

Di-n-butylphthalate, Rats

CAS #84-74-2

Sprague-Dawley rats, at 0.1, 0.5, and 1.0% in feed

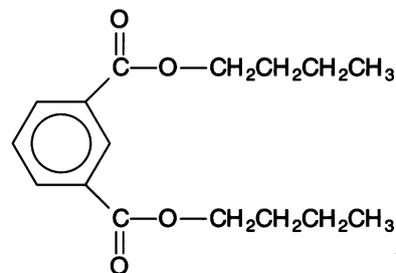
Robert E. Chapin, NTP/NIEHS Project Officer

Dushyant Gulati, and Leta Barnes, Environmental Health

Research and Testing

Started 7/20/89; Completed 9/13/91

NTIS #PB92111996



Di-n-butylphthalate (DBP) was tested using the standard RACB protocol in Sprague-Dawley rats. This was the second study to use Sprague-Dawley rats, and was conducted to generate some information on the relative susceptibility of adult versus juvenile plus adult exposure scenarios, and to develop some data in a second species. Body weights, food and water consumptions, and clinical signs in the dose-range-finding Task 1 study were used to set doses for the main study of 0.0, 0.1, 0.5, and 1.0% in feed. While the spacing of the doses differed from that used in the mouse study, the top dose level is the same. While food consumption was occasionally reduced slightly in the middle and high concentrations, there was no consistent or prolonged depression. Measures of food consumption produced calculated exposure estimates of approximately 65, 310, and 650 mg DBP/kg body weight/day.

During the continuous cohabitation phase (Task 2), two low dose animals were sacrificed moribund, because of paralysis and renal failure. In the remaining animals, there were no adverse clinical signs. Postpartum dams' weights after the successive litters in the high dose group during Task 2 were 1 to 12% lower than controls.

While the number of litters per pair was unaffected by DBP consumption, the mean number of live pups per litter was reduced by 8, 15, and 17% for the low through the high doses, respectively. Viability was unaffected, but pup weight adjusted for litter size was reduced in the middle and high dose groups by 4 and 10%, respectively.

These multiple effects on fertility triggered the performance of the Task 3 crossover mating using the control and high dose mice. This was performed after the last litter from Task 2 was weaned. There was no difference between the

groups in the proportion of the pairs that mated or delivered young. There was also no difference between the groups in terms of numbers of live pups or pup weight adjusted for litter size. Thus, the most sensitive sex could not be determined.

The last litter from Task 2 was evaluated during lactation. While viability at pnd 4, 7, 14, and 21 was not different across groups, body weights of neonates in the 1% DBP group were 12 to 16% less than controls at postnatal day 14 and 21.

While the second generation (all dose levels) was growing to the age of mating, the first generation control and 1% DBP rats were killed and necropsied. Body weights were insignificantly reduced (by 4%) in the DBP-exposed rats, and liver weight adjusted for body weight was increased by 15%. Kidney weight adjusted for body weight was also increased slightly, probably due to the slight body weight effect. There were no changes in epididymal sperm number, motility, or morphology, or in testicular spermatid head numbers. In DBP-exposed females, body weight was reduced by 14%, while adjusted liver weight and kidney weight was increased by 14 and 8%, respectively. Antemortem female estrous cyclicity was unaffected by DBP consumption.

In the mating trial for the second generation, body weights of 1% DBP-exposed rats were reduced at the high dose by 8 to 13% at the time of mating. There were significant effects in all DBP groups. At the high dose group, only 6 of 20 pairs mated, only one of those delivered any young. Mating and fertility indices in other groups were not different from controls. In the low and middle dose groups, there were no changes in the number of live pups per litter or the proportion born alive. However, live pup weight adjusted for litter size was

decreased in the low and middle dose groups by 5 and 8%, respectively. Thus, reductions in pup body weights were noted in the absence of other indications of effect.

After the F₂ litters were delivered and evaluated, they were killed, the F₁ dams were evaluated for estrous cyclicity, and the F₁ rats were killed and necropsied. In males, there were no DBP-related changes in body or organ weights in the low or middle dose group. In the high dose rats, was an 8% reduction in body weight and a 16% increase in liver weight. Also for high dose males, there were reductions in absolute testis weight, adjusted epididymis weight, prostate weight, and seminal vesicle weight, by 39, 10, 24, and 22%, respectively. Epididymal sperm concentration was reduced by 42% at the high dose, but motility and percent abnormal forms were unchanged. Testicular spermatid head counts were reduced only at the top dose, by approximately 50%. For females, DBP-related effects on weights were found only at the high dose: body weight was reduced by 13%. Adjusted organ weights were unchanged at all dose levels. Estrous cyclicity was unchanged at any level of DBP.

Histologically, there were no changes noted in ovaries or liver, while there was widespread testicular interstitial cell hyperplasia, and 10 of 10 rats examined at the high dose had either underdeveloped or "defective" epididymis.

In summary, di-n-butylphthalate produced significant reproductive toxicity in the absence of reductions in body weight. There was greater toxicity in the second generation than in the first, as evidenced by the reductions in pup number (at 1%DBP), adjusted pup body weights (all doses), and sperm measures. Additionally, there were developmental defects in the epididymides of high dose F₁ rats.

DI-n-BUTYLPHTHALATE, RATS

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: PB92111996

Chemical: Di-n-butylphthalate

CAS#: 84-74-2

Mode of exposure: Feed

Species/strain: Sprague-Dawley Rats

F ₀ generation	Dose concentration →	0.1%	0.5%	1.0%
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	—	—	—

F ₁ generation	Dose concentration →	0.1%	0.5%	1.0%
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?	Unclear
Study confounders:	None
NOAEL reproductive toxicity:	<0.1%
NOAEL general toxicity:	0.1%
F ₁ more sensitive than F ₀ ?	Yes
Postnatal toxicity:	Yes

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