201-16425A

U.S. EPA HIGH PRODUCTION VOLUME (HPV)
CHEMICALS CHALLENGE PROGRAM

Assessment of Data Availability and Test Plan for Dimethyl Isophthalate

(DMIP; CAS RN 1459-93-4)

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November 10, 2006

Assessment of Data Availability and Test Plan for Dimethyl Isophthalate (DMIP) (CAS RN 1459-93-4)

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CHEMICAL IDENTITY AND USE INFORMATION

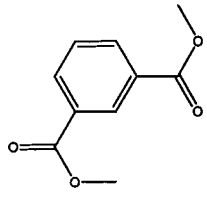
CAS RN

1459-93-4

Chemical Name

Dimethyl isophthalate

Structure, Molecular Formula, Molecular Weight

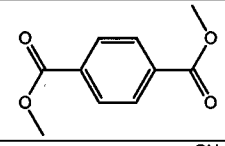
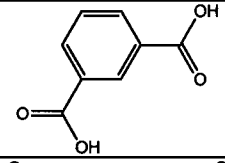
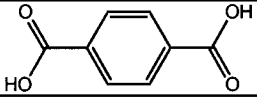


Molecular Formula: $C_{10}H_{10}O_4$
Molecular Weight: 194.19

OTHER CHEMICAL IDENTITY INFORMATION

DMIP
1,3-Benzenedicarboxylic acid, dimethyl ester
SMILES: O=C(OC)c(cccc1C(=O)OC)c1

STRUCTURAL ANALOGS

Chemical Name	CAS RN	Structure	Molecular Formula	Molecular Weight
Dimethyl terephthalate (DMTP)	120-61-6		$C_{10}H_{10}O_4$	194.19
Isophthalic acid (IPA)	121-91-5		$C_8H_6O_4$	166.13
Terephthalic acid (TPA)	100-21-0		$C_8H_6O_4$	166.13

DMIP and DMTP are structural analogs, differing only with respect to the positioning of their carboxylic acid groups on the benzene ring (1,3- and 1,4-, respectively). The physical/chemical properties, environmental fate and ecotoxicity, toxicological properties, and metabolism pathways of DMIP and DMTP are very similar. Where information for DMIP is lacking, supplemental information for DMTP is used to corroborate modeled values (*i.e.* aquatic toxicity endpoints) or for readacross (*i.e.* human health-related endpoints). IPA and TPA data provide additional supporting information for human health-related endpoints since they are the major metabolites of DMIP and DMTP, respectively. IPA and TPA also are structural analogs, differing only with respect to the positioning of their carboxylic acid groups on the benzene ring (1,3- and 1,4-, respectively). The metabolism pathways and toxicological properties of IPA and TPA are very similar.

USE PATTERN

Dimethyl isophthalate (DMIP) is used as a polymer modifier and as a chemical intermediate. Functions include:

- Modifies polyethylene terephthalate (PET) resins;
- Provides the isophthalate moiety in polyester production, *i.e.* REEMAY™;
- Acts as an additive for polyester bottle resin to retard crystallization for better clarity and strength;
- Lowers melting point of polyester, which promotes bonding properties of non-woven polyester; and
- Acts as an intermediate in X-ray contrast media.

AVAILABLE DATA TO FULFILL HPV SCREENING INFORMATION DATA SET (SIDS) ENDPOINTS

Text Table A: Test Plan

DIMETHYL ISOPHTHALATE CAS RN: 1459-93-4		Information	Guideline Study	GLP	Other Studies Available	Estimation Method	Acceptable	Testing Required
SIDS Endpoint	**STUDY**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL/CHEMICAL PROPERTIES DATA								
2.1	Melting Point	Y	N	N	Y	Y	Y	N
2.2	Boiling Point	Y	N	N	Y	Y	Y	N
2.4	Vapor Pressure	Y	N	N	Y	Y	Y	N
2.5	Partition Coefficient	Y	N	N	N	Y	Y	N
2.6	Water Solubility	Y	N	N	Y	Y	Y	N
ENVIRONMENTAL FATE DATA								
3.1.1	Photodegradation	Y	N	N	N	Y	Y	N
3.1.2	Stability in Water	Y	N	N	N	Y	Y	N
3.3.2	Transport and Distribution (Fugacity)	Y	N	N	N	Y	Y	N
3.5	Biodegradation	Y	Y	N	Y	N	Y	N
ECOTOXICITY DATA								
4.1	Acute/Prolonged Toxicity to Fish	Y	Y	Y	Y	Y	Y	N
4.2	Acute Toxicity to Aquatic Invertebrates	Y	N	N	Y	Y	Y	N
4.3	Toxicity to Aquatic Plants, e.g. Algae	Y	Y	Y	Y	Y	Y	N
HUMAN HEALTH-RELATED DATA								
5.1.1	Acute Toxicity	Y	N	N	Y	N	Y	N
5.4	Repeated Dose Toxicity	Y	N	N	Y	N	Y	N
5.5	Genotoxicity *In Vitro* (Bacterial Test)	Y	Y	Y	Y	N	Y	N
	Genotoxicity *In Vitro or In Vivo* (Chromosome Aberration Tests)	Y	N	N	Y	N	Y	N
	Genotoxicity *In Vitro* (Mammalian Cells)	Y	N	N	Y	N	Y	N
5.8	Reproductive Toxicity	Y	N	Y	Y	N	Y	N
5.9	Development Toxicity / Teratogenicity	Y	Y	Y	Y	N	Y	N

Note: Additional studies include: *in vitro* metabolism studies with two DMIP analogs, four *in vivo* metabolism studies with DMTP, and two and three *in vivo* metabolism studies with IPA and TPA, respectively.

Approach to Evaluate the Database for Dimethyl Isophthalate (DMIP)

The following approach was used to obtain and analyze data relevant to the assessment of DMIP.

