Weight-of-Evidence Evaluation of Endocrine Activity for Di-Isodecyl Phthalate (DIDP) and Di-Isononyl Phthalate (DINP)

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Abstract:

Exposure to certain phthalate compounds is reported to elicit thyroid changes in rodents. To evaluate the potential for DIDP and DINP to disrupt thyroid pathway homeostasis, a weight of evidence (WoE) assessment was conducted according to ECHA/EFSA endocrine disruptor (ED) guidance. A comprehensive search was carried out to identify DIDP/DINP primary literature, toxicology study reports, and high throughput screening (HTS) assay data (USEPA CompTox Chemical Dashboard). Search results were evaluated for relevant *in vitro* studies (Level 2 methods providing mechanistic data) and *in vivo* animal studies (Levels 3-5 methods: hazard identification and data for adverse effects of endocrine-relevant endpoints in adult and developing animals), in addition to epidemiological studies as supporting data. The evidence base identified for DIDP and DINP included Level 2 methods including HTS assay data (67 endpoints-DIDP and 24 endpoints-DINP), Level 4 methods (7 studies-DIDP, 8 studies-DINP), Level 5 methods (1 study-DIDP, 2 studies- DINP), along with supporting epidemiological data (1 study-DIDP, 8 studies-DINP). Findings indicated that administration of high doses of DIDP or DINP in animal models produced inconsistent or no changes in thyroid tissues across studies. There was a consistent increase in liver weights and histopathology suggesting induction of metabolizing enzymes. HTS assays mapped to the thyroid pathway were, in general, negative except for DIDP and DINP activation of PXR, suggesting the potential to induce with conjugating metabolic enzymes and possibly acceleration of thyroid hormone (TH) clearance. However, there was no evidence that either of these phthalates induced conjugating enzyme activity in exposed animal models. The lack of effect of DIDP/DINP on the thyroid pathway was supported by negative *in vitro* activity for selected molecular initiating and key events in thyroid adverse outcome pathways. The results from one assay for DIDP and DINP suggested that exposure could potentially affect TH synthesis through the modulation of NIS-mediated iodide update activity. Other *in vitro* assay data suggested that DINP had a minor effect on TH (T3) activity through antagonism. Neither DIDP nor DINP showed any consistent effects in thyroid tissue when animals were exposed to high concentrations of these phthalates. In general, the human studies reflected unreliable study designs and the inability to demonstrate a relationship between exposure and response and, as such, did not provide any confidence that DIDP/DINP was involved in the disruption of TH homeostasis. Based on the available DIDP/DINP evidence base, any observed changes in thyroid sensitive endpoints were unlikely to occur through perturbations of thyroid pathway for either of these phthalates.