment of GR to TRE

\(^e\) PPARG coactivator 1 alpha (PGC1\(\alpha\)), ERR\(_{\gamma/-}\alpha\), SREBF and CAR protein binding partner; and \(^\circ\) secondary activation of genes at \( P_{\text{eff}} \) 0.106 for variable duration as applicable to both pathways (ie UGT1A) \(^1\) gene loci sub-episode block structure (SEB) variations include non-contributory anisotropy (NCA), anisotropy converted to mesotropy (ACM), 0.5-factor adjusted stabilizing anisotropy or anisotropy converted to stabilizing isotropy for anisotropy or mesotropy (stIAfM, stIMfA or stIMfM), and/or extended block (ext) SEB; and \(^5\) gene(s) with previously reported episode and sub-episode block structure include INS/3 and GABPA \([22]\).

**SIM1** is a 2 A 5 initial and final SEB gene at \( x^-\), \( y\)-vertical axis angulation 54.9°. **SIM1** has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 2.9304E + 04, 1.50699E + 05, 3.3038E + 04 and 5.4889E + 04 intergene bases. **SIM1** has an uppasebsiwa and dppasebsiwa of 3.1171E + 04 and 1.02794E + 05 intergene bases with a \( P_{\text{eff}} \) of 0.303 esbsiwaao\(\text{T}_{\text{Q}}\) units (Table 10).

**RAPGEFL1** is a 2 A 5 initial and final SEB gene at \( x^-\), \( y\)-vertical axis angulation 55.9°. **RAPGEFL1** has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 5.474E + 03, 3.2272E + 04, 1.4334E + 04 and 3.7835E + 04 intergene bases. **RAPGEFL1** has an uppasebsiwa and dppasebsiwa of 9.904E + 03 and 3.5054E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.283 esbsiwaao\(\text{T}_{\text{Q}}\) units (Table 10).

**CDKN1A** is a 3 A 5 ACM stIMM\(_{\alpha}\) extended final SEB gene at \( x^-\), \( y\)-vertical axis angulation 56.7°. **CDKN1A** has an uppasebsiwa, dppasebsiwa, uppmsebsiwa and dppmsebsiwa of 4.400E + 03, 6.4050E + 04, 4.2285E + 04 and 1.05247E + 05 intergene bases. **CDKN1A** has an uppasebsiwa and dppasebsiwa of 2.3343E + 04 and 8.4648E + 04 intergene bases with a \( P_{\text{eff}} \) of 0.276 esbsiwaao\(\text{T}_{\text{Q}}\) units (Table 10).

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FABP4 is a 3 A 7 initial and final SEB gene at x-, y-vertical axis angulation 58.1°. FABP4 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 3.6724E + 04, 2.66777E + 05, 8.0092E + 04 and 1.76219E + 05 intergene bases. SIM1 has an uppesebssiwaa and dppesebssiwaa of 5.8408E + 04 and 2.21498E + 05 intergene bases with a P_{eff} of 0.264 esebsiwaagoT_Q units (Table 10).

NR3C2 is a 4 A 9 initial and final SEB gene at x-, y-vertical axis angulation 58.4°. NR3C2 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 2.4496E + 04, 1.86526E + 05, 7.8774E + 04 and 2.08856E + 05 intergene bases. NR3C2 has an uppasebssiwaa and dppesebssiwaa of 5.1635E + 04 and 1.97691E + 05 intergene bases with a P_{eff} of 0.261 esebsiwaagoT_Q units (Table 10).

MEG3 is a 2 A 2 ACMx2 ext final SEB gene at x-, y-vertical axis angulation 58.9°. MEG3 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 5.197E + 03, 1.77555E + 05, 1.05830E + 05 and 2.5514E + 05 intergene bases. MEG3 has an uppasebssiwaa and dppesebssiwaa of 5.5514E + 04 and 2.15416E + 05 intergene bases with a P_{eff} of 0.258 esebsiwaagoT_Q units (Table 10).

DFFA is a 3 A 5 initial and final SEB gene at x-, y-vertical axis angulation 58.9°. DFFA has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.4323E + 04, 1.44368E + 05, 5.9771E + 04 and 1.43444E + 05 intergene bases. DFFA has an uppasebssiwaa and dppesebssiwaa of 3.7047E + 04 and 1.43906E + 05 intergene bases with a P_{eff} of 0.257 esebsiwaagoT_Q units (Table 10).

FOS is a 3 A 9 ACM final SEB gene at x-, y-vertical axis angulation 59.1°. DFFA has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.5182E + 04, 1.39901E + 05, 4.4895E + 04 and 9.5063E + 04 intergene bases. FOS has an uppasebssiwaa and dppesebssiwaa of 3.0039E + 04 and 1.17482 + 05 intergene bases with a P_{eff} of 0.268 esebsiwaagoT_Q units (Table 10).

TIMM8B is a 3 A 8 ACMx2 ext final SEB gene at x-, y-vertical axis angulation 60.2°. TIMM8B has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 2.5423E + 04, 2.04260E + 05, 5.3871E + 04 and 1.16735E + 05 intergene bases. TIMM8B has an uppasebssiwaa and dppesebssiwaa of 3.9647E + 04 and 1.60497E + 05 intergene bases with a P_{eff} of 0.247 esebsiwaagoT_Q units (Table 10).

MIAT is a 2 M 6 acm final SEB gene at x-, y-vertical axis angulation 65.2°. MIAT has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.51841E + 04, 1.96677E + 04, 1.408E + 03 and 4.3151E + 04 intergene bases. MIAT has an uppasebssiwaa and dppesebssiwaa of 6.444E + 03 and 0.194 esebsiwaagoT_Q units (Table 10).

CYP17A1 is a 3 A 5 NCA ACM final SEB gene at x-, y-vertical axis angulation 65.8°. CYP17A1 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.4406E + 04, 1.79367E + 05, 4.2836E + 04 and 1.07414E + 05 intergene bases. CYP17A1 has an uppasebssiwaa and dppesebssiwaa of 2.8621E + 04 and 1.43391E + 05 intergene bases with a P_{eff} of 0.200 esebsiwaagoT_Q units (Table 10).

PLEKHG4 is a 2 A 9 ACMx2 final SEB gene at x-, y-vertical axis angulation 66.6°. PLEKHG4 has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 8.609E + 03, 7.77741E + 04, 1.0374E + 04 and 2.0179E + 04 intergene bases. PLEKHG4 has an uppasebssiwaa and dppesebssiwaa of 9.490E + 03 and 4.8961E + 04 intergene bases with a P_{eff} of 0.194 esebsiwaagoT_Q units (Table 10).

FLNA is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 67.8°. FLNA has an uppasebssiwaa, dppasebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 9.480E + 03, 8.6967E + 04, 1.2954E + 04, 3.5033E + 04 intergene bases. FLNA has an uppasebssiwaa and dppesebssiwaa of 2.21498E + 05 intergene bases with a P_{eff} of 0.169 esebsiwaagoT_Q units (Table 10).
CEBPD is a 5 M 11 initial and final SEB gene at x-, y-vertical axis angulation 69.7⁰. CEBPD has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 8.8872E + 04, 1.85923E + 05, 5.5818E + 04 and 6.74877E + 05 intergene bases. CEBPD has an upapesbssiwaa and dppsesbssiwaa of 7.2345E + 04 and 4.30400E + 05 intergene bases with a $P_{\text{eff}}$ of 0.168 esebsiwaago$T_Q$ units (Table 10).

SLC9A1 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 69.8⁰. SLC9A1 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.8999E + 04, 7.1281E + 04, 7.895E + 03 and 1.49186E + 05 intergene bases. SLC9A1 has an upapesbssiwaa and dppsesbssiwaa of 1.8447E + 04 and 1.10234E + 05 intergene bases with a $P_{\text{eff}}$ of 0.167 esebsiwaago$T_Q$ units (Table 10).

TFF1 is a 3 M 7 initial and final SEB gene at x-, y-vertical axis angulation 72.2⁰. TFF1 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 3.0485E + 04, 7.8313E + 04, 1.5753E 04 and 2.36160E + 05 intergene bases. TFF1 has an upapesbssiwaa and dppsesbssiwaa of 2.3119E + 04 and 1.57237E + 05 intergene bases with a $P_{\text{eff}}$ of 0.147 esebsiwaago$T_Q$ units (Table 10).

GSTA1 is a 2 M 7 final SEB gene at x-, y-vertical axis angulation 72.35⁰. GSTA1 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 7.761E + 03, 2.6442E + 04, 7.148E + 03 and 5.1039E + 04 intergene bases. GSTA1 has an upapesbssiwaa and dppsesbssiwaa of 7.454E + 03 and 5.1039E + 04 intergene bases with a $P_{\text{eff}}$ of 0.146 esebsiwaago$T_Q$ units (Table 10).

CYP11B2 is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 76.5⁰. CYP11B2 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.4767E + 04, 2.73740E + 05, 7.246E + 03 and 1.2312E + 04 intergene bases. CYP11B2 has an upapesbssiwaa and dppsesbssiwaa of 1.6007E + 04 and 1.43026E + 05 intergene bases with a $P_{\text{eff}}$ of 0.112 esebsiwaago$T_Q$ units (Table 10).

CYP11B1 is a 3 M 7 initial and final SEB gene at x-, y-vertical axis angulation 78.1⁰. CYP11B1 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.8541E + 04, 4.5978E + 04, 9.835E + 03 and 2.41300E + 05 intergene bases. CYP11B1 has an upapesbssiwaa and dppsesbssiwaa of 1.4197E + 04 and 1.43639E + 05 intergene bases with a $P_{\text{eff}}$ of 0.099 esebsiwaago$T_Q$ units (Table 10).

TGIF1 is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 80.3⁰. TGIF1 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 2.2126E + 04, 4.50996E +05, 1.6366E + 04 and 3.0205E + 04 intergene bases. TGIF1 has an upapesbssiwaa and dppsesbssiwaa of 1.9246E + 03 and 2.40600E + 05 intergene bases with a $P_{\text{eff}}$ of 0.099 esebsiwaago$T_Q$ units (Table 10).

**Gene expression effective pressure mapping for diethylstilbestrol (DES) as a ligand of the cell membrane ERα/β steroid axis receptor**

A2M is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 43.1⁰. A2M has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 8.931E + 03, 5.9005E +04, 5.7966E + 04 and 1.32425E + 05 intergene bases. A2M has an upapesbssiwaa and dppsesbssiwaa of 3.3448E + 04 and 8.6274E + 04 intergene bases with a $P_{\text{eff}}$ of 0.388 esebsiwaago$T_Q$ units (Table 11).

HOXA13 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation 48.2⁰. HOXA13 has an upapsebssiwa, dppasebssiwa, uppmsebssiwa and dppmsebssiwa of 1.04360E + 05, 2.55391E + 05, 1.9369E + 04 and 1.02576E + 05 intergene bases. HOXA13 has an upapesbssiwaa and dppsesbssiwaa of 6.1864E + 04 and 1.78884E + 05 intergene bases with a $P_{\text{eff}}$ of 0.346 esebsiwaago$T_Q$ units (Table 11).
Table 11. Effective intracellular pressure mapping of directional gene activation by DES via the cell membrane ERα receptor in the Mullerian axis in differentiation.

| Human gene (no. of bases, locus bases or n/a) | Gene locus (ch, strand) | Angle (°) | Episode category (final, initial SEB structure) | uppasebssiwaa, dppebssiwaa (Peff, adj) | Peff (ov) effect pathway |
|-----------------------------------------------|-------------------------|-----------|-----------------------------------------------|-----------------------------------------|--------------------------|
| A2M, alpha-2-macroglobulin (48,566; n/a)      | 12p13.31 (-)            | 43.2      | 2 A 5 (-)                                     | 3.3448E + 04, 8.6274E + 04 (0.388)       | Des (ovi)                |
| HOXA13, homeobox A13 (13,694; n/a)            | 17q15.3 (-)             | 48.2      | 2 M 5 (-)                                     | 6.1864E + 04, 1.7888E + 05 (0.346)       | Des (n/c)                |
| HOXA11, homeobox A11 (4,067; n/a)             | 7q15.3 (-)              | 49.9      | 2 M 8 acm (3 A 7)                             | 6.3386E + 04, 1.90703E + 05 (0.332)      | Des (dec, ut)            |
| CCND1                                         |                         |           | (0.290)                                       |                                         |                          |
| HOXA10, homeobox A10 (12,827; 17,827)         | 7p15.3 (-)              | 56.62     | 2 M 5 (-)                                     | 2.6583E + 04, 9.6199E + 04 (0.2763)      | Des (dec, ut)            |
| HOXA9, homeobox A9 (5,084; 17,827)            | -                       | 56.62     | -                                             | (> 0.2763)                              | Des (inc, ut; dec, ovi)  |
| FOS                                           |                         |           | (0.256)                                       |                                         |                          |
| KLF4, kruppel like factor 4 (5,631; n/a)      | 17q21.2 (+)             | 66.65     | 3 A 7                                        | 5.3916E + 04, 2.2184E + 05 (0.243)       | Des (ut)                 |
| TFF1                                          |                         |           | (0.147)                                       |                                         |                          |
| ESR2                                          |                         |           | 0.136 (0.1361)                                | E2 (inc)                                 |                          |
| WNT5A, Wnt family member 5A (39,547; n/a)    | 3q14.3 (-)              | 73.6      | 2 A 5 (-)                                     | 3.3867E + 04, 2.49146E + 05 (0.1359) #   | Des (inc, ut)            |
| CYP11B1                                       |                         |           | (0.099)                                       |                                         |                          |

DES, diethylstilbestrol; n/c, no change; uterine; ovi, oviduct

§, k same locus genes include HOXA9 with P eff towards ≥ 0.2763 (5’ downstream; P eff (adj) 0.27630) and HOXA10 with P eff 0.2763 (5’ upstream; P eff 0.27630); b HOXA9 z, y-plane alignment P eff (adj) is 0.27633 when (+) Δ P eff is 0.01078 (WNT5A, P eff 0.1359, DES; TFF1, P eff 0.1470, E2) and 5-digit adjustment is (P eff HOXA10 0.29788E - 05) sequentially I esebsiwaaagoT5Q to final P eff for WNT5A gene expression is: 0.0656, 0.0895, 0.1138, 0.1430, 0.1359, 0.1939; k Gene loci sub-episode block structure (SEB) variations include non-contributory anisotropy (NCA), anisotropy converted to mesotropy (ACM), 0.5-factor adjusted stabilizing mesotropy or anisotropy converted to stabilizing isotropy for anisotropy or mesotropy (stIAfM, stIMfM).

