[Oral presentation]

# Neuroendocrine Safety Assessment of DEHCH as a New Plasticizer Alternative: Insights from Green Toxicology

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**ABSTRACT**

Regrettable substitutions underscore the need for green toxicology to guide safer plasticizer substitution, particularly for phthalates. Although toxicology data link phthalates to neuroendocrine disruption, comprehensive, systematic evaluations of alternative candidates remain scarce. This study assessed and compared the neuroendocrine-disrupting potential of representative conventional plasticizers (CPs) and alternative plasticizers (APs), and evaluated whether the cyclohexane-based, non-phthalate substitute di(2-ethylhexyl) cyclohexane-1,2-dicarboxylate (DEHCH) merits consideration for sustainable substitution. We integrated three complementary approaches: (i) *in vivo* zebrafish larvae (locomotor activity, mRNA expression of nine endocrine-related genes, and levels of five neurosteroids by LC–MS/MS); (ii) *in vitro* ERα/AR transactivation (OECD TG 455/458) using stably transfected reporter lines; and (iii) *in silico* molecular docking to ERα, AR, GR, and TRα/β. Comparators included two CPs—di(2-ethylhexyl) phthalate (DEHP) and diisononyl phthalate (DINP)—and two APs—1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) and di-2-ethylhexyl terephthalate (DEHTP). *In vivo*, DEHCH did not alter locomotor activity, expression of the nine target genes, or any of the five neurosteroids, whereas DINCH, DEHP, and DEHTP induced hyperactivity; excluding DEHCH, the other plasticizers significantly upregulated at least one target gene. DINCH increased cortisol, and DEHP increased progesterone, allopregnanolone, and cortisol. *In vitro*, none of the tested plasticizers—including DEHCH—showed ERα or AR agonist/antagonist activity across tested concentrations. *In silico*, DEHCH did not rank as a top-affinity ligand for any receptor in the panel. To more comprehensively characterize DEHCH's neuroendocrine impact, future work should incorporate developmental stage– and sex-specific endocrine endpoints and delineate parent-compound/metabolite kinetics under longer-term exposures. Overall, this integrated three-approach framework can help identify suitable alternatives and inform plasticizer substitution within green and sustainable chemistry.

**Keywords:** Green toxicology, Neurotoxicity, Endocrine disrupting effect, Phthalate

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