1. The chemical name and CAS RN of DMIP were provided by Vertellus Performance Materials Inc.
2. The chemical names and CAS RNs of the structural analog of DMIP, dimethyl terephthalate (DMTP), and the respective metabolites, *i.e.* isophthalic acid (IPA) and terephthalic acid (TPA) were identified.
3. Published and unpublished reports obtained from Vertellus Performance Materials Inc. and other sources were organized and reviewed to identify studies that could fulfill SIDS endpoints.
4. Pertinent publicly available databases[1] were searched and all relevant reports were obtained to establish the full extent and nature of the published literature for DMIP, its structural analog, *i.e.* DMTP, and the respective metabolites, *i.e.* IPA and TPA.
5. A reference database was developed and maintained in order to track reports through the review, assessment and summarization process.
6. Each of the reports obtained for DMIP was reviewed to determine adequacy according to EPA criteria and reliability according to Klimisch *et al.* (1997).
7. Robust summaries were prepared for each DMIP report with a Klimisch score of 1 or 2, in accordance with the guidelines proposed by the EPA (U.S. EPA, 1999a) for each study type (see Appendix A). Summaries for relevant DMIP reports with a Klimisch score of 3 are also provided in Appendix A to serve as supporting data.
8. Summaries for DMTP, IPA and TPA were accepted as they appeared in their respective OECD SIAR and IUCLID dossiers.
9. Physical/chemical properties and environmental fate and ecotoxicity data were estimated by using appropriate Quantitative Structure Activity Relationships (QSARs) (U.S. EPA, 1999b).
10. Fugacity modeling (Level III) was performed to estimate transport and distribution of DMIP into relevant environmental compartments (Mackay *et al.*, 1996a,b).

[1] Databases include ChemIDplus, Existing Chemicals Database (IUCLID), OECD Integrated HPV Database, TSCATS (Toxic Substances Control Act Test Submissions), Syracuse Research Corporation PHYSPROP, DATALOG, BIOLOG, CHEMFATE AND BIODEG Databases, HSDB (Hazardous Substances Data Bank), CCRIS (Chemical Carcinogenesis Research Information System), GENETOX, DART/ETIC (Developmental and Reproductive Toxicology and Environmental Teratology Information Center), MEDLINE, TOXLINE, RTECS (Registry of Toxic Effects of Chemical Substances), NIOSH, NTP Database and Technical Reports and EPA HPV Database.

Use of Structure Activity Relationships for Dimethyl Isophthalate (DMIP)

Approaches recommended in the EPA document on the use of structure activity relationships (SAR) in the HPV Chemicals Challenge Program were employed in the assessment of DMIP (U.S. EPA, 1999b). Several SAR-based models, as well as Mackay-type fugacity-based modeling, were employed to support the review and assessment of DMIP. The SAR models for physical properties were used to estimate boiling point, melting point, aqueous solubility, octanol/water partition coefficient and vapor pressure. Other SAR models were used to estimate hydroxyl radical-mediated atmospheric photo-oxidation. Reliable experimental data were available to assess biodegradation potential. ECOSAR models were used to obtain estimates of acute toxicity to aquatic organisms. Some of the SAR models within the EPI Suite™ program rely on other physical properties. Whenever possible, such SAR models use experimental values for the other relevant physical properties (user-defined or a database structure match identified in a model subroutine) rather than relying on the corresponding model-predicted value. For DMIP, experimental database structure matches identified for melting point and boiling point were used to derive other model-predicted values (*e.g.* vapor pressure).

For human health-related endpoints, readacross from relevant studies available for DMTP, the structural analog of DMIP (see section on page 2 titled "Structural Analogs"), was used. Results of available metabolism studies support this approach for readacross and are summarized below.

Dibutyl isophthalate (DBIP), a close structural analog of DMIP, was metabolized to isophthalic acid (IPA) and monobutyl isophthalate in 60 minute *in vitro* incubations with rat liver, kidney, pancreas, small intestine, and blood tissue preparations (see Table 5 and Appendix A). Regarding IPA formation, the highest to lowest rates of activity in each tissue were as follows: liver microsome > kidney > liver homogenate > liver mitochondria > pancreas > liver supernatant > small intestine ~ blood. Similarly, with 60 minute *in vitro* incubations of rat tissue preparations (liver, kidney, pancreas, small intestine, and blood), dibutyl terephthalate (DBTP), a close structural analog of DMTP, was metabolized to terephthalic acid (TPA) and monobutyl isophthalate. For TPA formation, the highest to lowest rates of activity in each tissue were as follows: liver microsome > small intestine > pancreas > liver homogenates > kidney > liver mitochondria > blood. A value for liver supernatant was not determined. The authors concluded, "The present study shows that DBIP and DBTP were hydrolysed to their corresponding acids, IPA and TPA, by rat tissue enzymes, whereas PA [phthalic acid] was not formed from DBP [dibutyl phthalate] *in vitro*."

Several studies conducted in rats, rabbits, and mice have all indicated that DMTP is absorbed readily from the digestive tract and eliminated rapidly in the urine within 48-hours (see Table 5 and Appendix B). Most of the absorbed DMTP is metabolized to TPA *via* ester hydrolysis. Because DMIP and DMTP are close structural analogs, it is anticipated that DMIP is absorbed readily from the digestive tract, most of the absorbed DMIP is metabolized to IPA *via* ester hydrolysis, and IPA is eliminated rapidly in the urine.

Therefore, studies for IPA and TPA, the respective acid metabolites of DMIP and DMTP, were evaluated, as well as studies for DMTP, to support the assessment of DMIP. TPA is a structural

analog of IPA, differing only with respect to the positioning of the carboxylic acid groups on the benzene ring (see section on page 2 titled "Structural Analogs"). Both IPA and TPA are readily eliminated from the body, largely unchanged, *via* urinary excretion. Also, the toxicity profiles of these two acid analogs are very similar with the formation of urinary calculi and subsequent inflammatory changes of the urinary tract being the only notable effect after long-term repeated oral ingestion (see Tables 3 and 4 and Appendix B).

The use of DMTP data to fulfill human health-related endpoints for DMIP is an appropriate approach due to the principle that these chemicals are close structural analogs. Also, readacross from DMTP to DMIP for human health-related endpoints is appropriate because these structural analogs metabolize to form TPA and IPA, respectively, which also are close structural analogs that demonstrate similar toxicological properties and metabolism.

Physical/Chemical Properties QSAR Estimates and Correlation to Reliable Data

Physical/chemical properties data for DMIP and DMTP are summarized in Table 1. As expected, the physical/chemical properties data of these structural analogs are similar. Robust summaries for available reliable studies and QSAR estimates for physical/chemical properties of DMIP are presented in Appendix A. OECD SIAR and IUCLID summaries for available reliable studies and QSAR estimates for physical/chemical properties of DMTP are presented in Appendix B.

The physical/chemical property estimation program, Estimation Program Interface (EPI) Suite™ version 3.12, was used to derive estimates for DMIP. QSAR estimates are based on structure and, therefore, can be made only for substances for which a structure can be defined. Since DMIP has a defined structure, a complete set of model data was generated. QSAR estimates must be interpreted with a great deal of professional judgment; however, the model estimates for the physical/chemical properties of DMIP are, in most cases, comparable to the available reliable measured data. The available data for physical/chemical properties are summarized below.

