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Subject: Public Comments on the HPV Challenge Program Test Plan for Dimethyl Isophthalate (DMIP; CAS No. 1459-93-4) by Vertellus Performance Materials Inc.

The following comments on the HPV Challenge Program test plan for DMIP by Vertellus Performance Materials Inc. are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

DMIP is used as a polymer modifier and as a chemical intermediate. Vertellus Performance Materials Inc. proposes no additional testing for DMIP. In this exemplary test plan, mammalian toxicity endpoints are characterized by existing data for DMIP, its analog dimethyl terephthalate (DMTP) the metabolites terephthalic acid (TPA) and isophthalic acid (IPA). Calculated data were developed to characterize the aquatic toxicity of DMIP and corroborated by experimental data for DMTP.

DMTP is presented as a structural analog of DMIP, differing only with respect to the positioning of its carboxylic acid group on the benzene ring. Its physical/chemical properties are similar to those of DMIP and experimental or calculated physical/chemical properties values for DMTP are reported. Likewise, experimental results are presented indicating that DMTP and DMIP metabolize to form TPA and IPA, respectively, which also are close structural analogs that demonstrate similar toxicological properties and metabolism. As a result, read-across from DMTP to DMIP for human health-related endpoints is appropriate.

Acute oral toxicity data for DMTP in rats indicate LD_{50} values of 4390 mg/kg and >6590 mg/kg. An acute oral toxicity result is reported for DMIP in rats, also with an LD_{50} of 4390 mg/kg, but this value could not be substantiated. As a result, it is anticipated that DMIP presents a very low potential for toxicity via the oral route of exposure. DMTP was also shown to have low subchronic toxicity in rats, mice and guinea pigs via the oral and inhalation routes of exposure. High doses of DMTP may lead to the formation of renal and bladder crystals and calculi through the metabolism of DMTP to TPA with the resulting formation of TPA-calcium precipitates. The physical presence of these crystals and calculi leads to hematuria and to thickening of the bladder wall. It may be anticipated that DMIP at repeated high dose levels could cause the same effect by a similar mechanism.

Reproductive and developmental toxicity endpoints for DMIP are also satisfied by data for DMTP, as well as for TPA and IPA. No signs of toxicity were observed in either male or female parental rats in a 115-day fertility study with DMTP. While pups of parents administered 0.5 and 1.0 % DMTP in their diets had significantly lower mean body weights at weaning as compared to the control groups, this effect was probably due to their direct exposure to DMTP through lactation and food. A one-generation reproduction study with TPA is also summarized in which maternal and postnatal effects were observed at high doses (2 and 5% in their diets). No abnormal developmental effects and no pre- or post-implantation losses were observed in two studies with DMTP administered by either oral gavage or inhalation or in an inhalation study with TPA. No evidence of developmental toxicity or fetotoxicity was observed in rats exposed to IPA by inhalation.

In vitro and *in vivo* genotoxicity results with DMTP and IPA support the conclusion that DMIP is neither mutagenic nor genotoxic. Twelve in vitro genotoxicity assays with DMTP are summarized, ten of which produced negative results, one an equivocal result and one indeterminate activity. In addition, DMTP was shown to be negative in *in vivo* Drosophila sex-linked recessive lethal and mouse micronucleus assays. Gene mutation assays with IPA in bacteria produced inconsistent and equivocal results, while gene mutation and chromosomal aberration assays in mammalian cells produced consistently negative results.

ECOSAR was used to predict values for aquatic toxicity of DMIP. The ECOSAR 96-hour LC_{50} for acute toxicity to fish was predicted as 44.681 mg/l. Reliable measured data for DMTP for acute toxicity to fish were available for *Pimephales promelas* and *Brachydanio rerio* with 96-hour LC_{50} values ranging from 9.6 to 45 mg/l. Based on the similar physical/chemical properties of DMIP and DMTP and the corroborating measured DMTP data for fish, the predicted ECOSAR values for DMIP appear to be conservative estimates of the toxicity of DMIP to aquatic species.

Vertellus Performance Materials Inc.'s use of existing data for the DMIP analog DMTP and the metabolites, TPA and IPA, together with data calculated by ECOSAR is consistent with the HPV Challenge Program's goal of obtaining screening level hazard information, and this approach saves animals' lives by avoiding duplicative tests. Thank you for your attention to these comments. I may be reached at 610-586-3975, or via e-mail at josephm@peta.org.

Sincerely,

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Research & Investigations