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HOXA11 is a 2 M 8 ACM final SEB gene at x-, y-vertical axis angulation 49.9°. HOXA11 has an uppasebssiwaa, dppebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 1.14015E + 05, 2.54118E + 05, 1.2758E + 04 and 1.27288E + 05 intergene bases. HOXA11 has an uppasebssiwaa and dppebssiwaa of 6.3386E + 04 and 1.90703E + 05 intergene bases with a Peff of 0.332 esebsiwaagoT5Q units (Table 11).

HOXA9/HOXA10 is a 2 M 5 initial and final SEB gene at x-, y-vertical axis angulation ≥ 56.6°. HOXA9/HOXA10 has an uppasebssiwaa, dppebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 4.34614E + 04, 9.8407E + 04, 9.552E + 03 and 9.3991E + 04 intergene bases. HOXA9/ HOXA10 has an uppasebssiwaa and dppebssiwaa of 2.6583E + 04 and 9.6199E + 04 intergene bases with a Peff of ≥ 0.2763 esebsiwaagoT5Q units.

KLF4 is a 3 A 7 initial and final SEB gene at x-, y-vertical axis angulation 60.65°. KLF4 has an uppasebssiwaa, dppebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 2.9538E + 04, 3.7755E + 04, 7.8294E + 04 and 1.66138E + 05 intergene bases. KLF4 has an uppasebssiwaa and dppebssiwaa of 5.3916E + 04 and 2.2184E + 04 intergene bases with a Peff of 0.243 esebsiwaagoT5Q units (Table 11).

WNT5A is a 2 A 5 initial and final SEB gene at x-, y-vertical axis angulation 73.6°. WNT5A has an uppasebssiwaa, dppebssiwaa, uppmsebssiwaa and dppmsebssiwaa of 3.4162E + 04, 4.41140E + 05, 3.3572E + 05 and 5.7151E + 04 intergene bases. WNT5A has an uppasebssiwaa and dppebssiwaa of 3.3867E + 04 and 2.49146E + 05 intergene bases with a Peff of 0.1359 esebsiwaagoT5Q units (Table 11).
van der Waals diameter, structural lipophilicity and hydrophilicity parameters for small molecules with exterior or interior structural lipophilicity

Tetradotoxin (C₁₁H₁₄N₄O₄) has a Log D of -6.84, a vDW: 0.774 nm and a Log D/vdWD of -8.84 nm⁻¹. 2,4-diazatetracyclotetradeane (C₁₁H₁₄N₂O₄) has a Log P of 0.847, a vDW: 0.624 nm and a Log P/vdWD of 1.36 nm⁻¹. Tetradotoxin has a calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.085 (Table 12).}

Saxitoxin (C₁₉H₂₉N₇O₄) has a Log D of -7.12, a vDW: 0.764 nm and a Log D/vdWD of -9.32 nm⁻¹. 3,4-pyrrolo-4,5-imidazolo-6-methyl-piperazine (C₁₀H₁₂N₂) has a Log P of 0.13, a vDW: 0.682 nm and a Log P/vdWD of 0.19 nm⁻¹. Saxitoxin has a calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.101 (Table 12).}

m-xylenediamine (C₈H₁₄N₂) has a Log D of -5.84, a vDW: 0.635 nm and a Log D/vdWD of -7.40 nm⁻¹. 1,2-dimethylbenzene (C₉H₁₀) has a Log P of 3.00, a vDW: 0.598 nm and a Log P/vdWD of 5.02 nm⁻¹. m-xylenediamine has a calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.252, and a nl calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.092 (Table 12).}

Phthaleate (C₈H₄O₄) has a Log D of -4.70, a vDW: 0.633 nm and a Log D/vdWD of -7.42 nm⁻¹. Benzene (C₆H₆) has a Log P of 1.97, a vDW: 0.532 nm and a Log P/vdWD of 3.70 nm⁻¹. Phthaleate has a calc L/\text{H} \quad \text{polar group} \quad \text{ratio of 0.215, and a nl calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.078 (Table 12).}

1,2-diaminocyclohexane (C₁₀H₁₆N₂²⁺) has a Log D of -6.07 (-2.05), a vDW: 0.622 nm and a Log D/vdWD of -9.76 (-3.34) nm⁻¹. Cyclohexane (C₆H₁₂) has a Log P of 2.67, a vDW: 0.699 nm and a Log P/vdWD of 4.67 nm⁻¹. m-xylenediamine has a calc L/\text{H} \quad \text{polar group} \quad \text{ratio of 0.233 (0.470), and a nl calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.085 (0.171) (Table 12).}

N-acetylneuraminic acid (C₂₃H₃₀O₄; Neu5Ac) has a Log D of -7.40, a vDW: 0.790 nm and a Log D/vdWD of -9.37 nm⁻¹. Pentane has a Log P of 2.69, a vDW: 0.561 nm and a Log P/vdWD of 4.97 nm⁻¹. Neu5Ac has a calc L/\text{H} \quad \text{polar group} \quad \text{ratio of 0.2189, and a nl calc L/\text{H} \quad \text{polar group} \quad \text{quotient of 0.0796 (Table 12).}

Discussion

Molecular philicity interval for facilitated transport though cell membrane channels as determined by L/\text{H} \quad \text{polar group} \quad \text{of C₄ -C₄ alkane hydroxylate isomers}

The molecular philicity interval limit for facilitated transport though cell membrane channel pores is determined in this study by in silico modeling of transporter threshold for mono-, di-...
and poly-hydroxylate transport through the high affinity aquaporin-9 (hAQP-9) transport channel, which has a low-micromolar (uM) transport constant (Km) as determined in oocyte plasmid transfectants [19,20]. Since hAQP-3 and hAQP-9 have the lowest reflection coefficients (σ, a.u.) to the flux of 1,3-propanediol and 2,3-glycer-1-ol as the polarity-specific transport substrates, in this study the lipophilicity per molecular polarity is determined for C1 - C4 hydroxylates (Iexternal structure ∙ Hpolar group -1). Based on study findings, 2,3-glycer-1-ol has an external structure lipophilicity Log P/vdWD of 3.71 nm -1 with an unadjusted Log Palane ∙ vDWDA −1 /Log Palane ∙ vdwDOH -1 of 0.428 (0.545 nm; -3.38 nm -1) in reference to methane-1-ol (L·H -1, 2.75 (1.00); 1.275 nm -1), while S(+) -1,2-propanediol has a Iexternal structure ∙ Hpolar group -1 of 1.047, which is a competitive inhibitor for polarity-specific transport of glycerol through hAQP-9 [19]. Furthermore, based on study findings, hydroxylates, 1,3-propanediol with a L·H -1 of 1.113 (vdWD: 0.527 nm), 1,2-butanediol with a L·H -1 of 1.207 (vdWD: 0.562 nm) will be non-specific passive transport substrates for glyceroaquaporin-9, as compared to 1,2-ethanediol with a L·H -1 of 0.535 (vdWD: 0.486 nm), more hydrophilic channel substrates, mannitol (L·H -1, 0.304; vDWD: 0.672 nm, -5.55 nm -1) and lactate (L·H -1, 0.272, -1; vDWD: 0.526 nm, -7.04 nm -1), of which the latter demonstrates increased flux in its un-ionized form (L·H -1, 0.328, -0.893 nm -1) with maintained polarity-specificity for the channel. Therefore, based on the study findings, a Iexternal structure ∙ Hpolar group -1 of ≥ 1.07 is the molecular structure lipophilicity limit for non-specific carrier-mediated transmembrane diffusion through polarity-selective transport channels of the cell membrane (Table 1, Fig 1).

Pressure regulated gene activation by C2 - C4 halogenates, C9 - C12 alcohols and unsubstituted biphenyl with asphyxiant properties

The part-molecular structural Iexternal structure ∙ Hpolar group -1 of C2 - C4 halogenates and halogenate ethers (-O-) with vDWD in the 0.554 – 0.610 nm range was studied as a determinant of the potency of the halogenate-mediated effect on gene activation, as vDWD is shown to be an independent predictive determinant of end-tidal minimum alveolar concentration (MAC; vol%) based on trichloromethane (CHCl3; 0.505 nm), halothane (C2HBrClF3; 0.554 nm), isoflurane and enflurane (C2H2ClF3O; 0.588 nm), and sevoflurane (C2H2F2O; 0.610 nm) as standards 0.73 (R2 = 0.73) compared to respective molecular weights (da) (R2 = 0.29, Table 2). Further, based on the study findings, 1,1,1-trifluoro-2-chloroethane (C2H2ClF3; 3.48 nm -1), 1-chloro-1,2,2-trifluoroethane (C2H2ClF3; 2.99 nm -1) and 1,1,1-trifluoro-2-fluoroethane (C2H2F2Cl; 2.70 nm -1) are the primary determinant moieties of overall structural Iexternal structure ∙ Hpolar group -1 for Isoflurane (L·H -1: 4.09), Enflurane (L·H -1: 3.72) and Desflurane (L·H -1: 3.50); 1,1,1,3,3,3-hexafluoropropane (C2H2F6O; 3.85 nm -1) and fluoromethane (CH2F; 0.939 nm -1) are co-determinant moieties of overall structural L·H -1 for Sevoflurane (3.83), which bell curve (□) rank orders anesthetic potency of part-structure halogenates inclusive of Desflurane that deviates from the Meyer-Overton rule due to lower part-structural structural Iexternal structure ∙ Hpolar group -1, as do the aliphatic alcohols due to a lower Log Pcarbon; particularly C2 -C6 carbon length within a lower Log P/vDWD range [23] that deviate less than their non-polar alkane counterparts [24], in comparison to Halothane with more lipophilic substitution (C2HBrClF3; 3.82 nm -1, L·H -1: na) and uM Keff affinity for cytochrome P450 catalysis under atmospheric pressure in vitro [25].

Studies on gene activation upon exposure to C2 - C4 halogenates have shown the differential expression of characteristic genes in response to Sevoflurane, Isoflurane and Halothane or to a combination (COMB) of non-inhalation (ie pentobarbital, midazolam) or chloral hydrate (CH) alone in a spectrum of cells (hippocampal neuron, type II alveolar cell, hepatocyte, T-lymphocyte). In these studies it is shown that cellular FOSB expression (Peff 0.194) decreases with in vitro COMB or CH exposure while expression remains unchanged with Isoflurane exposure (4 vol %, 1 min).
HMOX1 expression ($P_{eff}$, 0.153) increases with *in vivo* Sevoflurane or Isoflurane exposure (2–4 vol %) [27]; SFTPC expression ($P_{eff}$, 0.257) increases with *in vitro* Halothane exposure (1–4 vol %) or with *in vivo* Pentobarbital analog exposure, and decreases with *in vivo* Halothane exposure.
Molecular size-exclusion limit for facilitated transport though cell membrane channels as determined by differential \( P_{\text{eff}} \) mapping of higher-substituted biphenyls

The molecular size-exclusion limit for facilitated transport through cell membrane channel pores is determined by study of the differential \( P_{\text{eff}} \) response to higher-substituted polychlorinated biphenyls, 3,4,4',5,5':-co-planar PCB-126 (0.749 nm) and co-, ortho-planar 2',3,4,4',5',6'-PCB-153 (0.758 nm). During applied exposure to 3’-OH-3,4,4',5,5':-co-planar PCB-126 in silico as a representative co-planar PCB at a chiral carbon \( x, y, z \)-plane van der Waals diameter of 0.752 nm, the lower limit of \( P_{\text{eff}} \) decreases to the \( x, z \)-plane alignment pressure for Dio3 (\( P_{\text{eff}} \) 0.096) during which the upper limit of \( P_{\text{eff}} \) decreases to 0.379 (CEA-CAM1\(^a\) [22]) and 0.331 (NFE2L2, NRF-2 [22]) esebsiwaago\( T_Q \) units during which contraction occurs; whereas, during applied exposure to PCB-153, the lower limit of \( P_{\text{eff}} \) decreases to 0.057 (TSPAN12) with contraction to \( P_{\text{eff}} \) 0.159 (CES2). Thus, there are distinct alterations in cell micro-compliance in response to TCDD and co-planar PCB (ie 5-OH-PCB-126; 2-OH-3,3',4,4'-PCB-77) in comparison to applied co-, ortho-planar PCB (ie 5-OH-PCB-153; 4-OH-PCB-54), which implies a lower affinity Dio-2 enzyme non-exothermy inactivation pathway for the former (co-planar; 3’-OH-PCB-126, vdWD: 0.752 nm) relative to the higher affinity Dio-1/-3 enzyme inactivation pathway in case of the latter (co-, ortho-planar; PCB-153, vdWD: 0.758).