Measured data for melting and boiling points (at 760 mm Hg) for DMIP are 67.5°C and 282°C, respectively. The EPIWIN MPBPWIN model-predicted value of -22.74°C for melting point is not comparable to the measured data and it is not plausible since DMIP is a solid under ambient conditions. On the other hand, the predicted boiling point for DMIP of 248.83°C is comparable to the measured boiling point of 282°C. The measured melting and boiling points for DMTP, the structural analog of DMIP, are 141°C and 280–288°C, respectively.

Vapor pressure for DMIP was estimated as 9.63×10^{-3} mm Hg at 25°C, whereas the EPIWIN MPBPWIN model-predicted value was 2.01×10^{-3} mm Hg at 25°C. The measured vapor pressure for DMIP's structural analog, DMTP, also was very low in two determinations at 25°C, *i.e.* 0.01 and 1.15 mm Hg. Neither DMIP nor DMTP is likely to enter the environment in significant quantities by volatilization.

The octanol/water partition coefficient (log K_{ow}) of DMIP predicted by the EPIWIN KOWWIN model was 1.66. For DMTP, DMIP's structural analog, the measured log K_{ow} was 2.25. Neither DMIP nor DMTP is likely to be persistent in the environment.

Measured data and the EPIWIN WSKOWWIN model prediction for water solubility were 290 mg/l and 1778 mg/l at 25°C, respectively. Measured values for DMTP of 19 – 37.2 mg/l at 25°C helps to corroborate the measured value for DMIP.

Environmental Fate and Ecotoxicity QSAR Estimates and Correlation to Reliable Data

Environmental fate and ecotoxicity data for DMIP and DMTP are summarized in Table 2. As expected, the environmental fate and ecotoxicity data of these structural analogs are similar. Robust summaries for the QSAR estimates for the environmental fate and ecotoxicity of DMIP are presented in Appendix A. OECD SIAR and IUCLID summaries for available reliable studies and QSAR estimates for the environmental fate and effects of DMTP are presented in Appendix B.

Modeling with EPIWIN AOPWIN indicated that DMIP would be expected to degrade at a moderate rate ($t_{½}$ = 16.805 days) upon exposure to ambient light (assuming a 12-hour day). A photo-oxidation half-life for DMTP was reported to be in the same range ($t_{½}$ = 4.7 – 46.6 days) as that of its structural analog DMIP.

The stability of DMIP in water was determined using the EPIWIN HYDROWIN model and was found to be pH dependent. At 25°C and pH 7, the K_b $t_{½}$ = 352.118 days and, at 25°C and pH 8, the K_b $t_{½}$ = 35.212 days. This suggests that DMIP is stable in water under environmentally relevant conditions. DMTP, the structural analog of DMIP, also was determined to be stable in neutral water at 25°C with a hydrolytic $t_{½}$ = 321 days.

Modeling for environmental transport and distribution (using a Mackay-type, EPIWIN Level III fugacity model) predicted distribution to water and soil (mass amounts of 28.2 and 70.6%, respectively) with no appreciable distribution to air or sediment following entry of DMIP into the environment *via* equal emissions to water, air and soil (1000 kg/hr). Similarly, the EPIWIN Level III fugacity model results for DMTP, the structural analog of DMIP, predicted distribution predominantly to water and soil (mass amount 34.4 and 51.6%, respectively).

Regarding biodegradation, reliable measured data exist from several studies conducted with various environmental media. The test types and results are summarized for DMIP in Table 2 and Appendix A, and for DMTP in Table 2 and Appendix B.

In a guideline study (OECD 301-C, MITI method), aerobic biodegradability of DMIP based on indirect analysis was 99% (as ThBOD) after two weeks. Direct analysis by HPLC and TOC measurement confirmed biodegradability over the two-week study period to be 100 and 96%, respectively. Degradation of DMIP was also demonstrated with a mixed bacterial culture from mangrove sediment; however, complete degradation required the biochemical cooperation between the two selective bacterial species, which were isolated from the sediment culture. While *K. oxytoca* Sc was able to completely transform DMIP (108 mg/l) to monomethyl isophthalate (MMIP) within approximately 36 hours, MMIP accumulated in the culture medium over this period and did not decrease over the extended incubation period (*i.e.* through five days).

M. mesophilicum Sr was able to degrade the intermediate MMIP to IPA within approximately 8 days. Both species demonstrated metabolism of IPA.

Similarly, aerobic degradation of DMTP was demonstrated in a guideline study (OECD 301-C, MITI method), in which DMTP (100 mg/l) was degraded by 84% in 14 days. DMTP was also determined to be readily biodegradable in an OECD 301D (Closed Bottle) study and a BODIS (ISO Method 10708) study, in which degradation reached 68 and 94%, respectively.

Measured data are not available for acute toxicity of DMIP to fish, aquatic invertebrates or aquatic plants; however, EPIWIN ECOSAR was used to predict values for acute fish, daphnid and algal toxicity. The EPIWIN ECOSAR 96-hour LC_{50} for acute toxicity to fish was predicted as 44.681 mg/l. The EPIWIN ECOSAR 48-hour EC_{50} for acute toxicity to the daphnid was predicted as 314.502 mg/l. The EPIWIN ECOSAR 96-hour EC_{50} for acute toxicity to green algae was predicted as 3.513 mg/l.

Reliable measured data for DMTP, the structural analog of DMIP, for acute toxicity to fish were available for *Pimephales promelas* (Fathead minnow) and *Brachydanio rerio* with 96-hour LC_{50} values ranging from 9.6 to 45 mg/l. Reliable measured DMTP data for acute toxicity to aquatic invertebrates was available for *Daphnia magna* with 48-hour EC_{50} values >30 mg/l. Reliable measured DMTP data for acute toxicity to aquatic plants was available for *Scenedesmus subspicatus* with 72-hour EC_{50} values of 20.1 and 27.6 mg/l (see Table 2 and Appendix B).

Based on the similar physical/chemical properties of DMIP and DMTP and the corroborating measured DMTP data for fish (*Pimephales promelas* and *Brachydanio rerio*), aquatic invertebrates (*Daphnia magna*), and aquatic plants (*Scenedesmus subspicatus*), the predicted EPIWIN ECOSAR values for DMIP appear to be conservative estimates of the toxicity of DMIP to aquatic species.

Human Health-Related Reliable Data

Human health-related data for DMTP, IPA and TPA, structural analogs of DMIP, are summarized in Tables 3 and 4. OECD SIDS and IUCLID summaries for available reliable studies on human health-related effects of DMTP, IPA and TPA are presented in Appendix B.

