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Nonmonotonic Dose-Response Curves and Endocrine-Disrupting Chemicals: Fact or Falderal?

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The shape of the dose response curve in the low dose region has been debated since the 1940s, originally focusing on linear no threshold (LNT) versus threshold responses for cancer and noncancer effects. Recently, it has been claimed that endocrine

disrupters (EDCs), which act via high affinity, low capacity receptors, commonly induce adverse effects displaying Nonmonotonic Dose-Response Curves (NMDRCs) at low doses. Effects that would be missed in standard EDC screening and multigenerational testing protocols. Case studies of chemicals that disrupt reproductive development and function via the androgen and estrogen signaling pathways were reviewed, including *in vitro* and *in vivo* multigenerational studies for LNT, threshold and NMDRCs responses. *In vivo* studies selected included comprehensive, robust, well designed studies that administered the chemical via a relevant route of exposure over a broad dose response range, including low doses. The chemicals include ethinyl estradiol, estradiol, genistein, bisphenol A, trenbolone, finasteride, flutamide, phthalate esters, selective estrogen receptor modulators and inhibitors of aromatase. Current conclusions are: 1) EDCs appear to induce some LNT effects. 2) NMDRCs are biologically plausible and occur frequently *in vitro*, but the points of

inflection occur at high concentrations that are not relevant *in vivo*. 3) NMRDCs appear to be more common a) in short- versus long-term exposures and b) with upstream, mechanistic events vs. downstream phenotypic effects. 4) A few adverse effects of EDCs are non-monotonic, but other effects in these studies displayed monotonic responses at lower dose levels. 5) A number of robust multigenerational studies of estrogens and antiandrogens showed NMDRCs were uncommon at low dose levels. 6) Multigenerational Test guidelines can be enhanced on a case-by-case basis to improve the sensitivity to low dose effects of some EDCs. 7) Additional data needs to be examined from robust, multigenerational studies using a broad range of dosage levels for other toxicity pathways. This abstract does not reflect USEPA policy