\( C_6 - C_{11} \) carbon length straight alcohols of increasing \( n \)-alkyl chain length and molecular weight (Da) have been shown to exert concentration dependent inhibitory effects on the P450 cytochrome monooxygenase activity (aminopyrine demethylation) in vitro, with disassociation constants (K\(_d\)) ranging between 1.3 mM (C\(_6\) hexanol) and 2.66 mM (C\(_{13}\) tridecanol) with uM inhibition by dodecanol (C\(_{12}\); 35 uM) [30, 31], indicative of a cutoff of enzyme activity at a chain length of between 12- and 13-C (vdWD: 0.744–0.762 nm) at the cell membrane channel pore vdWD, in which case C\(_2\)-ethanol (mM) is non-exothermic (\(-\Delta T\); °C) as compared to C\(_{16}\)-hexadecan-1-ol (C\(_{16}\)H\(_{34}\)O, cetyl; uM) with inhibitory effect at a CM receptor [32]. Therefore, the decrease in cell \( P_{\text{eff}} \) (0.153–0.160) due to C\(_{2.4}\) halogenate-mediated inner mitochondrial membrane (IMM) micro-compliance alteration is attributable to resultant ATP deficit, and synergistic with the affinity perturbation of CM by larger poly-substituted alcohols (ie C\(_{16}\)H\(_{34}\)O\(_4\) isomers) [33], which are convergent mechanisms of decreased cell micro-compliance (\(-\Delta C_{\text{micro}}\)) initially, prior to protein adduct effects on \( C_{\text{micro}}\). These findings support the study determinations of cell membrane channel pore size of > 0.752 and < 0.758 nm based on a 3-D ellipsoid model (substituted biphenyl), and within the molecular diameter size range 0.744 and 0.762 nm based on a 2-D elliptical model (acyclic alcohol) (Tables 2, 4 and 5).
Cell micro-compliance increase due to 2,3,7,8-tetrachlorodibenzo-\(\beta\)-dioxin exposure results in activation of the AhR-Er\(\beta\) (Arnt): Nrf-2:: Ppar\(\gamma\), Err\(\gamma\) (LxR\(\alpha\): Dio3/Dio2 (Tru)) pathway with limited response

There is an increase or decrease in the \(P_{\text{eff}}\) duration at the transcriptionally active zero (0)-degree \(x, z\)-transcription plane of genes as compared to a set of genes at baseline expression, for example as result of subacute \textit{in vivo} exposure to TCDD, PCB-126 and PCB-153 in a rodent model (p.o.) \[34, 35\]. Based on the differential gene expression \(P_{\text{eff}}\) mapping of these genes as standards, it is determined that there is an increase in cell micro-compliance (\(\Delta\)) that results in the activation of the AhR pathway by TCDD, as \(\beta\)-dioxin can be considered an unaspected size molecular standard with a non-chiral carbon 2-D spherical vdW distance at 0.735 nanometers, as it has been shown to localize intracellularly \[36\]. The AhR-\(\beta\)-dioxin-(Arnt)-Er\(\beta\) limb of the pathway is transcriptional active between a \(P_{\text{eff}}\) interval of between 0.381–0.379 and 0.106 (UGT1A7), as IGHM (\(P_{\text{eff}}\) 0.088) \[37, 38\] or other gene at equivalent \(P_{\text{eff}}\) decreases in expression with minimal contraction response. There is increased duration of activation (+\(\Delta\)) at \(P_{\text{eff}}\) cell pressures of 0.381 (COX8C; Cox\(\delta\) ortholog, +10.2), 0.379 (CEACAM1; Ceacam10 ortholog, +20.3), 0.373 (NR1D1, Rev-Erb\(\alpha\) +0.16), 0.331 (Nrf-2, NFE2L2, +0.07), 0.283 (DBP, +0.3), 0.282 (SOD; Sod2 ortholog, +0.16), 0.273 (MT1A, +0.07), 0.224 (FABP5, +0.07), 0.216 (CYP1A1, +33.5), 0.201 (CYP1A2, +1.0), 0.190 (EXOC7; Exoc3 ortholog, +1.05), 0.169 (CYP1B1, +24.3), 0.168 (ALDH3A1, +1.9), 0.147 (NQO1, +0.65), 0.135 (ME1, +0.10) and 0.106 (UGT1A7, +2.8), in which additional genes with increases place at \(P_{\text{eff}}\) pressures of 0.376 (SLC2A4, Glut-4), 0.374 (RASSF1A, +24.5), 0.322 (TRIP2B, +20.7), 0.223 (PI3K3C, +13.8), 0.191 (ARNTL, aka Bmal1), 0.178 (NCOR2), 0.177 (THRA), 0.173 (NRIP1), 0.136 (ESR2) and 0.096 (DIO3); and during which there is decreased duration of activation (-\(\Delta\)) at \(P_{\text{eff}}\) cell pressures of 0.348 (DAO, -4.1), 0.324 (ALAS1, -0.54), 0.183 (DIO2, -0.54), 0.158 (ASCMA2, -7.0) and 0.111 (CYP3A7, -37.6), in which additional genes with decreases place at \(P_{\text{eff}}\) pressures of 0.200 (NRF1), 0.196 (ESRRA), 0.184 (ESR1) and 0.179 (RARA) (Table 6, Fig 2 [top bracket]).

Based on the differential increases in \(P_{\text{eff}}\) pressure duration and interactions of characterized pathways, there is overactivation of the i) AhR (\(P_{\text{eff}}\) 0.395) [TCDD] ER\(\beta\)—RIP140 and intracellular ligand (E\(1\), E\(2\) or E\(3\))-tuned overactivation of both CYP1A1 and CYP1B1 with the former being dependent on Er\(\beta\) recruitment by AhR to XRE than the latter \[39\] for maximal nano-stability of transcription complex at \(z\), \(x\)-plane alignment \(P_{\text{eff}}\) and its maximal activation, while the latter being sensitive to ER\(\alpha\)/\(\beta\)-mediated transcription repression during recruitment to ERE and obligatory presence of common co-adapter RIP140 for ER and ERR, and the former via high affinity interaction. There is ii) Nrf-2 (\(P_{\text{eff}}\) 0.331) overactivation of MT1A \[3\], with overexpression of MT1A attributable to a decrease in % duration at \(P_{\text{eff}}\) 0.200 (NRF1) and NRF1 underexpression with resultant overactivation of both HMOX1 (\(P_{\text{eff}}\) 0.153) and NQO1 (\(P_{\text{eff}}\) 0.147) in the presence of transcription factor Nrf-2 and a potential Maf as an enhancer as co-adapter. Furthermore, there is overexpression of proximal and distal UGT1A locus genes (5') UGT1A7 and UGT1A6 (3'), with a concomitant decrease in expression of UGT1A1 \[34, 40\], which are AhR and Nrf-2 transcription factor-responsive genes at \(P_{\text{eff}}\) 0.106, while UGT1A1 is transcriptionally active during the presence of CAR (PXR). There is iii) an increase in the \(P_{\text{eff}}\) duration of transcriptional activation between \(P_{\text{eff}}\) interval 0.216 to 0.236, in which PPAR\(\gamma\) and TIPARP are activated, and ESR1 gene transcriptional repressor SIN3A \[41\] are overexpressed, while ESR2 remains activated at \(P_{\text{eff}}\) 0.136, as does RAPGEF11 (Link-GEFII; \(P_{\text{eff}}\) 0.283). There is likely a minimal increase in FABP5 expression (\(P_{\text{eff}}\) 0.224) \[34\] during \(\Delta\) \(C_{\text{micro}}\) duration at \(P_{\text{eff}}\) due to the presence of RARB gene activation (\(P_{\text{eff}}\) 0.222) along with binding partner for 9-cis-retinoic acid-RXR\(\alpha\) (\(P_{\text{eff}}\) 0.374) and transcriptional repression of
Fig 2. Alterations in cell micro-compliance due to sub-acute exposure to polychlorinated biphenyl high affinity metabolites with specificity for intracellular or extracellular deiodinases. Lower limit of the lower tier $P_{\text{eff}}$ for transcriptional activation is increased to 0.106 (Ugt1a7) during a micro-compliance response with a decrease in $P_{\text{eff}} C_{\text{micro}}$ to < 0.106 < 0.088 (Ighm) $esbessiwaago T_0$ units during the expansion response; and the lower limit of the upper tier $P_{\text{eff}}$ is increased to between ~0.395 (AhR) to 0.381 (Cox8c) - 0.379 (Ceacam1*) with an interval increase in $P_{\text{eff}} C_{\text{micro}}$ in juxtaposition to ≤ 0.416 (Ppara) ≥ 0.395 (AhR) $esbessiwaago T_0$ units. The upper tier apparent interval $P_{\text{eff}} C_{\text{micro}}$, contraction response is between a $P_{\text{eff}} C_{\text{micro}}$ of 0.348 (Dio1) - 0.331 (Nfe2L2) and 0.379 $esbessiwaago T_0$ units. The $C_{\text{micro}}$, contraction-expansion response range is 0.225–0.275 (min BoR; Cox8c, Nfe2L2, Ugt1a7) to 0.243–0.293 (max BoR; Cox8c, Nfe2L2, Ighm) [p-dioxin (TCDD), upper bracket, no. 1]. In the AhR-Elf (Amr), Ppara, Elf (LxRe): Dio3/Dio2 (Trox) pathway, the minimum expansion response phase of the positive $P_{\text{eff}}$ contraction-expansion is a result of transient Elf decrease in activation-mediated de-repression of Dio2. Lower limit of the lower tier $P_{\text{eff}}$ for transcriptional activation is increased to 0.130 (Lgal1) during a $C_{\text{micro}}$, contraction response with a decrease in $P_{\text{eff}} C_{\text{micro}}$ to < 0.088 ≥ 0.080 (Tgfβ) - 0.075 (Ighm) $esbessiwaago T_0$ units during the expansion response; and the lower limit of the upper tier $P_{\text{eff}}$ is increased to between ~0.395 (AhR) and 0.387–0.381 (Cox8c) with an interval increase in $P_{\text{eff}} C_{\text{micro}}$ in juxtaposition to ≤ 0.381 < 0.416 (Ppara) > 0.395 (AhR) $esbessiwaago T_0$ units. The upper tier apparent interval $P_{\text{eff}} C_{\text{micro}}$, contraction response is between a $P_{\text{eff}} C_{\text{micro}}$ of > 0.327 (Resp18) - 0.331 (Nfe2L2) and 0.381 $esbessiwaago T_0$ units. The $C_{\text{micro}}$, contraction-expansion response range is 0.201–0.251 (min BoR; Nfe2L2, Cox8c - Lgal1) to 0.2585–0.3085 (max BoR; Cox8c, Nfe2L2; Ighm, Tspan14 (avg)). The range of delta (Δ) micro-compliance ($C_{\text{micro}}$) for the bracket no. 2 (co-planar PCB-126) and no. 1 (TCDD, std) comparison is between 0.024 (0.89) [Δ, ratio contraction] and 0.0155 (1.05) [Δ, ratio expansion; a.u.]. In the AhR-Elf (Amr): Nrf-2: -2.2–2.7 Elfβ [ (+) Elfβ: Dio3/Dio2 (Trox) pathway, the expansion response phase of the positive $P_{\text{eff}}$ contraction-expansion is a result of Troβ-mediated overactivation of Dio3. Lower limit of the lower tier $P_{\text{eff}}$ for transcriptional activation is increased to 0.159 (Ces2) during a micro-compliance contraction response with a decrease in $P_{\text{eff}} C_{\text{micro}}$ to between 0.080 ≤ 0.063–0.057 (Tspan14) $esbessiwaago T_0$ units during the expansion response, and the lower limit of the upper tier $P_{\text{eff}}$ is increased to between 0.387 (Nr1H3, CAR, Trfβ) and 0.384 (FoxA1) with an interval increase in $P_{\text{eff}} C_{\text{micro}}$. In juxtaposition to between 0.427 (Hnf4α) and 0.418 (Ppara) - 0.416 (Dio1) $esbessiwaago T_0$ units. The upper tier apparent interval $P_{\text{eff}} C_{\text{micro}}$, contraction response is between a $P_{\text{eff}} C_{\text{micro}}$ of 0.324 (Cox8c, Ncoa1) and 0.312 (Nr1H2) $esbessiwaago T_0$ units. The $C_{\text{micro}}$, contraction-expansion response range is 0.165 [min BoR; Cox8c, Ces2; Cyp26b, Gs262] to 0.346 [max BoR; Dcakd, Nr1H3 (avg); Tspan12]. The range of delta (Δ) micro-compliance ($C_{\text{micro}}$) for the bracket no. 3 (ie PCB-95, -153) and no. 1 (TCDD, std) comparison is between 0.060 (0.73) [Δ, ratio contraction] and 0.053 (1.18) [Δ, ratio expansion; a.u.]. In the Car (Pxr), Rarβ: Ppara, Elfβ (Sreb1 - Elfβ): Arnt (AhR-Er): Dio1/Dio2 (Trfβ) pathway, in which the expansion response phase of the positive $P_{\text{eff}}$ contraction-expansion is a result of Trβ-mediated overactivation of Dio1 and transcriptional repression of Dio2 at $P_{\text{eff}}$ $esbessiwaago T_0$ units, plain text, increase in duration at $P_{\text{eff}}$ in reference to baseline; text in italics, increase in duration at $P_{\text{eff}}$ in reference to p-dioxin; and grey text in italics, decrease in duration at $P_{\text{eff}}$ in reference to baseline Legend text: maximum bounds of range (max BoR); minimum bounds of range (min BoR).

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PPARγ gene auto-repression due to the overexpression of SMRT, which is another non-canonical pathway gene. 

Thus, a transcriptional duration at P_{eff} increase of +0.16% for SCD is commensurate with minimal increased duration at P_{eff} % for PGC1α and LXRα; and analogous to Nrf-2 (P_{eff} 0.331, +0.07)-mediated target gene activation upon P_{eff} z, x-plane alignment, in which case a common co-activator such as Maf-g (P_{eff} 0.251) will be involved for activation of ALDH3A1 (P_{eff} 0.168, +1.9) as another non-canonical pathway gene (Table 6).

In addition to direct overactivation of the AhR (Arnt): Nrf-2 pathway by p-dioxin (TCDD), the other indirect pathways involved include the (+,-) Errγ and Dio2 (TRα), in addition to PPARγ gene auto-repression due to the overexpression of SMRT (NCOR2; P_{eff} 0.178) interaction that results in a non-increase, during which TRα (THRA, P_{eff} 0.177) transcription will also increase due to the presence of PCB-displaced free T_{4} ligand. The (+,-) Errγ pathway will result in re-activation of gene Arntl (P_{eff} 0.191) as there is an overactivation of std gene Rev-Erbα at P_{eff}, in which ARNTL will be overexpressed and enhance the transcription of GLUT-4 as does SREBF1, prior to Rev-Erbα autorepression [45]. This is further supported by the experimental data that Arntl gene mRNA levels increase in Revβ^{shRevβ} knockout cells, in which NR1D1 (Rev-Erbα, P_{eff} 0.373) levels decrease with NR1D2 (Rev-Erbβ, P_{eff} 0.242) knockdown [46]. During TCDD mediated co-activation of the (+,-) Errγ pathway, there is inactivation of ARNTL (P_{eff} 0.191) and cytochrome C (CYCS, P_{eff} 0.297), which are both ERRα target genes.

Based on study findings, hEXOC7 (P_{eff} 0.190) is overactivated, in which case rodent Exoc3 may be a remnant exocyst in humans (P_{eff} u.d.), as Exoc7 is a plasma membrane post-golgi vesicular docking complex protein such as Exoc4 [48]. EXOC7 is the Exoc3 gene homolog is supported by the finding that it is required for Glut-4 channel expression (SLC2A4, P_{eff} 0.376) and exocytosis [49], however PPARγ gene transcription is not affected at P_{eff} 0.222 upon mutant Exoc7 induction, which is a dioxin response element (DRE) responsive gene. There is an increase in duration at P_{eff} to +1.05 around the Arntl gene expression of P_{eff} at 0.191, based on which it is determined that there can be a decrease in P_{eff} via cell membrane (CM) exocytosis, and it is proposed to be the reason for the z, x-plane horizontal alignment of genes ESR1 (P_{eff} 0.184) and DIO2 (P_{eff} 0.183) for repressor interaction within the P_{eff} 0.183–0.186 interval in the TCDD pathway (Table 6). There is re-expression activation of ARNTL in this pathway at P_{eff} 0.191, which is proposed to be due to coupling of exocytosis transcription (P_{eff} 0.184) and endocytosis transcription (P_{eff} 0.191). The (+,-) Errγ pathway will be active during an increase in duration at upward contraction shift lower P_{eff} interval at 0.208–0.209 matched with an upper interval in-between 0.381 (COX8C) - 0.376 (SLC2A4) units.