An acute oral toxicity result is reported for DMIP in rats with LD_{50} = 4390 mg/kg (ITC/USEPA, 1982). Since this value could not be substantiated and no other study details are available, a Robust Summary was not prepared. Acute oral toxicity data for DMTP in rats indicate LD_{50} values of 4390 mg/kg and >6590 mg/kg; therefore, it is anticipated that DMIP would also present a very low potential for toxicity *via* the oral route of exposure. Although acute dermal toxicity data are not available, DMIP is predicted to present a very low potential for toxicity *via* the dermal route of exposure because of its high oral LD_{50}, it is unlikely to be absorbed efficiently through the skin, and an LD_{50} >5000 mg/kg in guinea pigs with DMTP. Acute inhalation toxicity data are not available, but DMIP is predicted to present a very low potential for toxicity *via* the inhalation route of exposure because of its low vapor pressure, its high oral LD_{50}, and a rat LC_{50} >6 mg/l with DMTP.

No studies are available with DMIP for repeated dose toxicity, *in vitro/in vivo* genetic toxicity, toxicity to reproduction, or teratogenicity/developmental toxicity; however, reliable studies with DMTP, the structural analog of DMIP, are available for all of these endpoints.

DMTP was studied for repeated dose toxicity in rats, mice, and guinea pigs in 14 studies ranging in duration from 10 days to at least 6 months (two inhalation studies are listed as chronic but the length of exposures are not defined in the information available). Also included are 2-year oral (dietary) carcinogenicity studies in rats and mice. High doses of DMTP were administered *via* the dietary, oral gavage or inhalation routes of exposure in these studies.

The numerous testing results for repeated dose toxicity studies with DMTP summarized in the following text table and in the text below, in addition to the data provided in Table 4 and Appendix B for DMTP and IPA support the conclusion that DMIP, as the structural analog of DMTP, has a low potential to cause systemic toxicity.

Text Table B: Summary of Repeated Dose Toxicity Studies for DMTP

Species; Number/group and Sex	Route	Dose/Exposure Levels	Duration	NOAEL (mg/kg bw/day)
Rat; NR	Oral (gavage)	5000 mg/kg/day	2 weeks (5 days/week)	Not determined
Rat; 13-18 M & 13-18 F	Oral (diet)	0.5, 1.0, 1.5, 2 or 3%	2 weeks	M: 660 (0.5%) F: 1277 (1.0%)
Rat; NR	Oral (diet)	5 or 10%	16 days	Not determined
Rat; 5 M	Oral (diet)	5%	28 days	Not determined
Rat; NR	Oral (diet)	500 mg/kg/day	35 – 39 days	500
Rat; 7-19 M & 7-19 F	Oral (diet)	0.5, 1.6 or 3%	13 weeks	Not determined
Rat; 10 M & 10 F Mouse; 10 M & 10 F	Oral (diet)	1750, 2500, 5000, 10,000 or 20,000 ppm	13 weeks	Rat: 5000 ppm Mouse: 20,000 ppm
Rat; 30 M	Oral (diet)	0.25, 0.5 or 1.0%	96 days	313 (0.5%)
Rat; NR	Inhalation	1-4 or 40-70 mg/m^3	5 months	Not determined
Rat; 30 M	Inhalation	16.5 or 86.4 mg/m^3	3 months	16.5 mg/m^3
Rat; NR Guinea pig; NR	Inhalation	15 mg/m^3	6 months	15 mg/m^3
Rat; NR	Inhalation	0.08, 0.4 or 1 mg/m^3	"Chronic"	Not determined
Rat; NR	Inhalation	0.08, 0.4 or 1 mg/m^3	"Chronic"	Not determined
Rat; 50 M & 50 F Mouse; 50 M & 50 F	Oral (diet)	2500 or 5000 ppm	2 year carcinogenicity	Negative in rats and female mice. An increase in lung tumors in male mice was considered equivocal.

M = Male; F = Female
NR = Not reported
Key study

DMTP was shown to possess a low level of subchronic toxicity in rats, mice and guinea pigs *via* the oral and inhalation routes of exposure in the reliable studies. The only target organ identified in oral dietary exposure studies was the urinary tract. However, the observed toxicity was not the result of a direct DMTP effect, but rather it was mediated through an indirect mechanism.

When DMTP is administered at high doses, renal and bladder crystals and calculi may be formed through the metabolism of DMTP to terephthalic acid (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. The minimum dose level and exposure duration at which these effects have been reported for DMTP are 1.5% (1890 mg/kg/day) in the diet for 14 days. However, crystal formation and hematuria are not consistently observed in all repeat dose studies. In particular, this phenomenon was not observed in the 2-year rat and mouse dietary carcinogenicity studies in which DMTP was administered in the diet at 2500 or 5000 ppm. It may be anticipated that DMIP at repeated high dose levels could cause the same effect by a similar mechanism.

When rats were exposed at up to 0.5% (approximately 250 mg/kg/day) isophthalic acid (IPA, the primary metabolite of DMIP) in the diet for 13 weeks, no adverse effects were observed. A dietary exposure level of 1.6% (approximately 800 mg/kg/day) administered in the diet produced small increases in the incidence of crystalluria (1/25 males, 2/25 females) and renal pathology (mild hydronephrosis, pelvic calcification, 5/25 males). Under the conditions of this study a NOAEL of 250 mg/kg/day and LOAEL of 800 mg/kg/day were established based on these kidney effects in rats. Sprague-Dawley rats were exposed by inhalation to 1.0, 5.0 or 10 mg/m^3 IPA aerosol for six hours/day, five days/week for four weeks. No treatment-related effects were reported for body weight gain, organ weights, hematology, or clinical chemistry parameters. This study identified a NOAEL of 10 mg/m^3 for subchronic inhalation exposures to IPA.

The *in vitro* and *in vivo* testing results with DMTP summarized in the following text table and in the text below, in addition to the data in Table 4 and Appendix B for DMTP and IPA support the conclusion that DMIP is neither mutagenic nor genotoxic.

