Letter to the editor

The publication “Cyclohexane-1,2-dicarboxylic acid diisononyl ester and metabolite effects on rat epididymal stromal vascular fraction differentiation of adipose tissue” by Enrico Campioll, Tam B. Duong, François De-schamps, Vassilios Papadopoulos, Environmental Research 140 (2015), 145–156, merits some critical comments

A BST R A C T

In essence, the authors report MINCH, a monoester and minor urinary metabolite (Koch et al., 2013) of a plasticizer marketed by BASF under the brandname Hexamoll® DINCH®, promotes the differentiation of preadipocytes derived from rat epididymal stromal vascular fraction (SVF) to adipocytes. The authors have over-interpreted their in-vitro data and missed important publicly available in-vivo data.

1. MINCH

According to Section 2.2., MINCH was synthesized by esterification of 1,2-cyclohexane-dicarboxylic acid anhydride with an isononyl alcohol. The monoester (MINCH) resulting from metabolic cleavage of the genuine plasticizer however consists of cis- and trans-isomers in a specific ratio and the C9-alcohol has a specific branching (NICNAS, 2012). Structural properties of ligands are of utmost importance for receptor-ligand interactions. Substance characterization as published by the authors is insufficient as parameters like purity by GC/MS or cis-/trans-isomer ratio are missing. Therefore, the wrong substance may have been tested. The monoester (MINCH) is the major metabolite in blood, but in contrast to rats, it is predominantly glucuronidated in human blood.

2. PPARγ–agonist

The authors suggest MINCH could be a potent PPARγ–agonist based on the following information: GW6471 (PPARγ–antagonist) inhibited the effect of MINCH while co-exposure with T0070907 (PPARγ–antagonist) did not prevent the MINCH-induced differentiation.

However, their conclusion “potent PPARγ–agonist” is in direct contrast with the results of animal studies. Oral treatment with the plasticizer did not give any indication for peroxisome proliferating activity in rat liver. The specific marker for peroxisome proliferating activity (cyanide-insensitive palmitoyl-CoA oxidation) was unchanged and histopathological evaluation confirmed lack of peroxisome proliferating activity (ECHA; EFSA, 2006; NICNAS, 2012; SCENIHR, 2015).

Information about how PPARγ in preadipocytes or adipocytes differs from PPARγ in liver is missing but would have been helpful to understand the claims made by the authors.

Based on the in-vivo data, the monoester is not a PPARγ–agonist.

3. Risk to specific populations

The authors failed to identify publicly available information (ECHA; NICNAS; SCENIHR; EFSA) regarding bioavailability of the plasticizer. Further, it would have been helpful to see how they calculated from active metabolite concentration in cell culture the respective external dose level of plasticizer. The statement, “a similar dose of DINCH in the environment could pose a health risk to specific populations such as occupational workers”, is ambiguous. The main route of human exposure to plasticizers is the oral route that is not relevant at the workplace. A plasticizer concentration in the gas phase higher than 0.5 μg/m³ is not achievable (Schossler et al., 2011). Dermal exposure at the workplace is unlikely due to standard personal protection equipment (gloves). Therefore exposure can be related to daily life: The exposure level for cyclohexane-1,2-dicarboxylic acid diisononylester in the general population of Germany (2012) is 0.14 μg/kg bw/day (1.07 μg/kg bw/day; 95th percentile) (Schütze et al., 2014). The actual exposure is orders of magnitude lower (i.e. 143,000 fold for the mean and 20,000 fold for the 95th percentile) as compared to the potential plasticizer exposure postulated by the authors. Exposure levels for the US population as published by CDC (2015) are even lower. In consequence, any possible risk from this non-genotoxic substance is negligible.

References


SCENIHR, 2015, final opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update) [http://ec.europa.EU/health/scientific_committees/emerging/docs/scenihr_o_047.PDF].


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