

2.1.- Environmental exposures linked to impairment of central nervous system myelination during development

[illegible]

2.2.- Cytotoxicity and Myelin DNT

Compound (Abbreviation)	Cytotoxicity in vitro			Myelin DNT			
	Conc.	notes	Ref.	Conc. / Dose	in vivo/in vitro; species	DNT Effect(s)	Ref.
Bisphenol A (BPA)	100 μ M	in vitro; rat oligospheres; highest non-cytotoxic conc.	Tiwari et al. 2015	0.1 mg/L H ₂ O	in vivo; rat	Disrupted OL ER signaling; enduring OL loss	Xu et al. 2016
	100 μ M	In vitro; mouse OPCs; almost 100% cells viable	Seiwa et al. 2004	100 μ M	in vitro; rat OL spheres	Decreased viability, proliferation, and differentiation of OPCs; altered immunoreactivity of fluoromyelin, MBP, and myelin-associated glycoprotein; altered expression and protein levels of myelination-regulating genes; caused myelin structural changes	Tiwari et al. 2015
				100 μ M	in vitro; mouse	Inhibited differentiation of OPCs; inhibited MBP expression	Seiwa et al. 2004
2,4-Dichlorophenoxyacetic acid (2,4-D)	1000 μ M	Cytotoxicity limit	EPA ToxCast	70 mg/kgBW (DMSO)	in vivo; rat	Decreased myelin proteins (CNPase, PLP, and MBP); disrupted myelin layers and reduced number of sheets (electronmicrograph) *also no effect on myelin structure was found in DMSO treated group	Konjuh et al. 2008
tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	6.71 μ M	Cytotoxicity limit	EPA ToxCast	0.001% (v/v) DMSO	in vivo; zebrafish	Detected in F1 eggs following parental exposure; MBP significantly downregulated in exposed F1 larvae	Wang et al. 2015
Bis(cyclohexanone) oxaldihydrazone (Cuprizone)				0.2% diet	in vivo; mouse	Demyelination in juvenile (3 weeks) and young-adult mice (6 weeks); reduction of myelin basic protein; loss of CC-1-positive mature oligodendrocytes	Wang et al. 2013
				0, 0.1 or 0.4% diet	in vivo; rat	Maternal exposure to 0.4% CPZ in the diet from gestational day 6 to day 21 decreases proliferative type-2 progenitor cells via endoplasmic reticulum stress-mediated apoptosis and inhibition of cholinergic signals to intermediate-stage progenitor cells following reduced oligodendrocyte production and suppression of the brain-derived neurotrophic factor signaling cascade	Abe et al. 2015
				25 μ M (for 1 hour, each day 2-12 days)	in vitro; rat OL and mixed glial-cell cultures	Treatment with cuprizone produced a slight decrease in the total number of O4-positive oligodendrocytes; cuprizone consistently and significantly reduced the numbers of the O4-positive cells that would mature to the O4+/MBP+ stage	Cammer, 1999

Sodium metavanadate	300 μ M	in vitro; mouse OL spheres; IC50	Mustapha et al. 2014	300 μ M	in vitro; mouse OL spheres	Decreased expression of oligodendrocyte specific proteins: CNPase, OSP / Claudin	Mustapha et al. 2014
Nicotine				3 mg/kg BW	in vivo; rat	Significantly altered myelin gene expression, indicating that exposure disturbs OL development and myelin formation	Cao et al. 2013
Pentabromodiphenyl oxide (DE-71)	1000 μ M	Cytotoxicity limit	EPA ToxCast	0.16, 0.8, 4.0 μ g/L H ₂ O	in vivo; zebrafish	Residue of DE-71 was detected in F1 eggs upon parental exposure; Genes of central nervous system development (e.g., myelin basic protein, synapsin IIa, α 1-tubulin) were significantly downregulated in larvae	Chen et al. 2012
	500 mg/mL	hippocampal neurons; 50% reduction in mitotic index	Giordano et al. 2008				
	2.2 μ M	hippocampal neurons; IC50					
	8.9 μ M	SK-N-SH neuroblastoma; MTT reduction; threshold	Yu et al. 2008				
	22.1 μ M	SK-N-SH neuroblastoma; LDH release; threshold					
	6.4 μ M	SK-N-SH neuroblastoma; apoptosis; PI staining; threshold					
Methylmercury				2 mg/kg BW	in vivo; rat	Reductions in total and individual MBP splice variant mRNA levels suggest that methylmercury-induced perturbation in MBP gene expression occurred due to decreased oligodendrocyte cell population	Padhi et al. 2012

OL = oligodendrocyte

NSC = neural stem cell

OPC = oligodendrocyte progenitor cell

OSP = oligodendrocyte specific protein

MPB = myelin basic protein

PLP = myelin proteolipid protein

CNPase = 2',3'-Cyclic-nucleotide 3'-phosphodiesterase

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EPA ToxCast - <https://actor.epa.gov/dashboard>

PubChem - <https://pubchem.ncbi.nlm.nih.gov>