Antagonism of the intracellular T_{α}/rT_{3}-Dio2 enzyme pathway by thyroxine (T_{4}) structural mimicry is proposed to be the umbrella mechanism for the decrease in delta (Δ)-C_{micro} from the maximum expression range of this pathway (0.361, max; 0.79), which is the C_{micro} range of the expansion response of the Arnt (AhR) pathway. The C_{micro} contraction in response to p-dioxin to within the < 0.183 to 0.169 P_{eff} units range in addition results in the transcriptional activation of THRA (TRα, P_{eff} 0.177) and will its target genes via intracellularly-accumulated
T₄ agonism [49, 50], as the transcription of both std genes ME1 ($P_{eff}$ 0.135) and DBP ($P_{eff}$ 0.283). Furthermore, since NRIP1 is z, x-plane aligned at $P_{eff}$ 0.173, RIP140 can function either as a higher-binding affinity partner for (AhR) ERα/β ($P_{eff}$ 0.136, 0.184) [51], or as a lesser binding affinity co-adaptor for ERα/γ ($P_{eff}$ 0.196/0.209) in comparison to related receptor affinity for PGC1α ($P_{eff}$ 0.279) [52], which is via its dual ligand binding domains for estrogen receptor and related receptors. Therefore, p-dioxin (TCDD) exposure results in gene activation of AhR (Arnt)-ERβ, Nrf-2, Rev-Erbα, Errγ, LxRα and T₄/T₃-Trα limbs in which there is an increase in retinoic X receptor α expression (RXRA, $P_{eff}$ 0.374) with a decrease in cell micro-compliance ($C_{micro}$) due to high affinity intracellular Dio2 enzyme antagonism when at lesser than $10^{-12}$ affinity for the aryl hydrocarbon receptor (AhR) associated with CYP450 metabolism of p-dioxin.

Cell micro-compliance increase due to co-planar polychlorinated biphenyl exposure results in activation of the AhR-Errα/β (Arnt): Nrf-2:: Rev-Erbβ, Errβ: Dio3/Dio2 (Trα) pathway with contraction-expansion response

The AhR-co-planar PCB-(Arnt)-ERα limb of the pathway is transcriptional active between duration of increase at $P_{eff}$ of greater than (> 0.381–0.379 to < 0.096 (DIO3) > 0.057 (TSPAN14) inclusive of expansion response, with contraction increases in $P_{eff}$ at 0.331 (NFE2L2) and 0.130 (LGAL1) of the positive $C_{micro}$ response. There is increased duration of activation (+Δ% or ratio) at $P_{eff}$ cell pressures of 0.331 (NFE2L2, 1.14), 0.309 (CYP5A, +2.2), 0.297 (CYCS, +0.30), 0.273 (MT1A, 1.57), 0.241 (COL1A1, +0.60), 0.245 (GADD45A, +0.34), 0.220 (CAT, +0.87), 0.216 (CYP1A1, 1.28), 0.211 (COX6C, +0.34), 0.201 (CYP1A2, 2.60), 0.1686 (GSTM2, +6.6), 0.147 (NQO1, 1.22), 0.135 (ME1, 1.53) and 0.130 (LGAL1, +0.90), in which additional genes with increases place at $P_{eff}$ pressures of 0.262 (NOS1), 0.242 (NRID2, Rev-Erbβ), 0.196 (ESRRA), 0.184 (ESR1) and 0.096 (DIO3); and during which there is decreased duration of activation (−Δ%) at $P_{eff}$ cell pressures of 0.427 (HNF4A, -0.24), 0.384 (CEACAM1, 0.68–0.69), 0.381 (COX8C, 0.24–0.25), 0.331 (PCK1, -0.36), 0.327 (RESP18, -0.84), 0.324 (ALAS1, -0.24), 0.278 (FASN, -0.72), 0.190 (EXOC7; Exoc3 ortholog, 0.22), 0.1687 (CYP1B1, 0.81), 0.168 (ALDH3A1, -0.10), 0.237 (SREBF1, -0.24), 0.183 (DIO2, -0.24), 0.131 (IGHA1, -0.84) and 0.106 (UGT1A7, 0.19), in which additional genes with decreases place at $P_{eff}$ pressures of 0.376 (SLC2A4, 0.374 (RXRA), 0.279 (PPARGC1A), 0.223–0.222 (TIPARP, SIN3A, PPARG), 0.200 (NRFL1), 0.191 (ARNTL) and 0.136 (ESR2) (Table 7, Fig 2 [middle bracket]).

The difference between the AhR-co-planar PCB and AhR-TCDD pathway $P_{eff}$ regulation limb includes a $P_{eff}$ contraction shift to within the 0.135 (ME1) to 0.147 (NQO1) eusbssiva-gogocyte $T_{c}$ units interval with micro-expansion in-between a $P_{eff}$ interval of 0.147 and 0.136 (ESR2), and similarly contraction within the 0.211 (COX6C) to 0.220 (CAT) $P_{eff}$ gene expression interval, which results in an increase in the transcription of CYP1A1 ($P_{eff}$ 0.216) during increased overall ER expression (ERα) at $P_{eff}$ due to decreased SIN3A activation at $P_{eff}$ thus increased ERα recruitment to ERE for decreased nano-stability at promoter, and relative CYP1B1 gene de-activation during activation of CYP1A1 at $P_{eff}$ with AHR ($P_{eff}$ 0.395) bound-xenobiotic response elements (Table 7). The decrease in expression of std gene DBP ($P_{eff}$ 0.283) [34], is consistent with increased CRY1 at the DBP promoter E-box motif (CANNTG) [47], and an increase in lower affinity Rev-Erbβ ($P_{eff}$ 0.242) at RRE response elements with limited availability of co-adaptor BMAL1 (ARNTL1, $P_{eff}$ 0.191), which is ERαx activated only on reporter assay [47] in the 0.191–0.196 $P_{eff}$ interval during a concomitant increase in the activation of ME1 at $P_{eff}$ 0.135 (1.53x) [34, 53], as both Dbp and Me1 are $T_{c}$ liganded-TRα (RXRα) TRE-response pathway regulated genes [49]. The intracellularly accumulated $T_{c}$-Trαβ/β pathway is the higher affinity pathway ($K_{d}$, $10^{-10}$) [54] than the $T_{c}$/r$T_{c}$-extracellular (Dio-1/-3) or
-intracellular (Dio-2) deiodinase enzyme pathways \((K_d, 10^{-7} \text{ to } 10^{-9})\) [55]. Therefore, the probability exists that chiral configuration halogenated molecules (ie PCBs) with 1- to 2-orders lower affinity co-planar affinity for AhR could be higher affinity substrates for deiodinases as antagonists as proposed.

There are also \(P_{\text{eff}}\) contraction shifts in activation to in-between 0.297 (CYCS) and 0.309 (CYP5A1) and to in-between 0.262 (NOS1) [56] and 0.273 (MT1A) from deactivation within the 0.278–0.282 \(P_{\text{eff}}\) interval by which activation of FASN decreases (-0.72, std) decreases in which \(P_{\text{eff}}\) interval genes PPARGC1A and RXRB transcribe. The increase in activation of CYCS \((P_{\text{eff}} 0.297)\) [57], as well as COX6C \((P_{\text{eff}} 0.211)\) as a NRF1-responsive gene [58], is attributable to the transient overexpression of ERRα \((P_{\text{eff}} 0.196)\) and target gene CYCS \((P_{\text{eff}} 0.297)\) due to lesser duration \(EXOC7\) gene activation \((P_{\text{eff}} 0.208, 0.22x)\) and decrease in \(C_{\text{micro}}\) as compared to during sub-acute TCDD exposure; whereas, increases in activation of MT1A and GSTM2 can be attributed to an increase in in duration at \(P_{\text{eff}}\) for NFE2L2 and a common Maf co-activator during the decrease in \(P_{\text{eff}}\) at 0.200 and NRF1 inactivation. A \(P_{\text{eff}}\) contraction-expansion shift to \(P_{\text{eff}}\) at 0.130 results in LGAL1 activation in response to co-planar PCB-126 metabolite exposure, a half-site TRE and ERE containing gene [59], as an example of gene that is activated at a preferred intracellular pressure uppesebssibwa, dppesebssibwa point increase in duration at \(P_{\text{eff}}\) to 0.130 during \(C_{\text{micro}}\) expansion within the \(P_{\text{eff}} > 0.131\) (IGHA1) ≤ 0.135 interval (ME1), and during a contraction within the \(P_{\text{eff}} ≥ 0.262\) (NOS1) < 0.278 interval (FASN); there is a ~2.5-fold increase in LGAL1 expression by qRT-PCR in response to applied IL-1β [60] at the upper bounds of the expansion interval, which is thus delineable as being at \(P_{\text{eff}}\) 0.130, during which the increase in activation at its \(P_{\text{eff}}\) setpoint results in an increase in pJUN \((P_{\text{eff}} 0.267)\), pFOS \((P_{\text{eff}} 0.256)\)-bound ½ site TRE response elements; whereas, the decrease in the same (LGAL1) in response to the combination of IL-1β and dexamethasone (Dex) is attributable to an upward shift of the \(P_{\text{eff}}\) contraction interval with expansion, when de-phosphorylation of AKT and ERK1/2 occurs (+\(Δ\) \(C_{\text{micro}}\)) during decreased cell compliance. Furthermore, the extracellular Dex-induced repression of LGALS1 activation via intracellularly-ligated GR (Dex/Cort)/MR (Cortisol) \((P_{\text{eff}} 0.261)\) recruited to dephosphorylated JUN at LGALS1 promoter TRE response elements, within which interval Dex-mediated contraction \(P_{\text{eff}}\) responsive DUSP1 activation will occur at \(P_{\text{eff}}\) 0.272 during recruitment to GREs (GR). Therefore, co-planar PCB exposure (ie PCB-126) exposure results in gene activation of AhR-(Arnt), Nrf-2, Retinoic acid X receptor (RXRA) remains transcribable \((P_{\text{eff}} 0.374)\) while RXRB gene transcription decreases \((P_{\text{eff}} 0.282)\) with a \(Δ\) \(C_{\text{micro}}\) contraction response due to high affinity PCB metabolite antagonism of cell surface Dio3 enzymatic deiodoxethoxythermy, which is a TRα activated gene [61], in addition to intracellular Dio2 \((P_{\text{eff}} 0.183, -0.24\%)\) antagonist by CM channel substrates (~PCB-OH, ~S (= O)-Ch3) with its repression at minimum during de-activation of ESRRA \((P_{\text{eff}} 0.183)\) [62], in competition with AhR at equivalent or lower concentration in a binding affinity dependent manner.

The pathway overactivation following co-planar-PCB-126 metabolite exposure represents the hepatocyte cell population subset at-risk for neotransformation, which are at a differential \(P_{\text{eff}}\) basal over contraction-expansion response within the lower limit \(P_{\text{eff}}\) interval range of ≥ 0.080 (Tgfβ1) ≤ 0.088 (Igdm) units. The basal transcription \(P_{\text{eff}}\) setpoint(s) preference for differential gene expression for the co-planar-PCB-126 metabolite exposed cell population is determined in case of interposed genes, ESR1 \((P_{\text{eff}} 0.184)\) as an example of one that is determined to be decreased in duration at \(P_{\text{eff}}\), in comparison to ESR2 \((P_{\text{eff}} 0.136)\) as an example of one that is determined to be increased in duration at \(P_{\text{eff}}\) based on reporter assay \(P_{\text{eff}}\) expression correlation, as there is a requirement of estradiol \((E_1)\) for activation of a non-integrated ERβ reporter plasmid (+E2) [63], which requires endogenously transcribed ESR2 in its native locus position that expresses at \(P_{\text{eff}}\) 0.136, whereas a ERα reporter plasmid can be expressed in
control conditions (Δ_E). This finding implies that a P_eff 0.184 is one basal transcription P_eff set-point within an interval of the same in a vito-immortalized well-differentiated cell type (ie HepG2) [64] with an above baseline contraction lower bounds for differentiated cells, which are (GPER+)/ERα+/Erbα-and AR- cell types that are at risk for a switch to GPER+/ERα+/Erbβ+ status [65].

Cell micro-compliance increase due to co-, ortho-/ortho-planar polychlorinated biphenyl exposure results in activation of the Car (PXR, Rary): Pparα, Rxrβ (Srebfi, -Lxrβ): Arnt (AhR-Erbβ)/Ar:: Dio1/Dio2 (Trβ) pathway with contraction-expansion response

In comparison to the p-dioxin and co-planar PCB pathways, the extracellular co-, ortho-planar PCB pathway is transcriptional active between duration of increase at P_eff 0.387 (NR1I3, CAR) to 0.096 (FABP6, DIO3) with maximal apparent expansion increases intermittently to 0.418 (DCAKD) from 0.387 and from 0.106 to 0.057 (TSPAN14) during delta (Δ) expansion of 0.053 P_eff C_microw units (ratio, 1.18) as compared to the same for cellular response to applied p-dioxin (TCDD) modeled in silico, wherein the contraction response limb results in maximum transcriptional gene activation at P_eff point 0.324 (CYP2B6, NCOA1) in addition to between 0.157 – 0.159 (CYP3A5, CES2) esbsiwaago Tq units, delta-contraction of 0.060 P_eff C_microw units (ratio, 0.73). There is increased duration of differential activation (+Δ%) at P_eff of 0.384 (FOXA1, +0.7), 0.331 (DCAKD, +1.0), 0.3238 (CYP2B6, Cyp2b2 ortholog: +30.3), 0.292 (CIDEA, +1.3), 0.285 (MIR132), 0.278 (CUL2, +1.0), 0.282 (SCD, +7.2), 0.227 (ALAS2, +0.7), 0.159 (CES2, +1.3), 0.157 (CYP3A5, CYP2B15/-12 ortholog: +44.7), 0.096 FABP6, +1.0) and 0.057 (TSPAN14, +2.0), in which additional genes with increases place at P_eff pressures of 0.416 (PPARA), 0.406 (DDIT3, alias CHOP), 0.387 (TFRBC), 0.387 [NR1I3, CAR], 0.374 (RXRA), 0.373 (NR1D1) 0.342 (FKBP5), 0.312 (NR1I2, PXR), 0.309 (RARG), 0.288 (THRB), 0.282 (RXRB), 0.252 (CEACAMS), 0.252 (MAFG), 0.251 (SCD5), 0.237 (SREBF1), 0.236 (DIO1), 0.223 (TIPARP), 0.222 (PPARG), 0.161 (NCOR1), 0.160 (CASP3), 0.156 (AR), 0.136 (ESR2), 0.149 (CYP4A11), 0.129 (PPP1R9B), 0.128 (FABP3), 0.106 (UGT1A1) and 0.063 (ARNT). There is decreased duration of differential activation (−Δ%) at P_eff of 0.333 (PCK1), 0.272 (DUSP1), 0.224 (MBP), 0.183 (DIO2) and 0.140 (GTF2IRD1), in which additional genes with decreases place at P_eff of 0.395 (AHR), 0.324 (NCOA1), 0.281 (CYP3A4), 0.270 (NR1H2, Lxrβ), 0.184 (ESR1) and 0.096 DIO3 (Table 8, Fig 2 [bottom bracket]).

