



Response to NTP-CERHR Report on Di-isononyl Phthalate (DINP)

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We wish to respond to the NTP-CERHR Expert Panel report on di-isononyl phthalate (DINP). The Panel report focused on reproductive effects of DINP, however, it also reviewed other effects such as systemic, long-term and carcinogenic. While we are in general agreement with the Expert Panel's assessment on the reproductive effects of DINP, we have derived a no observed-effect-level (NOEL) for systemic effects, which is different from that adopted by the Panel.

Two chronic studies were available for DINP (Lington et al., 1997; Moore, 1998). The Expert Panel report reviewed the systemic effects of the two studies and adopted the conclusions of their authors, including the NOEL of 1,500 ppm

In the first study (Lington et al., 1997), groups of 110 Fischer 344 rats of each sex were exposed to 0, 0.03, 0.3 and 0.6% DINP1 diet up to two years. Expressed as mg of DINP1 ingested, the dose levels are 0, 15, 152, and 307 mg/kg bw/day in male rats and 0, 18, 184, and 375 mg/kg bw/day in females. Groups of animals were killed after 6, 12, 18 and 24 months of study. A significant reduction in body weight gain, increased relative liver and kidney weights, and elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed at 0.3% (3,000 ppm) DINP and higher. A no-observed-effect level was demonstrated at a dietary level of 0.03 wt% (300 ppm, approximately 17 mg/kg bw/day).

In the second two-year study (Moore, 1998), groups of 70-85 Fischer 344 rats were fed 0, 500, 1,500, 6,000 and 12,000 ppm DINP1 diets (males: 0, 29.2, 88.3, 359 and 733 mg/kg bw/day; females: 0, 36.4, 109, 442, and 885 mg/kg bw/day) up to 104 weeks. Subsets of animals were killed after 26, 52, 78 and 104 weeks of exposure. While more severe effects were observed in the groups given 6,000 and 12,000 ppm DINP1, hematological (decreased erythrocytes and hematocrit) and biochemical (elevated serum ALT and AST) effects were also noted in female rats exposed to 1,500 ppm, and killed at weeks 26, 52 and 78. The author did not consider these hematological and biochemical effects treatment-related on the grounds that they were not observed at week 104, and were not seen in male rats. A NOEL of 1,500 ppm was reported for DINP 1 (male: 88 mg; female: 109 mg/kg bw/day).

After a review of Moore's study, we derived a NOEL of 500 ppm (males: 29.2 mg/kg bw/day; females: 36.4 mg/kg bw/day). An examination of the Moore's report (1998) revealed that the actual dose of DINP1 (mg/kg bw/day) ingested by the 1,500 ppm male rats is lower than that of the corresponding females. While both sexes consumed diets of the same concentration, female rats that were killed at weeks 24, 52 and 80 ingested 28-42% more DINP1 (mg/kg bw/day) than males (Table 1). Further, the female rats killed in weeks 24, 52 and 80 ingested 20-28% more of the test substance (mg/kg bw/day) than those terminated at week 104.

In our opinion, the higher dose of DINP ingested by the female rats offers a reasonable explanation for the discrepancies in the biochemical and hematological effects observed in the two sexes. This observation is typical of a dose-dependent effect, and elevated serum

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transaminases suggest a liver injury in the female rats exposed to the 1,500 ppm DINP1. At week 104, both sexes consumed a substantially lower dose of DINP and hence did not exhibit these effects. This observation is consistent with those reported by Lington et al. (1997) who demonstrated that rats exposed to 0.3% dietary DINP (males:152 mg/kg bw/day, females: 184 mg/kg bw/day) had increased relative liver and kidney weights, and elevated serum transaminases.

Table 1. Amount of DINP ingested in different time periods in Moore's (1998) two-year study

Time (week of study)	Male Rats (mg/kg bw/day)	Female Rats (mg/kg bw/day)
24 ^a	69	97.6
52	71	100.9
80 ^a	74	94.9
104	73.9	79

a

No food consumption data were reported for 26 or 78 week and the consumption data of the nearest weeks were presented.

Based on the above analysis we conclude the NOEL for the systemic effects of DINP1 in the Moore study to be 500 ppm in diet (males: 29.2 mg/kg bw/day; females: 36.4 mg/kg bw/day).

References

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Moore MR (1998) Oncogenecity study in rats with di isononyl phthalate including ancillary hepatocellular proliferation and biochemical analyses. Volume I, Covance Laboratories Incorporated, Vienna, VA 22182, May 13, 1998. Covance 2598-104. EPA/OTS Doc # 89-980000308/0556283-2.

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