Text Table C: *In vitro* and *In vivo* Mutagenicity/Genotoxicity Studies for DMTP

Test System	Test Object	Concentration of Substance	Results
Ames assay	*S. typhimurium* TA98, TA100, TA1535, TA1537	3.3 – 333 µg/plate	Negative[a,b]
Ames assay	*S. typhimurium* TA98, TA100	NR	Negative[a,b]
Ames assay	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537, TA1538	0.5 – 5000 µg/plate	Negative[a,b]
Mutatox™ Assay	*Photobacterium phosphorium*	NR	Equivocal
DNA single-strand break assay	Rat hepatocytes or Chinese hamster embryo cells	727.5 – 2910 µg/ml 727.5 – 2910 µg/ml	Negative Negative[b]
Unscheduled DNA synthesis assay	HeLa Cells	5 – 5000 µg/ml	Negative[a,b]
Chromosomal aberration assay	Human lymphocyte cells	50 – 500 µg/ml	Negative[b]
Micronucleus assay	Human lymphocyte cells	50 – 500 µg/ml	Negative[b]
DNA amplification assay	Syrian hamster embryo	2.5 – 10 µg/ml	Negative[b]
Gene mutation assay	Mouse L5178Y lymphoma cells	up to 100 µg/ml	Negative[a,b]
Chromosomal aberration and Sister chromatid exchange assays	Chinese hamster ovary cells	10 µg/ml	Negative[a,b]
Transformation assay	Mouse BALB/c-3T3 cells	0.644 – 5.15 mM	Indeterminate activity[b]
In vivo Sex-linked recessive lethal assay	*Drosophila melanogaster* (male and female)	1000 ppm diet 400 ppm injection	Negative
In vivo Sex-linked dominant lethal assay	*Drosophila melanogaster*	NR	Positive
In vivo Micronucleus assay	Mouse/B6C3F1 (male and female)	438 – 1750 mg/kg/day i.p. injection for 3 days	Negative
In vivo Micronucleus assay	Mouse/C57B1/6j × CBA (male and female)	0.20 – 1.00 mmole/kg i.p. injection for 1 day	Positive

[a] With metabolic activation.
[b] Without metabolic activation.
NR = Not reported
Key study

The available battery of 10 negative, one equivocal and one indeterminate activity *in vitro* genotoxicity assays with DMTP is adequate to conclude that DMIP does not pose a genotoxicity concern for humans. In addition, DMTP was shown to be negative in an *in vivo* sex-linked recessive lethal assay with *Drosophila melanogaster* and an *in vivo* mouse micronucleus assay, which further indicate an absence of *in vivo* genotoxicity potential for DMIP. The significance of an increase in micronuclei formation in one of the two *in vivo* mouse micronucleus tests with DMTP is questionable due to many irregularities in the study methodology as well as evidence of toxicity from the vehicle (DMSO).

Three gene mutation studies with *S. typhimurium* were performed with IPA. Each study was conducted both in the absence and presence of a metabolic activation system. The maximum concentration of IPA investigated in one of the studies was 5000 µg/plate, whereas the other two studies evaluated concentrations up to 10,000 µg/plate. In the first study, no mutagenic activity was observed with or without metabolic activation. In the second study, a dose dependent increase in the number of revertants with TA98, TA1537, and TA1538 tester strains in the presence and absence of metabolic activation was reported. Finally in the third study, a positive response with TA98 and TA1538 tester strains was seen in the presence of metabolic activation and with tester strain TA1538 in the absence of metabolic activation. It is noteworthy that both studies yielding positive responses evaluated concentrations up to 10,000 µg/plate. At concentrations of 5000 µg/ml and higher, one study reported that IPA visibly precipitated in the plates and the bacterial lawn was adversely affected. The assays for gene mutation in bacteria produced inconsistent and equivocal results.

In Chinese hamster ovary cells, IPA concentrations up to 5000 µg/ml, with and without metabolic activation, did not produce an increase in chromosomal aberrations. Similar results were observed in Chinese hamster ovary cells when IPA concentrations up to 3000 µg/ml were evaluated for mutations at the HGPRT locus. Finally, no increase in mutation frequency was reported in a mouse lymphoma mutation assay using test concentrations up to 950 µg/ml. In contrast to the bacterial mutation assays, IPA provided negative responses in assays investigating gene mutation in two different mammalian cell systems and chromosomal aberration in mammalian cells. Therefore, the weight of evidence suggests that IPA is not mutagenic in mammalian cells and is unlikely to be mutagenic *in vivo*.

Evaluation of potential for reproductive effects is satisfied for DMIP by a 115-day fertility study with DMTP and a one-generation reproduction study with TPA both by the dietary route of administration (see Table 4 and Appendix B). Evaluation of potential for developmental effects is satisfied for DMIP by inhalation and oral gavage developmental toxicity studies with DMTP and inhalation developmental toxicity studies with IPA and TPA (see Table 4 and Appendix B).

Reproductive toxicity was evaluated by exposing male rats to diets containing 0.25, 0.50 or 1.0% DMTP for 115 days. These males were then mated with females that had been on the same DMTP diet for six days. After mating, females remained on the diet through lactation. No signs of toxicity were observed in either the male or female parental animals (P_1). Pups (F_1) of parents administered 0.5 and 1.0% DMTP had significantly lower mean body weights at weaning as compared to the control groups. The parental NOEL was 1.0% (636 mg/kg/day) and the NOEL for their offspring was 0.25% (152 mg/kg/day). This effect on the offspring probably was due to their exposure to DMTP through lactation and having access to the dams' food during the same period, and hence it was toxicity from direct exposure to DMTP.

No adverse effects on fertility were noted in adult rats administered up to 5% terephthalic acid (TPA) in the diet during a one-generation reproduction study. However, maternal and postnatal effects occurred in the 2 and 5% groups. The NOAEL for maternal (P_1) toxicity and for the offspring (F_1) was 0.5% TPA in the diet (240 – 307 mg/kg/day), whereas the NOAEL for

reproductive effects was >5.0% (2480 – 3018 mg/kg/day). There were increased numbers of pup deaths on postnatal Day 1 and decreased survivability to Day 21 as compared to control groups. Several large litters of pups were lost to dams suffering obvious signs of maternal toxicity, probably because these dams did not attend to their litters or allow their pups to nurse. Unscheduled deaths occurred during the post-weaning period in the 5% groups and were associated with a very high incidence of renal and bladder calculi in the weanling animals. It is noteworthy that weanling animals exhibited a higher incidence of calculi compared to adults consuming the same dietary level of TPA. This may be attributed to the comparatively large amount of diet consumed in relation to body weight for young rapidly growing animals as compared to mature adults. Weanling animals were not found to be more sensitive to TPA toxicity when the results were expressed on an mg/kg/day basis.

In a Segment II Inhalation Teratology Study, IPA was administered by inhalation at 0, 1, 5, or 10 mg/m^3 aerosol on gestation days 6 through 15 to four groups of 16-18 timed-pregnant primiparous Sprague-Dawley rats. No statistically significant differences in mean dam body or uterus weights, litter weights, or dam body weight gains were evident between the IPA-exposed groups and the control groups. Gross external, skeletal, and soft tissue examinations failed to show any significant increase in the incidence of fetal malformations or anomalies in the IPA-exposed litters compared to the controls. Maternal reproduction and litter viability data (average litter size; male:female ratio; mean number of resorptions) were similar for all groups. In summary, no evidence of developmental toxicity or fetotoxicity was observed in rats exposed by inhalation to 0, 1, 5, or 10 mg/m^3 IPA aerosol on gestation days 6 through 15.

