

Di-n-hexylphthalate

CAS #84-75-3

Swiss CD-1 mice, at 0.3, 0.6, and 1.2% in feed

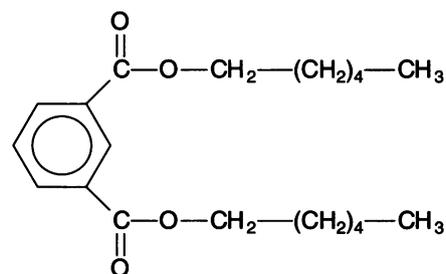
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Di-n-hexylphthalate (DHP) was tested using the standard RACB protocol in both sexes of Swiss CD-1 mice (Lamb et al., *Toxicol Appl Pharmacol* 88:255-269 [1987]). Data on food and water consumptions, body weights, and clinical signs collected in the Task 1 dose-range-finding study were used to set doses for the continuous breeding part of the study at 0.0, 0.3, 0.6, and 1.2% in feed. Food consumption was not altered by the presence of DHP. These concentrations yielded calculated consumption estimates of approximately 0.38, 0.80, and 1.67 g DHP/kg/day.

In the continuous breeding phase, there were no live pups at the high dose and one litter of four pups at the middle dose. At the low dose, there was a significant reduction in the mean number of litters per pair (3.4, vs 4.9 for the controls). Also at the low dose, the number of live pups per litter was reduced from 12.3 (controls) to 3.4, the proportion born alive was reduced by 14%. Pup weight adjusted for litter size was unchanged. These effects occurred in the

absence of an effect on postpartum dam body weights.

These significant reproductive effects prompted the determination of the affected sex in the Task 3 crossover mating trial using the control and 1.2% DHP-treated mice. Each group had 17 to 20 pairs of mice. The mating index (proportion of pairs showing copulatory plugs) in groups with 2 control partners, with a DHP-treated male, or a DHP-treated female, was 90, 56*, and 88% (* indicates significantly different from controls), showing that the treated females were cycling and could be receptive, and that mating capability was reduced in the group of treated males. However, no treated females bore any litters, and only 1 of 18 treated males sired a litter. Effectively, both sexes were infertile at this level of DHP exposure.

After the litters from the crossover were examined and discarded, the F₀ adults from the control and 1.2% DHP groups were killed and necropsied. Body weight in the high dose males was 10% less than controls,

and absolute testis weight was 70% less. Body-weight-adjusted liver and prostate weights were increased by 34 and 9%, respectively, and adjusted weights of kidney, epididymis, and seminal vesicles were reduced by 9, 23, and 18%, respectively. Body weight of DHP-exposed F₀ females was 6% less than controls, while adjusted weights of liver was increased by 32% and adjusted kidney weights were decreased by 6%. Not surprisingly, epididymal sperm concentration was reduced by 93%, and motility was reduced by 80%. Morphologic abnormalities were unchanged.

There were insufficient animals from any DHP-treated group to provide F₁ mice for an evaluation of the second generation.

These data clearly demonstrate that di-n-hexylphthalate is a reproductive toxicant in mice. The relative sensitivity of the liver and the reproductive system cannot be judged from these data, but the reproductive effects occurred in the absence of large changes (at the top dose) or any changes (low and middle doses) in body weight.

Di-n-HEXYLPHTHALATE

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: PB85249332/AS
 Chemical: Di-n-hexylphthalate
 CAS#: 84-75-3
 Mode of exposure: Feed
 Species/strain: Swiss CD-1 mice

F ₀ generation	Dose concentration →	0.3%	0.6%	1.2%
General toxicity		Male, female	Male, female	Male, female
Body weight		—, —	—, —	↓, ↓
Kidney weight ^a		•	•	↓, ↓
Liver weight ^a		•	•	↑, ↑
Mortality		—, —	—, —	—, —
Feed consumption		—, —	—, —	—, —
Water consumption		•	•	•
Clinical signs		—, —	—, —	—, —

Reproductive toxicity				
\bar{x} litters/pair		↓	↓	↓
# live pups/litter; pup wt./litter		↓, —	↓, —	•
Cumulative days to litter		↑	↑	•
Absolute testis, epididymis weight ^a		•	•	↓, ↓
Sex accessory gland weight ^a (prostate, seminal vesicle)		•	•	↑, ↓
Epidid. sperm parameters (#, motility, morphology)		•	•	↓, ↓, —
Estrous cycle length		•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	—	1.2%

F ₁ generation	Dose concentration →	•	•	•
General toxicity		Male, female	Male, female	Male, female
Pup growth to weaning		•	•	•
Mortality		•	•	•
Adult body weight		•	•	•
Kidney weight ^a		•	•	•
Liver weight ^a		•	•	•
Feed consumption		•	•	•
Water consumption		•	•	•
Clinical signs		•	•	•

Reproductive toxicity				
Fertility index		•	•	•
# live pups/litter; pup wt./litter		•	•	•
Absolute testis, epididymis weight ^a		•	•	•
Sex accessory gland weight ^a (prostate, seminal vesicle)		•	•	•
Epidid. sperm parameters (#, motility, morphology)		•	•	•
Estrous cycle length		•	•	•

Summary information	
Affected sex?	Both
Study confounders:	None
NOAEL reproductive toxicity:	Unknown
NOAEL general toxicity:	0.6%
F ₁ more sensitive than F ₀ ?	Unclear
Postnatal toxicity:	No

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. ^aAdjusted for body weight.