Based on study findings, the common mechanism pathway for extracellular co-, ortho-planar PCBs and higher affinity-substituted PCB metabolites (−OH, −MeSO4; ie 4′-OH-2,2′,3,4,4′,5,5′-PCB-172 (0.781 nm; 9.92 nm−2), and applicable to cell membrane (CM)-permeable co-, ortho-PCBs (ie 4′-OH-PCB-95; 0.752 nm, 8.43 nm−2) also, is the constitutive androstane receptor (NR1I3, P_eff 0.387) regulatory pathway as duration at P_eff increases at target genes CYP2B6 (P_eff 0.324) [66], CYP3A4 (P_eff 0.281) [66], CES2 (P_eff 0.159) and UGT1A1 (P_eff 0.106) [46], during pregane X receptor (PXR) recruitment (NR1I2, P_eff 0.312) to phenobarbital responsive elements (PBREM; ie CYP2B6) and/or CAR recruitment to PXRE response elements (ie CYP3A4). The expression of PPAα (P_eff 0.416) results in the transcriptional activation of target genes at various durations at P_eff and x, z-plane aligned for transcription, which include CIDEA (P_eff 0.292) [67, 68], CYP4A11 (P_eff 0.149) [69], FABP3 (P_eff 0.128) and FABP6 (P_eff 0.096; +1.0) [70], including SREBF1 (P_eff 0.236) with a predicted increase in the transcription factor gene RXXB (P_eff 0.282), which can be a recruited co-adapter, in addition to the presence of RXRA (P_eff 0.22) [71]. And, the activation of SREBF1 at P_eff 0.237 will result in the transcriptional activation of target genes SCD (P_eff 0.282; +30.3) and SCD5 (P_eff 0.251), for which the increase in duration at P_eff will be attributable to a decrease in LXRβ (P_eff 0.270),
during over-basal transcription at $P_{\text{eff}}$ 0.209 (ERRγ, LXRα) and 0.222 (PPARγ), which is with interaction between LXRα and CAR and SRC-1; the pathway limbs are thus mutually antagonistic on known pathway gene expression, murine CYP2B10 (hCyp2b6) and CYP3A11, which are induced by CAR pathway agonist, 1,4-Bis[2-(3,5-Dichloropyridyloxy)]benzene (TCPOBOB) with activity at nM concentration in vivo [72]; while, the underexpression of LXRγ is transcriptionally synergistic. Furthermore, there is secondary lesser involvement of the common AhR-Arnt pathway [73] can be expected as per study determination, and limited by transcription of the AHR gene with a decrease in duration for $P_{\text{eff}}$ at 0.395 during the expansion response phase with an increase in intracellular $P_{\text{eff}}$ at 0.063 that favors transcription of the ARNT gene and the presence of Arnt as the obligate transcription factor for activation of CYP1A1 [74], which will be in addition to CAR enhanced gene activity at proximal cis-ER8 motif PBREM binding elements with recruited pregnane X receptor [75]. Thus, CAR/PXR pathway limb become primary, as compared to the AhR driven by Arnt, during sub-acute ortho-planar PCB exposure, for which the preferred co-adaptor is PGC1α (PPARGC1A, $P_{\text{eff}}$ 0.279) [76], as it is for SREBF1 during decreased ERRγ/α in response to ΔC_mic (E/C, 1.18/0.73). Furthermore, gene NCOR1 is overexpressed at $P_{\text{eff}}$ 0.161 in this pathway based on study findings, which thus is the other co-regulator of co-, ortho-planar-activated limbs and will serve as the adaptor for ligand-dependent TRβ-mediated gene transcription (ie Dio1, Thrb) as compared to NCOR2 (P_eff 0.178; Dio3, Thrα), and consistent with the intracellular presence or absence of liganded TRα/β (Tα, Tβ) [77], which appears to result in lesser suppression of PPARγ and target genes as compared in the applied TCDD model in silico.

Rodent Cyp2b15/-12 shows expression in normal un-differentiated cells of skin origin (keratinocytes, sebaceocytes) [78], and skin microsomal CYP Cyp2b2 shows antibody reactivity [79]; thus, based on sesbissiwaagoTQ determinations of keratinocyte marker CYPs 2B6 (P_eff 0.324), 2E1 (P_eff 0.344) and 3A5 (P_eff 0.157) [80], respective human orthologs of rCyp2b2 and rCyp2b15/-12 can be CYP2B6 (P_eff +7.2) and CYP3A5 (P_eff +44.7), as only these two place at the respective predicted (pred) constitutive intracellular pressures for overexpression in the $P_{\text{eff}}$ interval at which NCOA1 (SRC-1) is with interaction while CYP2B6 is overactivated, and in the $P_{\text{eff}}$ interval of 0.157–0.159 within which CES2 increases in duration at $P_{\text{eff}}$ with CYP3A5, which is an alternatively activated CAR/PXR pathway gene with EMSA supershift indicative of CAR dimerization possibly at full site PBREM [81], while CYP3A4 is PXR (SRC-1) activatable during presence of FOXO1 [82]. Thus, since CYP2B6 as the only B series hCYP, and CYP3A5, are both constitutively overexpressed in normal human keratinocytes, as are genes hSCD and hSCD5 in murine epidermis-dermal junction at a common post-natal day [43], while CYP3A4 is dexamethasone (Dex)-inducible [81–83] in contrast to std marker gene DUSP1 (P_eff 0.272), which is deactivated at $P_{\text{eff}}$ in response to Dex [60]; therefore, this finding is consistent with partial trans-differentiation to alternative lineage in a co-, ortho-ortho-planar PCB-treated hepatocyte (Table 8), and will be applicable to other differentiated cell types.

The overactivation pathway following co-, ortho-planar PCB metabolite exposure results in delta (Δ) C_mic activation of gene locus within the 0.384 to 0.387 $P_{\text{eff}}$ interval, which include FOXA1 at $P_{\text{eff}}$ 0.384, PMCH at $P_{\text{eff}}$ 0.386 in addition to NR113 (CAR) at $P_{\text{eff}}$ 0.387, in relation to a ΔC_mic-mediated increase inactivation duration at $P_{\text{eff}}$ for transcription of SREBF1 at $P_{\text{eff}}$ 0.236 and PPARG at $P_{\text{eff}}$ 0.222 and target genes (ie FABP3, P_eff 0.128) based on study determination, during which there can be tuned de-activation of genes such as PCK1 (Pepck; $P_{\text{eff}}$ 0.333) in the basal presence of Creb binding protein (CBP) with decreases in NF-IB, NF-1X [84] and/or Errγ. Additionally, there is a ΔC_mic activation relationship between gene activation at $P_{\text{eff}}$ 0.236 and $P_{\text{eff}}$ 0.156 (AR), and furthermore, at $P_{\text{eff}}$ 0.223–0.222, at which there is relative activation of TIPARP, an AhR/Arnt-β-dioxin responsive but a Dht (AR) activatable gene at $P_{\text{eff}}$ [85], during which there is relative de-activation of PPARG (P_eff 0.222) as a result of
SREBF1 recruitment by AR/Kruppel-like factor (KLF) [86] to the subset of $\Delta C_{\text{micro}}$ activatable AR/KLF pathway target genes including FKBP5 at $P_{\text{eff}}$ 0.342, a GRE element-containing gene with a significantly-enriched distal intronic ARE (AR) [87], which is a low affinity binding sequence for co-adapter SRC-1 (NCOA1, $P_{\text{eff}}$ 0.324). Therefore, since NCOA1 is transcriptionally repressed during increased duration at $P_{\text{eff}}$ 0.324, NCO1 will be the binding partner for $T_3$, $\beta$TRB ($THRB$, $P_{\text{eff}}$ 0.288) for transcriptional activation of DIO1 at $P_{\text{eff}}$ 0.236 during $\Delta C_{\text{micro}}$ contraction phase, that results in the expansion phase during exposure to ortho-planar PCBs (ie PCB-95, -136, -153). This mechanistic correlation is in agreement with DIO1 being transcriptionally active at in vivo at $P_{\text{eff}}$ during the availability of $T_3$, TR$\alpha$ [88] and co-adaptors SRC-1 [9], or NCOR1 and NCOR2 for ligand independent activation of $TRH$ and $TSH$ genes [89], for high affinity TRE (AF-2) sequence-bound transcription in NCOA1$^{+/−}$/THRB$^{E457A}$ and $T_3$, TR$\beta$ ligand-dependent TSH gene repression [9], which is in lieu of activation by TR$\alpha$ variant isoforms ($THRA$, $P_{\text{eff}}$ 0.177) [90], as it is the lower affinity TRE-binding partner for DIO1 ($P_{\text{eff}}$ 0.236). Furthermore, apoptotic trans-differentiation occurs with $P_{\text{eff}}$ interval matches of 0.285 ($MIR132$) - 0.292 ($CIDEA$) [34; 67, 68] and 0.155 ($CREB1$) - 0.160 ($CASP3$) [91], in addition to decreased transcription around 0.241 ($COL1A1$) [22] and 0.224 ($MBP$) $P_{\text{eff}}$ intervals for induction of focal adhesion kinase, and with an increased risk for neurotoxicity [92, 93] during transcriptional activation of myelin basic protein gene repressor DDIT3 ($P_{\text{eff}}$ 0.406) in this pathway [94]. The findings of this study by further delineation of specific pathways are thus consistent with trans-differentiation to a sex steroid receptor expression pattern of ectodermal origin cells, sebaceocytes of the dermis epidermis junction [95,96], in which there is $\Delta C_{\text{micro}}$ co-activation of $ESR2$ at $P_{\text{eff}}$ 0.136, in addition to AR at $P_{\text{eff}}$ 0.156, with a decrease in $ESR1$ gene expression ($P_{\text{eff}}$ 0.184) during transcriptional repression by Sin3A ($P_{\text{eff}}$ 0.223) with interaction.

**Spectrum of p-dioxin, co-planar and co-, ortho-/ortho-planar polychlorinated biphenyl metabolite exposure-related cell micro-compliance contraction-expansion response**

Exposure to co-, ortho-OH-PCB-107 (intracellular), -PCB-136 and -PCB-146, or co-, ortho-planar PCBs OH-PCB-172 and -PCB-187 (extracellular), respectively, has been assessed in dual cohort studies of maternal exposure and infant response, in which it is shown that there is graded homuncular toxicity of the developmental eLMN-to-UMN neuroaxis in association with thyroid axis/deiodinase type 3 enzyme (Dio3) dysfunction [55], and in which a decrease in serum TSH level has been shown to be a sensitive indicator of exposure to biphenyl [98], as it has for exposure to penta-/hexa-substituted brominated diphenyl ethers such as BDE-100 and BDE-153 (vdWD: 0.775–0.793 nm) with available-3, 3’ positions for hydroxylation bioactivation [99]. Based on this proposed mechanism as per study determination, the increase in $T_3$/$rT_3$ ratio, elevation in serum thyroxine-T4 and $\cdot T_3$ [97] is due to co-, ortho-planar PCB metabolite inhibition of the high affinity, high $V_{\text{max}}$ deiodinase activity-exotheny of CM Dio3 (contraction phase) [55] during a decrease in intracellular $Tr\alpha$ concentration ([]) and DIO3 gene de-activation at $P_{\text{eff}}$ with a resultant decrease in T4 to $rT_3$ conversion in contraction phase, and an increase in intracellular $T_3$ liganded-TR$\beta$ [!] in DIO1 gene transcription at $P_{\text{eff}}$ at higher serum T4 [!] in expansion phase (transient hyperthyroidism), and $T_3$ liganded-TR$\alpha/\beta$ [!] $TSH$ gene inactivation. Furthermore, the finding of increased blubber tissue levels of both TR$\alpha$ and TR$\beta$ can be considered [100], if pan-exposure is considered with mutual-inclusivity of pathways involved (p-dioxin, co-planar PCB and ortho-planar PCB); and since there is decreased duration at $P_{\text{eff}}$ for ALAS1 ($P_{\text{eff}}$ 0.324) in the p-dioxin pathway, and increased duration at $P_{\text{eff}}$ for ALAS2 ($P_{\text{eff}}$ 0.227) in the co-, ortho-planar PCB pathway, for example due to
2',2',3,3',4,4'-PCB-128 (Arochlor 1260, vDW: 0.758 nm) exposure [101]. Alas1, Alas2 mRNA levels could be indicators for exposure assessment.