The potential for DMTP to induce developmental toxicity in rats was evaluated following an inhalation exposure to DMTP at 1 mg/m^3 throughout gestation and after oral gavage administration with 1000 mg/kg/day DMTP during gestation days 7-16. In addition, inhalation exposures to TPA, the primary metabolite of DMTP, at test chamber concentrations up to 10 mg/m^3 were assessed during gestation days 6-15 in rodents. No abnormal developmental effects and no pre- or post-implantation losses were noted in these three studies.

SUMMARY OF TEST PLAN

The available data for physical/chemical properties are summarized in Table 1. Vertellus Performance Materials Inc. contends that the existing measured and modeled data on DMIP for melting point, boiling point, vapor pressure, octanol/water partition coefficient, and water solubility are acceptable to fulfill these endpoints under the U.S. EPA HPV Chemicals Challenge Program. No additional data development is suggested for DMIP.

The available data for environmental fate and ecotoxicity are summarized in Table 2. Vertellus Performance Materials Inc. contends that the existing measured and modeled data on DMIP and DMTP for photodegradation, stability in water, transport and distribution, biodegradation, toxicity to fish, toxicity to aquatic invertebrates, and toxicity to aquatic plants are acceptable to fulfill these endpoints under the U.S. EPA HPV Chemicals Challenge Program. No additional data development is suggested for DMIP.

The available human health-related data are summarized in Tables 3 and 4, and relevant *in vitro* and *in vivo* metabolism studies are summarized in Table 5. Vertellus Performance Materials Inc. contends that the existing measured data for acute toxicity, repeated dose toxicity, genotoxicity *in vitro* and *in vivo*, reproductive toxicity, and developmental toxicity on DMIP, DMTP, IPA and/or TPA are acceptable to fulfill these endpoints under the U.S. EPA HPV Chemicals Challenge Program, especially when the relevant *in vitro* and *in vivo* metabolism studies also are considered (see Table 5). No additional data development is suggested for DMIP.

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Table 1

Physical/Chemical Properties Data for Dimethyl Isophthalate and Dimethyl Terephthalate

Chemical Name	CAS RN	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure	Partition Coefficient (log K_{ow})	Water Solubility at 25°C (mg/l)
Dimethyl isophthalate	1459-93-4	*-22.74* [a] 67.5	*248.83* 282	*9.63× 10^{-3} mm Hg at 25°C* *2.01× 10^{-3} mm Hg at 25°C*	*1.66*	*1778* 290
Dimethyl terephthalate	120-61-6	141	280 - 288	0.01 mm Hg at 25°C 100 mm Hg at 208°C 1.15 mm Hg at 25°C	2.25 2.35*	37.2 19 *140* 28.7 at 20°C*

Notes: Reliable data for Dimethyl isophthalate are summarized in greater detail in Appendix A.
Italicized values reflect model data for Dimethyl isophthalate. Estimated and experimental data for Dimethyl terephthalate could not be confirmed, and thus are not differentiated here.
Shaded cells indicate data for supporting chemical as referenced in the respective SIDS Dossier provided in Appendix B, unless otherwise indicated.
* Indicates data for supporting chemical as referenced in the respective IUCLID Dataset provided in Appendix B.
[a] Modeled result is not plausible since DMIP is a solid under ambient conditions.

Table 2
Environmental Fate and Ecotoxicity Data for Dimethyl Isophthalate and Dimethyl Terephthalate

Chemical Name	CAS RN	Photodegradation	Stability in Water	Transport & Distribution [a]	Biodegradation	Acute/ Prolonged Toxicity to Fish 96-hr LC_{50} (mg/l)	Acute/Chronic Toxicity to Invertebrates 48-hr LC_{50} (mg/l)	Toxicity to Aquatic Plants 96-hr EC_{50} (mg/l)
Dimethyl isophthalate	1459-93-4	*OH rate constant: 0.6365×10^{-12} cm^3/molecule·sec; $t_{1/2}$ = 16.805 d*	*2.278×10^{-1} L/mol·sec at pH>8 and 25°C; $t_{1/2}$=35.212 d at pH 8; $t_{1/2}$=352.118 d at pH 7*	*Mass Amounts: Air = 1.1% Water = 28.2% Soil = 70.6% Sediment<0.1%*	MITI: 99% degradation (as ThBOD) in 14 days 100% degradation in ~36 h (mangrove sediments)	*44.681*	*314.502*	*3.513*
Dimethyl terephthalate	120-61-6	$t_{1/2}$ = 4.7 - 46.6 d	Hydrolytic $t_{1/2}$ = 321 d $t_{1/2}$ = 1-4 wk in surface water $t_{1/2}$ = 2-8 wk in ground-water	*Mass Amounts: Air = 13.9% Water = 34.4% Soil = 51.6% Sediment = 0.134%*	MITI: 84% degradation (as ThBOD) in 14 days OECD 301D: Readily biodegradable (68% in 28 d) * BODIS Test (ISO 10708): Readily biodegradable (94% in 28 d) *	9.6 45 14.2 13* 18.8* 14.3*	> 100 (96-h) >30 = 30.4	72 h (Biomass) EC_{50} = 27.6 NOEC = 10.8 72 h EC_{50}= 20.1*

Notes: Reliable data for Dimethyl isophthalate are summarized in greater detail in Appendix A.

Italicized values reflect model data for Dimethyl isophthalate. Estimated and experimental data for Dimethyl terephthalate could not be confirmed, and thus are not differentiated here, except as noted.

Shaded cells indicate data for supporting chemical as referenced in the respective SIDS Dossier provided in Appendix B, unless otherwise indicated.

* Indicates data for supporting chemical as referenced in the respective IUCLID Dataset provided in Appendix B.

[a] Only one modeled emission scenario summarized here. Entry into the environment was assumed here to be 1000 kg/hr emissions each to air, water and soil.

Table 3

Acute Human Health-Related Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Acute Oral Toxicity (mg/kg)	Acute Inhalation Toxicity (mg/l)	Acute Dermal Toxicity (mg/kg)
Dimethyl isophthalate	1459-93-4	Rat LD_{50}: 4,390[a]		
Dimethyl terephthalate	120-61-6	Rat LD_{50}: > 6,590 4,390	Rat LC_{50}: > 6	Guinea pig LD_{50}: > 5,000
Isophthalic acid	121-91-5	Rat LD_{50}: > 5,000 13,000 10,900 10,400	Rat LC_{50}: > 11.37	Rabbit LD_{50}: > 2000 > 23,000
Terephthalic acid	100-21-0	Rat LD_{50}: >5000 >15380 1960 18800 2000 Mouse LD_{50}: >5000 6400 1470	Rat LC_{50}: > 2.02 > 1	Rabbit LD_{50}: >2000

Notes: Shaded cells indicate data for supporting chemicals as referenced in the respective SIDS Dossiers provided in Appendix B unless otherwise indicated.
Empty block denotes data either are not available or are available and judged inadequate.
[a] ITC/USEPA (1982) as cited in Hazardous Substances Data Bank (HSDB); value could not be substantiated, therefore a Robust Summary was not prepared.

