Reproduction/Developmental Toxicity Screen and Extended One Generation Reproductive Toxicity Study of Decahydronaphthalene in Sprague Dawley Rats

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Abstract:

Background and Purpose: Decahydronaphthalene (DHN) is used as an industrial solvent, as an intermediate product in the aroma and fragrances industry, and in the production of naphthalene sulphonate for concrete. We carried out a reproduction/developmental toxicity screen (OECD TG 421) and an extended one generation reproductive toxicity study (OECD TG 443) of DHN to evaluate its potential reproductive and developmental toxicity.

Methods: Current OECD TG 421 and TG 443 (without developmental neurotoxicity and immunotoxicity cohorts) study designs were carried out using Sprague Dawley rats dosed orally with DHN in corn oil. For the TG 421, dosages of 0, 100, 300, or 1000 mg DHN/kg BW/day (mg/kg/d) were administered for 2 weeks prior to and during mating; males were dosed for a total of at least 28 days, and dosing of females continued to lactation day (LD) 13, prior to termination of females and pups. Female fertility, gestation index, pre- and post-implantation loss, live births, postnatal viability and growth of pups were assessed. Male and female reproductive organs were weighed and examined histologically. For the TG 443, doses were initially 0, 30, 100, or 300 mg/kg/d; due to lack of toxicity, doses were increased to 60, 200, and 600 mg/kg/d on test day 30. The F0 rats were dosed for 10 weeks prior to and during mating. F0 males were dosed through weaning of F1 pups. F0 females were dosed through gestation and lactation. F1 pups were dosed directly for 10 or 11 weeks; F2 litters were exposed via nursing until PND 22. All endpoints in the TG 421 were also evaluated in the TG 443, plus balano-preputial separation or vaginal opening, genital abnormalities, thyroid and reproductive hormones. Sperm evaluations were conducted in F0 and F1 males.

Results: In the TG 421, females at 1000 mg/kg/d showed post-dose salivation, piloerection, estrous cycle disruption, loss of hindlimb function, and lower body weight (BW) on gestation day (GD) 20. Litter size and weight were lower at 300 and 1000 mg/kg/d; at 1000 mg/kg/d there were fewer implantations and higher post implantation loss. In the TG 443, F0 male BW at necropsy and female BW on GD 21 were lower at 300/600 mg/kg/d. Findings in males were unremarkable other than dose-related higher kidney weights due to a-2-microglobulin male rat specific effect. F0 300/600 mg/kg/d females showed estrous cycle disruption; this high dose group and mid dose group females had fewer implantations and pups per litter, and lower litter weight; pup weight was not affected. Females at the mid and high doses showed clear signs of maternal stress, including lower BW, dose-related disruption of the estrous cycle, higher adrenal gland and lower thymus gland weights, adrenocortical hypertrophy and higher severity of thymic atrophy. Mated F1 females also had lower BW on GD 21 and lower F2 litter weight due to fewer pups per litter; F2 pup weight was unaffected.

Conclusions: DHN related effects including prolonged/irregular estrous cycling, fewer implantation sites

and fewer pups per litter indicate that ovarian function was impaired. Females in the mid and high dose groups showed clear signs of stress, including increased adrenal gland weight, adrenocortical hypertrophy, lower thymus weight and increased thymic atrophy. Given that the ovary is known to be highly sensitive to stress, these results indicate that the reproductive effects of DHN are secondary to maternal stress. As such, these adverse outcomes in rats are not likely to be relevant to human health.