Loss of neuronal extension has been determined in response to intracellular co-, ortho-planar 4-OH-2',3,3',4,4'-PCB-106 (vDW: 0.752 nm) and extracellular 4-OH-2',3,3',4,5,5'-PCB-162 (vDW: 0.767 nm) at high affinity binding concentration (10^{-11} to 10^{-12} M) [102] relative to the binding affinity of hydroxylated PCBs (K_D, 33–90 nM) for thyroid hormone receptor beta (TRβ) [103]. This favors an affinity concentration gradient between serum transthyretin (pre-albumin) and sulfated (Ch_3-SO_4) PCBs (K_D, 20 nM) [104] for high affinity CM deiodinase exothermy antagonism (Do-1,2,3), in potential spatial association of, to a CM or RER receptor such as the ryanoide (RyR1/R2) with low binding affinity for ortho-polychlorinated biphenyls (ie PCB-95 and 4-OH-PCB-30), which is suggestive of an interrelationship between ΔC_microp, contraction-expansion response and opening of the RyR-associated Mg^{2+} deactivated Ca^{2+} channel. In further support of the contraction-expansion mechanism as determined is a decrease in osteoblast cell width observed in the murine double D1/D2KO gene transgenic efficiency model, in which male mutants have been determined to have decreased appendicular bone volume with resultant increased stiffness and development of brittle bone disease [105], and agrees morphologically with the study determination of enhanced cellular contraction during deiodinase antagonism, however with an expansion response in WT cells. Additionally, sexually dimorphic axial and appendicular skeletal morphometric responses have been observed in offspring in response to dam PCB-180 exposure (7–10 d, acute, p.o.), in which 0.1 mm decreases in buccolingual molar spacing are noted in female pups, while the opposite trend is noted in male pups [106], which as per study determination is attributable to an estradiol (E_2)-opposed contraction response with resultant expansion at minima [E_2 expansion (e) + co-, ortho-planar PCB contraction-expansion (c/e)], and dihydroxytestosterone (Dht)-agonism contraction response with resultant expansion at maxima [Dht c/e + co-, ortho-planar PCB c/e], and 0.1 increased separation of molars in male pups.

It has been determined in a pituitary GH3 luciferase reporter cell model that a TRE reporter plasmid is activated only secondarily after CYP450 monooxygenase activation (CYP1A1), and presumably due to the formation of PCB hydroxylate metabolites [107]. Since in this study, it is shown that there is a minimal 0.5x-over fold increase in LUC activity over control due to applied PCB 6 mix with co-, ortho-planar PCBs (PCB-138, -153) as opposed to a 2.5x-over fold increase during T3 application that the activation, this further supports the study mechanism of z, x-plane aligned TRE sequence-containing genes being activated by intracellular thyroxine-T3 displaced from endogenous Dio1 enzyme due to OH-/Ch_3(S)O_2-PCB in competition, and in the would be presence of TRβ. Furthermore, since the ΔC_microp contraction-expansion interface for the co-, ortho-planar PCB pathway is within the 0.140 (Gft2ird1) - 0.149 (Cyp4a11) P_{eff} interval, there is an inactivation of gene TFF1 (pS2, P_{eff} 0.147) with applied co-, ortho-planar PCB-104 [108]. Thus, when paraquat, a weakly intracellularly-localizing endocytic agent with 1+ IS/SS 1+ ionicity at the lower limit of cationicity [109], results in a (+) P_{eff} ΔC_microp contraction-expansion response when it is applied in a PCB model (co-, or ortho-) [110], it potentiates a convergent oxidative stress pathway with gene re-activation.

\textbf{P_{eff} grade of effect on delta-cell micro-compliance for regulation of gene transcription}

Corticosteroids, sex steroids and the subset of inverse agonist ligands can be studied by overall structural \textit{log} partition coefficient (P) \cdot vDW^{-1} ratio (nm^{-1}), based on which probable steroid axis ligand-to-receptor interaction can be determined as mineralocorticoid/glucocorticoid (Ald, 1.23 –Dex, 1.92 nm^{-1}), estrogen/estrogen-related receptor (E_2, 4.73 –Des, 6.60 nm^{-1}), and
androgen (R1881, 3.16—Dht, 4.15 nm−1), within which intracellular and extracellular bisphenols (Bpa -e, 0.727–0.744 nm; Bfap, 0.774 nm) classify as xenoestrogens based on overall structural partitioning parameters (Bpa, 5.14 –Bpaf, 6.17 nm−1). The grade of Peff duration for effect is then determined for the extracellular subset of small molecule hormone nuclear receptor ligands (Ch,O nl Iexternal structure/Hpolar group: 0.461, Dex− 1.31, Des) with molecular diameters within the 0.774 nm (Bpaf)– 0.873 nm (Dex) vdWD range with a minimum of di-polar hydroxylation hydrophilicity (- 2.10 nm−1), which is on the basis of small molecule hormone and inverse agonist potential for disassociation over range of exposure concentration (Ka) and binding affinity over time (t1/2) as plotted independent variables for semi-exponential power-regression extrapolation of half-life at receptor of unknowns (R2 = 0.955), and applied whole cell receptor density based on magnetic bead-enhanced amphotropic detection or radioligand competition assay studies (Bmax; n) for multiplicative in silico modeling of pressure regulatory grade of effect for gene expression in a mono-compliant cell type. The half-lives at receptor (t1/2) for dihydrostilbestrol (Des) at ERα is 663 min, and that for dihydrotosterone (Dht) and methyltrienolone (R1881) at AR are within the 38–53 minutes (min) interval, as the Kd approximates 0.9–1.0 nM (see ref 118). The strata order for ligand - receptor grade of duration at Peff, from positive with contraction-expansion response-to-negative, is 1.4215E + 04 (Cort− MR (GR)), 3.0270E + 04 (Ald · MR (GR), 1.3338E + 05 (Dex − Corticosterone · GR (MR)), 1.79812E + 05 (Dht · AR), 2.47340E + 05 (R1881 · AR), 1.2E +06 (E2 · ERα), 1.867345E + 06 (DES · ERα) adjusted for whole cell receptor count (Σ min-count), from positive to negative (Table 9).

Bisphenol AF with an inhibitory constant (IC50) of 19 and 53 nM, as compared to 17β-estradiol (E2) with an IC50 of 0.88 and 2.17 nM (ERα, ERβ), will be an inverse agonist in pharmacokinetic non-competition at trough E2 levels, and result in a positive (+) Δ Cmicro, bisphenol AF effect at CM ERα/β with upward shift in the contraction-expansion and in non-activation of the ESR2 gene (Peff 0.136), however with maintained ESR1 gene transcription at around Peff 0.184 as is at a Δ Cmicro Peff 0.290 (see ref 128), as in LUC ERE reporter plasmid transfected Hela cells with pcDNA3.1 integrated ESR1 and ESR2 genes [117]. Thus, based on study determinations, the gene expression pattern for small molecule hormone receptor interaction between the 2.6 x 105 to 2.1 x 106 min-count range results in a negative Δ Cmicro, response and an initial downward shift in the contraction with unilateral expansion as compared to positive Δ Cmicro response with contraction and bidirectional expansion, and irrespective of the specific steroid axis receptor class (ER, AR). Furthermore, it appears that an initial negative (-) Δ Cmicro response within the 1.86 x 106 to 1.94 x 106 (IGF-II · IGF-IIR) min-count range is coupled to a positive Δ Cmicro response, as Dht or R1881 · CM AR (1.79E + 05–2.45E + 05, + Peff) results in the transcription of pro-proliferative genes [118,119], that is proposed to be by an initial (-) Peff X then an (+) Peff Y intermediate step coupled to resultant transcriptional activation of MKI67 (Peff 0.329) [Part I, not cited; 38] (Table 9); thus, expression of a focal adhesion or endocytic component may be involved, which would apply to calvarial osteoblasts that overexpress the IGF-IIR/M6P receptor [120], and similarly to transformed cells with Peff shift to IGF1R expression [121], and could result in altered cell phenotype such as mononucleated: multinucleated [5], or lineage commitment such as glial: non-glial during the pre: post exposure period without interaction [122]. Several further studies point in the direction of paradoxical responses to dexamethasone (Dex) treatment, as example of a biologic mimic that produces a parabolic peak grade of positive Peff response and corticosterone surrogate, in which case observed divergent gene expression responses upon applied Dex are in dissimilar cell types [123], due to dose response and variant GR receptor affinity [124], or during the tuned activation of Dex responsive genes with GRE sequence sites in proximity to the TSS [125]. The magnitude of differential gene
expression response in cultured primary astrocyte and neurons to Dex stimulation is consistent with respective increases in duration at $P_{\text{eff}}$ contraction-expansion phase gene expression in a less and more compliant cell type to the same agent (ie PER1, FKBP5; 5.3x) [123], in which case it appears that the difference in magnitude of differential gene expression achieved in-between cell types is unlikely attributable to ligand \cdot receptor min-count, as astrocyte GR mRNA is 3x-overfold neuronal in which case only an apparent difference in $t_{1/2}$ at receptor exists; whereas, the same in the high affinity variant porcGR (ala610Val) transgenic model, in which an under-expression of GLC (P$_{\text{eff}}$ 0.477) and PCK1 (P$_{\text{eff}}$ 0.333), and overexpression of FKBP5 (P$_{\text{eff}}$ 0.342) follows a saturable dose-escalation differential gene expression pattern [124], and is attributable to an upward contraction-expansion shift in $P_{\text{eff}}$ response with maintained range of ligand \cdot receptor affinity. Moreover, the finding that there is repression of genes with Dex responsive intergenic sequences 10e4 to 10e5 kb of the transcription start site (TSS) [125], is consistent with $\Delta C_{\text{micro}} z\cdot x$-plane alignment of the majority of Dex responsive genes at $P_{\text{eff}}$ for gene transcription, as 70% of GR (Dex/Cort)-responsive genes are unbound by GR, while the tuned transcriptional activation of genes with half-site GRE: half-TRE sequences within around 10e3 of the TSS within intronic promoter regions.

$P_{\text{eff}}$ at duration intervals for endogenous steroid axis ligands

Based on study determinations, the grade of $P_{\text{eff}}$ at duration results in positive $P_{\text{eff}}$ contraction with negative $P_{\text{eff}}$ expansion responses for endogenous ligands at cell membrane (CM) receptors that results in $P_{\text{eff}}$ regulated maximal transcription of NR3C2 (MR; $P_{\text{eff}}$ 0.261) during the presence of either Cort \cdot GR or Ald \cdot MR at the promoter site P2 with basin transcription of the non-integrated plasmid being at 3x-fold [126, 127], of NR3C1 (GR; $P_{\text{eff}}$ 0.376) during the minimum presence of Cort \cdot GR with $\frac{1}{2}$ GRE site co-activators over 35 bases at a P site (ie -4559–4525) [128], and of constitutive transcriptional activation of AR ($P_{\text{eff}}$ 0.376) by Dht (or Dhea) with binding partner SREBF1 or KLF [ie PMCH, $P_{\text{eff}}$ 0.376; 85]. Furthermore, exogenous intracellularly-localizing ligands directly at nuclear receptors ERR$\gamma$ and ERR$\alpha$ (Bpa), also result in increased $P_{\text{eff}}$ intervals from the respective peri-nadir, for example to between < 0.146 (GSTA1; ERR$\gamma$/$\alpha$ \cdot Bpa) > 0.135 (ME1) as compared to $P_{\text{eff}}$ $\geq$ 0.168 (CEBPD) in response to Dex/Cort (GR) and $P_{\text{eff}}$ $\geq$ 0.156 (AR) in response to Dht (AR), which results in the partial activation of TIPARP ($P_{\text{eff}}$ 0.261) and FKBP5 ($P_{\text{eff}}$ 0.342) in lieu of overactivation by AhR and Dex/Corticosterone, respectively. In comparison, there is a decrease in the $P_{\text{eff}}$ contraction interval to in-between 0.290 (CCND1) and 0.147 (TTF1) esebsiwaagot$\gamma$Q units, these being nuclear ER$\alpha$ \cdot $E_1$, $E_2$ or $E_3$ transcriptionally-tuned genes during duration at $P_{\text{eff}}$ with GR (JUN) recruitment to half-site GRE during $\Delta C_{\text{micro}}$ FOXA1 ($P_{\text{eff}}$ 0.384) co-activation within which $P_{\text{eff}}$ at 0.290 (CCND1) remains transcribable at $\Delta C_{\text{micro}}$ (E2; E2 + Dex) [117, 129], and associated with a concomitant negative $P_{\text{eff}}$ expansion $\Delta C_{\text{micro}}$ response with a decrease in $P_{\text{eff}}$ interval to between $P_{\text{eff}}$ 0.147 ($Tff1$) and 0.111 (Cyp3a7) (Table 10, Fig 3).

In the A549 lung carcinoma/HepG2 HCC cell model for AhR gene reporter plasmid expression [64], applied TGF$\beta$1 results in activation of $z\cdot x$-plane transcription-ready plasmid upon endogenous TGF1I transcription at $P_{\text{eff}}$ 0.080 as the SMAD co-adapter is required for RNA polymerase transcription, however without the need for applied TGF$\beta$1 in A549 cells that demonstrate a bidirectional negative expansion $\Delta C_{\text{micro}}$ response $P_{\text{eff}}$ of 0.080 as compared the nadir for HepG2 cells, which would between $P_{\text{eff}}$ 0.130 (LGAL1) and 0.106 (UGT1A1). The in vitro application of aldosterone (Ald) to SkBr3 mammary carcinoma and tumor-associated endothelial cells results in the transcriptional overactivation of GPER1 (GPR30; $P_{\text{eff}}$ 0.376) and SLC9A1 (NHE-1, $P_{\text{eff}}$ 0.167) [130], and will result in an increase in GR expression concomitantly (NR3C1, $P_{\text{eff}}$ 0.376) (Table 10), with an increase in pEGFR/ERK1,2
levels as part of the negative $C_{\text{micro}}$ expansion response phase, as will occur with application of a combination of $E_2$ and inverse agonist(s) \cite{131} with a resultant equivalent increase in intracellular pressure to $P_{\text{eff}}$ 0.112 at which $CYP11B2$ (Ald Synthase) transcription increases at $P_{\text{eff}}$ during $\Delta C_{\text{micro}}$ contraction; whereas, the in vivo application of Dex ($\sim$Corticosterone) to normal adrenocortical cells results in a 0.5x-fold decrease in $CYP11B1$ (11-β-hydroxylase; $P_{\text{eff}}$ 0.099) decrease at duration at $P_{\text{eff}}$ while an increase with ACTH \cite{132}, while GABPA ($P_{\text{eff}}$ 0.494) and $TSPAN14$ ($P_{\text{eff}}$ 0.057) increase in duration at $P_{\text{eff}}$ during maintained sensitivity to Dex at CM GR in human B-cell ALL in a vitro-transformed cell type \cite{133}, which reaffirms $P_{\text{eff}}$ 0.057 as the maximum lower limit of the contraction-negative $P_{\text{eff}} C_{\text{micro}}$ expansion response to positive $P_{\text{eff}}$ regulation away from $P_{\text{eff}}$ 0.088 ($Ighm$) \cite{37}, 0.088 ($Ighm$) and 0.075 ($Ighg$) \cite{134}. Since the maximum $P_{\text{eff}} C_{\text{micro}}$ contraction-expansion response to Dex is at the lower limit of cell expansion $P_{\text{eff}}$ and equivalent to the $\Delta C_{\text{micro}}$ response applied co-, ortho-planar PCB-153, this implies GRE and TRE site-tuned parallel pathway involvement (ie CAR, AR), as there is known GR · half-site GRE enhancement of $THRB$ gene transcription \cite{135} with the potential for JUN (FOS) recruitment of GR to half-site TRE \cite{89} and regulation of $DIO1$ ($P_{\text{eff}}$ 0.236) gene transcription at $P_{\text{eff}}$.