Table 4

Human Health-Related Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Repeated Dose Toxicity NOAEL (mg/kg)	Genetic Toxicity *In vitro/ In vivo*	Toxicity to Reproduction (mg/kg/day)	Teratogenicity/ Developmental Toxicity (mg/kg/day)
Dimethyl isophthalate	1459-93-4				
Dimethyl terephthalate	120-61-6	**Short Term Repeated Dose Toxicity** 10 d (gavage, rat): No NOEL determined 14 d (diet, rat): NOEL = 0.5% (♂) & 1.0% (♀) 16 d (diet, rat): No NOEL determined. 28 d (diet, rat): No hematological or histopathological abnormalities. >34 d (oral, rat): NOEL = 500 **Subchronic Toxicity** 13 wk (oral, rat): No NOEL determined. 13 wk (diet, rat & mouse): NOAEL = 5000 ppm (rat), NOAEL = 20000 ppm (mouse) 96 d (diet, rat): NOEL = 313 5 mos (inhalation, rat): 30% mortality, rhinitis, depilation, dystrophic changes in the liver & kidneys, hemorrhage of the lungs, brain & myocardium, & hyperemia of the internal organs. 3 mos (inhalation, rat): NOEL = 16.5 mg/m^3 6 mos (inhalation, rat & guinea pig): NOEL = 15 mg/m^3	**Bacterial *In Vitro*** Ames Test (TA1535, TA1537, TA98 & TA100): Negative w/ and w/o metabolic activation. Ames Test (TA98 & TA100): Negative w/ and w/o metabolic activation. Ames Test (TA1535, TA1537, TA98, TA100, TA102 & TA1538): Negative w/ and w/o metabolic activation. Mutatox™ Assay (*P. phosphorium*): equivocal **Mammalian *In Vitro*** DNA Single-Strand Break Assay (Rat hepatocytes & CHE cells): Negative UDS Assay (HeLa cells): Negative Chromosomal Aberration Assay (Human Lymphocytes): Negative Chromosomal Aberration Assay (CHO cells): Negative	115 d (diet, rat): NOEL (P_1) = 636 NOEL (F_1)= 152	Throughout Gestation (inhalation, rat): No developmental effects and no pre- or post-implantation losses were noted at dose of 1 mg/m^3. Gestation Days 7-16 (gavage, rat): NOAEL > 1,000

Table 4 *(Continued)*

Human Health-Related Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Repeated Dose Toxicity NOAEL (mg/kg)	Genetic Toxicity *In vitro/ In vivo*	Toxicity to Reproduction (mg/kg/day)	Teratogenicity/ Developmental Toxicity (mg/kg/day)
Dimethyl terephthalate *(continued)*	120-61-6	**Chronic Toxicity** Inhalation (rat): No NOEL determined. Inhalation (rat): No NOEL determined. **Carcinogenicity** 2 year (diet, rat): Negative 2 year (diet, mice): Negative (♀), An increase in lung tumors in male mice was considered equivocal.	**Mammalian *In Vitro (Continued)*** Micronuclei Assay (Human Lymphocytes): Negative DNA Amplification Assay (Syrian Hamster Ovary): Negative Gene Mutation Assay (Mouse Lymphoma): Negative Transformation Assay (BALB/c-3T3 Cells): Indeterminate Activity **Non-Bacterial *In Vivo*** Sex-linked Recessive Lethal Assay (*D. melanogaster*/ Canton-*S* ♂ and *Basc* ♀): Negative Sex-linked Dominant Lethal Assay (*D. melanogaster*): Positive **Mammalian *In Vivo*** Micronuclei Assay (mouse): Negative Micronuclei Assay (mouse): Positive		

Table 4 *(Continued)*

Human Health-Related Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Repeated Dose Toxicity NOAEL (mg/kg)	Genetic Toxicity *In vitro/ In vivo*	Toxicity to Reproduction (mg/kg/day)	Teratogenicity/ Developmental Toxicity (mg/kg/day)
Isophthalic acid	121-91-5	**Short Term Repeated Dose Toxicity** 4 wk (inhalation, rat): NOAEL > 10 mg/m^3 No significant effects up to 10 mg/m^3, 6 hours/day for 5 days/week. **Subchronic Toxicity** 13 wk (diet, rat): NOAEL = 250, LOAEL = 800. Slight increase in the incidence of crystalluria (1/25 ♂, 2/25 ♀) and renal pathology (mild hydronephrosis, pelvic calcification: 5/25 ♂).	**Bacterial *In Vitro*** Ames (TA1535, TA1537, TA1538. TA98 & TA100): Negative w/ and w/o metabolic activation. Ames (TA100, TA1535, TA1537, TA1538 & TA98): Dose-dependent increase in the number of revertants with strains TA1537, TA1538 & TA98 w/ and w/o metabolic activation. Ames (TA100, TA1535, TA98 & TA1538): Positive with TA98 and TA1538 w/metabolic activation and with TA1538 w/o metabolic activation. **Mammalian *In Vitro*** Chromosomal Aberration Assay (CHO cells): Negative w/ and w/o metabolic activation. HGPRT Mutation Assay (CHO cells): Negative w/ and w/o metabolic activation. Mouse Lymphoma Mutation Assay (L5178Y cells): Negative w/ and w/o metabolic activation.		Gestation Days 6-15 (Inhalation, rat): No maternal or developmental toxicity at inhalation exposures up to 10 mg/m^3.