**Bisphenol A grade of $P_{\text{eff}}$ at duration effect on gene transcription as a high affinity agonist for the Estrogen-Related Receptor (ERR)-PGC1α and NcoR1, NcoR2-TR pathway overactivation with contraction-expansion response**

The biological effects of high affinity bisphenols with the potential for health effect at biological concentration exposure doses in comparison to non-specific concentration-dependent effects \cite{136, 137}, in the absence or presence of an extracellular high affinity ER inverse agonist with potentially-extended $t_{1/2}$ at receptor due to substituted external structure (ie ICI 182,780; $C_{12}H_{17}F_3O_3S$), for determination of ER ligand gene expression effects solely attributable to GPR30 receptor inverse agonism \cite{138}, as its mid-affinity nuclear/RER receptor intracellular pathway effect. It has been further determined that there exists the potential for sexually dimorphic-imprinted polymorphism for a subset of certain genes sensitive to residual BPA dose effect, for example in progeny of exposed murine dams and/or mates (ie $F_0$ – $F_2$) in a ~20 μg/kg per day subacute consumption study model \cite{139}.

Based on determination of gene expression $\Delta C_{\text{micro}}$, $P_{\text{eff}}$ of bisphenol A-induced genes, it appears that low dose biologic exposure results in BPA mediated high affinity binding of ERRγ to PGC1α ($P_{\text{eff}}$ 0.279), in parallel to binding of NcoR1/NcoR2 (TRα/β), with repression of $THRA/THRB$ gene transcription but with an increase in TSH gene transcription at nM (10$^{-9}$) \cite{140, 141}. The putative recruitment to EREs of highly-enriched target genes \cite{49} such as $TIMM8B$ at $P_{\text{eff}}$ 0.247 is proposed, which is within $\Delta C_{\text{micro}} P_{\text{eff}}$ interval of convergence with bisphenol AF (BPAF) effects at CM ERα/β receptors and overactivation of apoptotic pathway gene $GADD45A$ at $P_{\text{eff}}$ 0.245. The transcriptional activation of the direct pathway limb, during which there is shown to be a dimorphic response on mRNA levels of $ESRRG$ ($P_{\text{eff}}$ 0.209) \cite{142}. As per this mechanism, there is underactivation of BPA responsive genes begins at nM concentration and includes adiponectin ($ADIPOQ$) \cite{143}, which could would be due to deficit in PGC1α, as a binding partner for SREBF1 or PPARγ transcriptional activators at $P_{\text{eff}}$ and decreased NcoR1 and NcoR2 co-adapter activity at $PPARG$ ($P_{\text{eff}}$ 0.222) due to BPA-enhanced recruitment to TRβ-integrin β3 \cite{141}.

There is an increase in duration at $P_{\text{eff}}$ for activation of genes within $P_{\text{eff}}$ interval at 0.153 ($HMOX1$), 0.194–0.196 ($PLEKHG4$ \cite{139}; $ESRRA$, $FOSB$), 0.256 to 0.258 ($MEG3$ \cite{140}, $FOS$ \cite{138}; $DFFA$), 0.264 to 0.267 ($FABP4$, aP2 \cite{144}; $JUN$), and 0.345 to 0.349 ($DLK1$, Pref-1;
include at 0.276 (CYP3A4)– 0.279 (Dusp1; PC12 cell, AS49) and P_\text{eff} = 0.057 (Tspan14, B-cell ALL) with decreases in P_\text{eff} duration at 0.376 (Nr3c1, GR; AS49 lung ca), P_\text{eff} = 0.194 (Foxb, PV neuron) and P_\text{eff} = 0.099 (Cyp11b1; adrenal cortex, nl). The CORT/DEX pathway \( \Delta C_{\text{micro}} \) contraction-expansion response increase in the lower P_\text{eff} interval is 0.111 from the maximum expansion interval (punctate bracket). DHT pathway increases in duration at P_\text{eff} include at 0.386 (Pmch; neuroendocrine, hypothal), P_\text{eff} = 0.200 (Cyp17a1, 17,20-lysase; Leydig) and 0.156 (Ar, PC cell) with decreases in P_\text{eff} duration at 0.120 (Igfg1; B-cell, nl) and P_\text{eff} = 0.075 (Igfg3). The DHT pathway \( \Delta C_{\text{micro}} \) contraction-expansion response increase in the lower P_\text{eff} interval is 0.067 from the maximum expansion interval (punctate bracket). BPA pathway increases in duration at P_\text{eff} include at 0.394 (Ins3, Leydig cell)– 0.345 (Dlk1, pre-adipocyte stromal cell), P_\text{eff} = 0.308 (Adam8)– 0.303 (Sim1, whole brain), P_\text{eff} \leq 0.258 (Meg3)– 0.256 (Fos, spermatocyte), P_\text{eff} = 0.205 (Miat) and P_\text{eff} = 0.194 (Plekhg4) with a decrease in duration at P_\text{eff} = 0.146 (Gsta1). BPAF pathway increases in duration at P_\text{eff} include at 0.276 (Cdkn1a) and 0.245 (Gadd45a). The pathway C_{\text{micro}} contraction-expansion response increase in the lower P_\text{eff} interval is \( \geq 0.040 \) from the maximum expansion interval (punctate bracket) for bisphenol A (BPA, intracellular) and bisphenol AF (BPAF, extracellular). DES pathway increases in duration at P_\text{eff} include at 0.038 (A2m), 0.27633 (Hoxa9, uterine), 0.243 (Klf4) and 0.136 (Wnt5a, Esr2) with decreases in duration at P_\text{eff} = 0.27630 (Hoxa10, uterine) and P_\text{eff} = 0.332 (Hoxa11). The DES pathway upwards shift in C_{\text{micro}} contraction is to P_\text{eff} = 0.1359–0.1361 (Wnt5a, Esr2) with response expansion to \( -0.099 \) (Cyp11b1) \(+\) upward shift \( \Delta C_{\text{micro}} \) contraction with maxima expansion pathway. In comparison, Estradiol (E2) pathway increases in duration at P_\text{eff} include at 0.290 (Ccncl1; MCF-7 cell), P_\text{eff} = 0.147 (Tff1, pS2; MCF), with decreases in P_\text{eff} duration at 0.136 (Esr2, skeletalcyte). The E2 pathway results in downward shift C_{\text{micro}} contraction is a P_\text{eff} 0.14703 (Tff1) and a P_\text{eff} setpoint lower with minimal expansion \( [-\) downward shift \( \Delta C_{\text{micro}} \) contraction with minima expansion pathway]. black text, dexamethasone (Dex)/corticosterone common GR receptor pathway; magenta brown text, dihydroxytestosterone (Dht) AR receptor pathway; blue text, estradiol (E2) ER receptor pathway; green text, intracellular bisphenol inverse agonist pathway; teal text, extracellular bisphenol pathway; gold text, diethylstilbestrol (DES) ER receptor pathway; italics text, decreases in P_\text{eff} duration at activation or increases in repression duration at P_\text{eff} (2^\text{minima})\); solid black bracket, max contraction interval during increase in duration at P_\text{eff} (co-, ortho-planar PCB std); dotted brackets, lower P_\text{eff} expansion intervals; dashed brackets, lower limit range of P_\text{eff} expansion interval.

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INSL3 [136]), in addition to a decrease in duration at P_\text{eff} for deactivation of AR pathway genes, PMCH (P_\text{eff} 0.386) [139] and CYP17A1 (steriod lysase, P_\text{eff} 0.200), which is rate-limiting,
as part of the indirect limb(s) of the high affinity BPA pathway, within which there is less of an increase in pCREB [145] during a delayed duration $P_{\text{eff}}$ expansion as compared to with applied estradiol $E_2$ and minimal expansion (Table 10, Fig 3). The concurrent limbs of pathway for low-dose applied BPA for sub-acute duration exposure ($\geq 1–2$ d) at octimolar concentration ($10^{-9}$ M) include the NRF1 de-activation/NFE2L2 activation (GGLC, $P_{\text{eff}}$ 0.477; UGT1A1, $P_{\text{eff}}$ 0.106) with possible Jun (Fos)/AP-1 at half-site TRE repression of GSTA1 ($P_{\text{eff}}$ 0.146) as an additionally involved indirect limb of the intracellular pathway based on study determination, during which HMOX1 ($P_{\text{eff}}$ 0.153) is un-repressed and transcriptionally active at $P_{\text{eff}}$ 5 to 25 μg/kg per day in a 1-month cumulative exposure to BPA male rodent model [146], while GADD45B ($P_{\text{eff}}$ 0.332) is transcriptionally active at ≤ 5 μg/kg per day, which is agreement with secondary activation of the Nrf2 (Nrf1) limb at the 20 μg/kg per day subacute BPA exposure dose. Since UGT1A1 is overexpressed at $P_{\text{eff}} \geq 0.10640$ at the positive pole in the UGT1A7 (UGT1A1-UGT1A6) readthrough locus, this implies that the CAR/PXR minus LXRβ pathway is involved (hybrid co-pathway).

BFAP exposure and extracellular ligand · CM ERα/β pathway activation, also results in co-activation of common Nrf2 (Nrf1) limb pathway genes at $P_{\text{eff}}$, which include CYP1A1 ($P_{\text{eff}}$ 0.216) and UGT1A1 ($P_{\text{eff}}$ 0.106), while distinct genes activated at $P_{\text{eff}}$ include CDKN1A ($P_{\text{eff}}$ 0.276) and GADD45A ($P_{\text{eff}}$ 0.245) [138], which are involved in cell cycle cessation and p53-mediated apoptosis, and activatable at a minimum concentration of $10^{-8}$ to $10^{-9}$ M concentration [117, 138]. Thus, the secondarily-activated Ahr/Nrf2 (NFE2L2) limb co-dominates during saturation of the ERRγ(α) pathway-associated limbs, since there exists a contraction-expansion response with apparent upper and lower limits at $P_{\text{eff}}$ 0.477 (GGLC) and 0.106 (UGT1A1) similar to the delta ($\Delta$)-C$_{\text{micro}}$ due to subacute p-dioxin/ exposure (13 wk). In further comparison, higher dose, lower affinity binding partner recruitment effect [PPARY · BPA (PGC1α)] occurs at 70 μg/kg per day of subacute exposure [147,148]. Therefore, the overall effect of BPA on otherwise normal cells appears to be overactivation of ERR (PGC1α) and concurrent pathway limbs [Nrf2 (Nrf1)/AP-1] with resultant dysregulation of both stem cell progenitor (DLK1) and differentiated cell gene expression (INSL3; CYP17A1) in addition to apoptosis stage (DFFA), thus results in pre-mature cell fate determination and depleted stem cell population. Furthermore, since overactivation of the Nrf2 (Nrf1)/AP-1 limb results in BPA exposed cells, which are transiently apoptotic, there exists the potential for cell cycle progression to proliferation in neotransformed (SkBr3, GPER+/ERα+) [149,150] and associated cells subject to 30-min short-term duration BPA exposure with ERRγ, GPR30 pathway activation in a high affinity, low affinity inverse agonist in vitro model [151]. The differences between the $C_{\text{micro}}$ contraction-expansion responses of normal epithelial cells, and mammary carcinoma cells such as T47D (GPER+/ERα+/Erβ+) and SkBr3, to BPA are attributable to high affinity binding of endogenous estradiol ($E_2$) to ERα and GPR30 (K$_d$, $10^{-10}$) [11, 112] delta ($\Delta$)-C$_{\text{micro}}$ downward shift in $P_{\text{eff}}$ with resultant activation of additional anisotropic genes (EGR1 $P_{\text{eff}}$ 0.199; CCN2, CTGF $P_{\text{eff}}$ 0.166 [22]) [150], inclusive of gene transcription at $\Delta C_{\text{micro}}$ $P_{\text{eff}}$ 0.184, at which variant ESRI and FLNA co-express with potential for polymorphism [93, 152]. Therefore, it appears that the intermittent negative $\Delta C_{\text{micro}}$ response ($E_2$ expansion) in neotransformed cell types results in an intermediate (+) $\Delta C_{\text{micro}}$ step within the $P_{\text{eff}} > 0.235$ (EMD [22]) and < 0.256 interval that results in oscillatory progression into the G1/S cell cycle phase.