Table 4 *(Continued)*

Human Health-Related Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Repeated Dose Toxicity NOAEL (mg/kg)	Genetic Toxicity *In vitro/ In vivo*	Toxicity to Reproduction (mg/kg/day)	Teratogenicity/ Developmental Toxicity (mg/kg/day)
Terephthalic acid	100-21-0	**Short Term Repeated Dose Toxicity** 4 wk (inhalation, rat): No adverse effects other than minimal respiratory tract irritation at 3 mg/m^3. **Subchronic Toxicity** 15 wk (diet, rat): NOAEL(♂) = 1220 and NOAEL(♀) = 1456. Primary effects observed were bladder calculi formation and hyperplasia of the bladder epithelium. 6 mos (inhalation, rat & guinea pig): No adverse effects. **Carcinogenicity** 2 year (diet, rat): Increased incidence of calculi, hyperplasia and tumors in the bladder.	**Bacterial *In vitro*** Ames (multiple tests; TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538): Negative with and without metabolic activation **Mammalian *In vitro*** Micronuclei Assay (Human Lymphocytes): Negative Chromosomal Aberration (CHL fibroblasts): Negative DNA Single-Strand Break Assay (Rat hepatocytes): Negative **Mammalian *In vivo*** Micronuclei Assay (mouse): Negative	One Generation (>150 d) (diet, rat): 0.03, 0.125%, 0.5, 2.0 & 5.0% (equivalent to: CD♂: 14, 59, 240, 930 & 2499 CD♀: 17, 67, 282, 1107 & 2783 Wistar♂:14, 61, 249, 960 & 2480 Wistar♀: 19, 78, 307, 1219 & 3018) Parental Effects: CD♂: NOAEL = 240 CD♀: NOAEL = 282 Wistar♂: NOAEL = 960 Wistar♀: NOAEL = 1219 Reproductive Effects: CD♂: NOAEL > 2499 CD♀: NOAEL > 2783 Wistar♂: NOAEL > 2480 Wistar♀: NOAEL > 3018	Gestation Days 6-15 (inhalation, rat): No maternal or developmental toxicity at exposures up to 10 mg/m^3.

Table 4 *(Continued)*

Human Health-Related Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Repeated Dose Toxicity NOAEL (mg/kg)	Genetic Toxicity *In vitro/ In vivo*	Toxicity to Reproduction (mg/kg/day)	Teratogenicity/ Developmental Toxicity (mg/kg/day)
Terephthalic acid *(continued)*	100-21-0			No effects on fertility up to 5% Offspring Effects: CD♂: NOAEL = 240 CD♀: NOAEL = 282 Wistar♂: NOAEL = 960 Wistar♀: NOAEL = 1219 Developmental effects at 2 and 5% included increased postnatal deaths, decreased survivability, high incidence of renal and bladder calculi and histopathological sequelae associated with the presence of the calculi.	

Notes: Shaded cells indicate data for supporting chemicals as referenced in the respective SIDS Dossiers provided in Appendix B unless otherwise indicated.
Empty block denotes data either are not available or are available and judged inadequate.

Table 5

Pharmacokinetics and Toxicokinetics Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Pharmacokinetics and Toxicokinetics
Dimethyl isophthalate (DMIP)	1459-93-4	*In vitro*, 60 min incubation (liver, kidney, pancreas, small intestine and blood tissue preparations; rat)[a]: DBIP was metabolized to IPA and monobutyl isophthalate. For IPA formation, the highest to lowest rates of activity in each tissue were as follows: liver microsome > kidney > liver homogenate > liver mitochondria > pancreas > liver supernatant > small intestine ~ blood.
Dimethyl terephthalate (DMTP)	120-61-6	*In vitro*, 60 min incubation (liver, kidney, pancreas, small intestine and blood tissue preparations, rat)[b]: DBTP was metabolized to TPA and monobutyl terephthalate. For TPA formation, the highest to lowest rates of activity in each tissue were as follows: liver microsome > small intestine > pancreas > liver homogenate > kidney > liver mitochondria > blood. (A value for liver supernatant was not determined.)
		5 day (diet, rat): Readily absorbed and primarily excreted by the kidneys. Trace amounts of DMTP were detected in the urine, while the primary metabolite detected was terephthalic acid (TPA).
		3 wks (diet, rat)*: Only TPA was detected in the urine of the treated animals; no DMTP was detected.
		Single Dose (gavage, rat and mouse): 90% of administered dose (radiolabeled DMTP) was recovered in urine and feces. In rats, DTMP was metabolized to TPA; in mice DMTP was metabolized to monomethyl terephthalate (70%) and to TPA (30%).
		Single and Multiple-Dose (ocular, dermal, intratracheal & gavage, rabbit and rat): Radiolabeled DMTP was not well absorbed by ocular (29-37%), dermal (11-13%) or intratracheal (53-62%) as compared to oral (86-91%). Rapid excretion in the urine occurred irregardless of dose route.
Isophthalic acid (IPA)	121-91-5	13 wk (diet, rat): IPA blood levels increased in a dose-dependent manner at collection periods. Urinary excretion data (collected over 24-hours on Days 7, 30, 60 and 90) indicate that IPA is primarily excreted in the urine.
		4 wk (inhalation, rat): Immediately following a 6-hour exposure to 10 mg IPA/m^3, IPA was detected in the blood at serum levels of 5.3-9.3 µg/ml (♀) and 1.4-3.4 µg/ml (♂). One week following exposure, IPA was not detected in the blood.
Terephthalic acid (TPA)	100-21-0	Single and Multiple-Dose (ocular, dermal, intratracheal & gavage, rabbit and rat)*: TPA was rapidly absorbed and excreted in rats following single or multiple oral or intratracheal doses. There was little evidence of tissue accumulation following single or multiple doses of exposure by any route.
		25 day (inhalation, rat): Following a 6-hour exposure/day to 10 mg TPA/m^3, TPA was not detected in the blood for 5 days; however, TPA was detected after 10 days of continuous exposure and increased over the exposure period. Peak TPA blood levels reached 2.7 µg/ml after 25 days of exposure. TPA was detected in the blood throughout the 28 post-exposure period, but reached less than 1 µg/ml after seven days.

Table 5 *(Continued)*

Pharmacokinetics and Toxicokinetics Data for Dimethyl Isophthalate, Dimethyl Terephthalate, Isophthalic Acid and Terephthalic Acid

Chemical Name	CAS RN	Pharmacokinetics and Toxicokinetics
Terephthalic acid (TPA) *(continued)*	100-21-0	13 wk (diet, rat)^: TPA blood levels increased in a dose-dependent manner at collection periods. Urinary excretion data (collected over 24-hours on Days 7, 30, 60 and 90) indicate that IPA is primarily excreted in the urine.

Note: Shaded cells indicate data for supporting chemicals as referenced in the respective SIDS Dossiers provided in Appendix B unless otherwise indicated.
[a] This study was conducted with Dibutyl isophthalate (DBIP), a structural analog to DMIP and a robust summary is provided in Appendix A.
[b] This study was conducted with Dibutyl terephthalate, (DBTP), a structural analog to DMTP and a robust summary is provided in Appendix A.
* Indicates data for supporting chemicals as referenced in the respective IUCLID Datasets provided in Appendix B.
^ Indicates data referenced in the IPA (CAS RN 121-91-5) SIAR Dossier provided in Appendix B.