**Diethylstilbestrol as a small molecule receptor ligand at cell membrane receptor due to positive contraction shift-expansion delta-micro cell compliance**

Diethylstilbestrol is known to be toxic to reproductive axis cells along continuum of developmental teratogen to carcinogen over age based on subsequent follow-up of a prospective
with local intraperitoneal (i.p.) exposure of dams for example, ERα-dependent homeobox cluster A (HOXA_1) gene expression is dysregulated in the developing Mullerian system [154], with resultant differential expression of single locus readthrough genes, reverse strand (-) HoxA9 and HoxA10 genes (P_{eff} ≥ 0.2763) in uterine tissue cells, during which there is a decrease in HoxA10 transcription, and an increase in HoxA9 (P_{eff} (5-digit adj) 0.27633) with a decrease in oviductal expression of the same. Therefore, based on this study’s findings, it appears that multiple promoter locus genes can be transcribed during (+) Δ C_{micro} and in a (+) to (-) P_{eff} gradient direction (5’ to 3’), particularly at less sensitive C_{micro} intracellular pressure intervals inclusive of at around P_{eff} 0.267 (Jun) and 0.256 (Fos) (Table 11, Fig 3). Furthermore, during study of high dose cumulative p.o. DES effects on WT ERα+/+ transgenic mice pups [155], similar uterine effects are noted for HoxA10 and HoxA11 (P_{eff} 0.332) in addition to differential expression of Wnt5a (P_{eff} 0.1359) as compared to autoregulatory genes Wnt4 and Wnt7a in response [156]. Based on this study’s findings on std marker gene expression cell micro-compliance P_{eff} considered together, DES exposure results in contraction shift to P_{eff} 0.136 due to a coupled-positive P_{eff} response (ie focal adhesion) due to the grade of DES at CM receptor interaction (1.863745E + 06 min-count) with a range of 0.388 (A2M [157])– 0.136 (WNT5A, ESR2), and contraction response expansion proposed to be to ~0.099 esebssiwaagoT_{Q} units (CYP11B1), which is within the interval range for transformed cell types (Tcdd, co-planar PCB). In comparison, applied E2 results in downward shift contraction to a P_{eff} of 0.147 (TFI) and setpoint lower with minimal expansion, during an intra-locus shift in gene transcription from positive P_{eff} pole (Hoxa10) to negative (Hoxa9, P_{eff} 0.27633). There appears to be directional P_{eff}-mediated gene transcription due to the proximal intra-oviductal pressure potential, which appears to result from relatively increased in intracellular P_{eff} (decreased Δ C_{micro}) compared to the distal ambient atmospheric pressure potential required for HoxA13 gene expression (P_{eff} 0.346). Furthermore, P_{eff} at 0.256 (FOS) is an in-sensitive intracellular pressure, since transcription increases in case of both Bpa and Des exposures, while re-expression of stem cell required factor Klf4 at P_{eff} 0.243, and Wnt5a or Esr2 that are expressed at P_{eff} 0.136 could be considered markers for an increased early developmental risk of neotransformation, or temporally for delayed clear cell carcinoma risk in aged cells with acquired mutations over time.

Molecular philicity interval grades of increase for bioelimination of small molecule lipophiles as compared to grade of molecular philicity for molecular exclusion at the cell surface glycocalyx

CYP1A1 CYP450 monooxygenase hydroxylation of p-dioxin (I_{ext} H^{-1}: 4.31) followed by UGT1A6/7 transferase glucuronidation of 8-OH-2,3,7-TriCDD (I_{ext} H^{-1}: 1.91) to 2,3,7-TriCDD glucuronate (I_{ext} H^{-1}: 0.419) in-between the philicity per polar group interval of 0.328 (I_{ext} H^{-1} Lactic acid) and 0.428 (I_{ext} H^{-1} 2,3-glycer-1-01) results in hepatobiliary bioelimination [158], as an example of the primary mode of bioactivation metabolism and bioelimination clearance of polyhalogenates (PDBE, PCDD) in addition to PCBs, co-planar and co-, ortho-planar. This is in comparison to bioabsorption metabolism of smaller, less hydrophilic vdWD phthalates ≤ 0.81 nm [21] by esterase hydrolysis, which includes mono- n-butyphthalate (BP, 1.; vdWD: 0.724 nm; I_{ext} H^{-1} 0.322) that are permeable across epidermis interepithelial junctional complexes [159], as opposed to di-n-buty phthalate (DBP, vdWD: 0.797 nm; I_{ext} H^{-1} 1.49) at the cusp for mono-/part-neutral small molecule permeation in absence of endocytosis-enhanced junctional permeability (ie GI barrier); whereas, the non-absorption of phthalate (2., I_{ext} H^{-1} 0.078; vdWD: 0.633 nm) upon skin esterase BP conversion is due to the hydrophilicity barrier to transepithelium absorption [21]. Furthermore, above the I_{ext} H^{-1} interval ranges for binding affinity to CYP450 (1.91–4.31), glucuronosyltransferase (UGT,
1.73–2.69) and esterase (0.322–1.49) is the hydrophilicity binding affinity interval for binding affinity to N-acetyl-neuraminic acid (Neu5Ac; 0.790 nm, -9.37 nm⁻¹; $L_{\text{int}} \cdot H^1$; 0.080) based on study determination (Fig 1), the upper limit of which is at a $L_{\text{int}} \cdot H^1$ of 0.101 (saxitoxin ester amide; vdWD: 0.764 nm) with a lower limit of $L_{\text{ext}} \cdot H^1$ around 0.092 ($m$-xylenediame). Therefore, exogenous small molecule hydrophiles that stratify as such, stand to be toxins or toxicants with extended duration bioactivity due to a cell surface glycocalyx hydrophilicity barrier to clearance, with 1,2-diaminocyclohexane (vdWD: 0.622 nm; $L_{\text{ext}} \cdot H^1$; 0.085, 0.171) being an example of an older epoxy part-resin known to cause type I hypersensitivity in painters [38, 160], which is could be an endocytic agent at a cell membrane (CM) receptor by caveolar mechanisms within the $L_{\text{ext}} \cdot H^1$; 0.085–0.171 interval, and during co-exposure to aliphatics. Based on findings, $m$-xylenediameine ($L_{\text{ext}} \cdot H_{\text{polar group}}^{-1}$; 0.092) · CM receptor aliphatic solvent co-exposure APC pathway activation in previously primed B-cells (IgE⁺) will result in a type I contact hypersensitivity response [38] due to a synergistic $\Delta C_{\text{micro}}$ contraction-expansion response. Saxitoxin ester amide (STX) and tetradoxo (TTX; $L_{\text{ext}} \cdot H^1$; 0.085–0.101) are puffer fish gland toxins that demonstrate nM affinity for sodium (Na⁺) channel subunit V (NAV) (unlabeled STX $K_d$ = 2.1 nM) as channel blockers [161,162], application of which dissipates membrane potential, and the negative (-) $\Delta C_{\text{micro}}$ results in a pan-depression in gene transcription at an apparent $P_{\text{eff}}$ with the lowest probability for a decrease in duration at $P_{\text{eff}}$ for mitochondrial genes, $TFB2M$ ($P_{\text{eff}}$ 0.267; $JUN$) and $COX6C$ ($P_{\text{eff}}$ 0.211) [163], which is suggestive of additional compensatory molecular weight-maintained micro-compliance, and supported by the recent finding of limited gene overaction in $AHR$ gene silenced cells [164].

$\alpha$-tocopherol transfer protein (αTTP) binds reserved ligands $\alpha$-tocopherol (tocotrienol; $L_{\text{ext}} \cdot H^1$, 2.92; vDWD: 0.960) and 13'-hydroxy-$\alpha$-tocopherol ($L_{\text{ext}} \cdot H^1$, 1.73) for extended serum/half-life [165], and is a gene that can be transcriptionally-activated by LXRα/β [166] during overexpression of $SCD$ ($P_{\text{eff}}$ 0.282), while $\alpha$-tocopherol as a ligand agonist of PXR [167] results in the overactivation of genes, CYP3A4 (mCyp3a11, $P_{\text{eff}}$ 0.281) and CYP3A5 ($P_{\text{eff}}$ 0.157) in the proposed minus LXRβ/PPARα pathway, in addition to CAR pathway genes with co-recruitment (ie CYP2B6, $P_{\text{eff}}$ 0.324). $co$-planar PCB exposure (ie OH-PCB-77, -126) results in significant over-fold expression of $\alpha$-tocopherol responsive genes such as $CAT$ ($P_{\text{eff}}$ 0.220), and SOD to a lesser extent [168,169], during the concurrent activation of ERRα pathway (- $P_{\text{eff}}$) and biometabolism / bioactivation pathway genes (+ $P_{\text{eff}}$), which is indirectly indicative of $\alpha$-tocopherol overutilization deficit during oxidative stress-mediated pathway activation as it has been shown to be in γ-TMT poor plants, and could be due to decreased αTTP protein levels. Since hepatobiliary neotransformation can result from applied $p$-dioxin (0.225, $\Delta C_{\text{contraction}}$, 0.293, $\Delta C_{\text{expansion}}$) $> co$-planar PCB (0.201, $\Delta C_{\text{contraction}}$, 0.3085, $\Delta C_{\text{expansion}}$), as compared to with $co$, ortho-/ortho-planar PCB (0.165, $\Delta C_{\text{contraction}}$, 0.346, $\Delta C_{\text{expansion}}$) exposure, maintained $\alpha$-tocopherol levels would be protective, as two in series $L_{\text{ext}} \cdot H^1$ intervals are required to ready toxicants for glucounidation elimination ($L_{\text{ext}} \cdot H^1$, 0.419–0.459). Furthermore, since cell coupled nucleic mechanisms can be also be studied in vitro, by direct tension generation measurements (N/m; AFM), study of nuclear protein displacement (MSD) or chromatin condensation parameters (EED) [170], the application effects of such toxicants (ie PCB, bisphenol) on intracellular effective pressure are to be further confirmed in pluripotent stem cell populations in bioengineered systems [171], as the findings herein apply to differentiated cells that activate either of the three primary detoxification pathways in response, and de- or re-differentiate.

**Conclusions**

*In silico* modeling of molecular philicity by part structure reveals that a $L_{\text{ext}} \cdot H_{\text{polar group}}^{-1}$ of $\geq 1.07$ is the molecular structure lipophilicity limit for non-specific carrier-
mediated transmembrane diffusion through CM polarity-selective transport channels for small molecules with a vDW < 0.758 (3-D ellipsoid, chiral) - 0.762 nm (2-D elliptical), the subset of halogenated vapors that initially perturb the inner MM categorize, for which vDW is predictive of the required MAC for anesthetic potency. It also reveals that the L - H polar group \(^{-1}\) interval range for the cell surface glycalyx hydrophilicity barrier is between 0.101 (Saxitoxin, Stx; \(l_{\text{MM, internal structure}}\) - H polar group \(^{-1}\)) and 0.092 (m-xylenediamine, \(l_{\text{MM, external structure}}\) - H polar group). In silico modeling of \(\Delta P_{\text{eff}}\) cell micro-compliance \((C_{\text{micro}})\) alterations in response to applied small molecule hormone ligands, biphenyls and bisphenols reveals that differential gene expression is a result of various grades of contraction-expansion response.

Subcellular or cell membrane Cyp-associated perturbation by non-endogenous molecules within a \(l_{\text{MM, external structure}}\) - H polar group \(^{-1}\) interval of 1.91–4.31 results in various grades of preferential transcriptional activation of either: i) the AhR (Erβ)/Nrf2 limb in addition to the Pparα, ERRγ (Lxrα), Dio3/Dio2 and TRα limbs with p-dioxin/metabolite (TCDD; OH-TCDD), in which increased duration at \(P_{\text{eff}}\) includes for Ceacam1, Rarβ, Scd, Exoc7, Nrip1, Ncor2 and Slc2a4; ii) the AhR (Era/β)/Nrf2 limb in addition to the Rev-Erbβ, ERRα, Dio3 and TRα limbs with OH-co-planar PCB as the toxicant in which increased duration at \(P_{\text{eff}}\) includes for Ceacam1, Rarγ, Nrip1 and Exoc7 with a \(\Delta C_{\text{micro}}\) contraction of 0.89/\(\Delta C_{\text{micro}}\) expansion of 1.05 as compared to p-dioxin; or iii) the Car/Pxr limb in addition to the Rary, Pparα/γ (Sreb1, -LXRβ), Arnt (Ah-R-Erβ)/Ar, Dio1, Trβ limbs with OH-co-, ortho-planar PCB in which increased duration at \(P_{\text{eff}}\) includes for Cyp2B6, Cyp3a5, Pgc1α, Ncor1, Ceacam5, Magf and Scd5 with a \(\Delta C_{\text{micro}}\) contraction of 0.73/\(\Delta C_{\text{micro}}\) expansion of 1.18 consistent with trans-differentiation as compared to p-dioxin. Therefore, based on study determination of PCB exposure pathway limbs, the mechanism for toxicant is via alterations in cell micro-compliance via p-dioxin/PCB metabolite Dio enzyme exothermy-antagonism (Δ contraction) coupled with T \(\gamma / rT \gamma\) - TRα or TRβ agonism and Dio3/Dio2 or Dio1 gene transcription (Δ expansion), which implies the intervals of altered cell compliance that result in increased risk for neotransformation (Tcdd, co-planar PCB; Des), or trans-differentiation (co-, ortho-planar PCB).

Bisphenol A, as small molecule ligand within a \(l_{\text{MM, external structure}}\) - H polar group \(^{-1}\) of 1.08–1.12 (BPA, BPE), results in direct transcriptional activation of the ERRγ-[intracellular bisphenol]-PGC1α pathway (Timm8β) with an expansion phase \(\Delta C_{\text{micro}}\) of 0.040 (Dffα) and indirect activation of a DEX responsive hybrid Ahh/Nrf-2, Car/Pxr co-limb pathway during a decrease in duration at \(P_{\text{eff}}\) at Nrf1 gene transcription and consistent with cell de-differentiation. Since the Dht - AR \(\Delta C_{\text{micro}}\) expansion phase is 0.067 with a grade of duration at \(P_{\text{eff}}\) \((\text{min-count})\) of 1.8–2.53x10^5 (Dht/R1881), sexually dimorphic differences result in gene transcription duration at \(P_{\text{eff}}\) with co-exposure (Dht, Bpa) due to an additive (+) \(\Delta C_{\text{micro}}\) contraction-expansion phase, as compared to a coupled (+) \(\Delta C_{\text{micro}}\) \(P_{\text{eff}}\) increase to 0.136 (Wnt5a, Esr2) with applied DES (1.86x10^6) as compared to estradiol E2.

Based on study determinations of PCB and bisphenol actions in the biological system modeled in silico as mutually exclusive inverse ligands of endogenous small molecule hormone receptors or enzymes, the mechanism for toxicant is via alterations in cell micro-compliance via p-dioxin, co-planar co-, ortho-planar PCB metabolite liganded deiodinase enzyme exothermy-antagonism/ligated TRα or TRβ agonism. Furthermore, \(\Delta C_{\text{micro}}\) z, x-plane alignment of genes with respect to intergene distance trophy results in differential gene transcription, in which case non-aligned genes are inactive unless bound by a repressor at \(P_{\text{eff}}\) interaction. \(\Delta C_{\text{micro}}\) results in z, x-plane alignment of genes with respect to intergene distance trophy and in differential gene activation, in which case non-aligned genes are inactive as are repressor-bound genes at \(P_{\text{eff}}\). Study findings will be applicable to the field as it offers perspective on the basis for pressure regulated gene transcription by alterations in cell micro-compliance with maintenance of the effective pressure potential.
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Conceptualization: Hemant Sarin.
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Formal analysis: Hemant Sarin.
Funding acquisition: Hemant Sarin.
Investigation: Hemant Sarin.
Methodology: Hemant Sarin.
Supervision: Hemant Sarin.
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