FOREWORD INTRODUCTION

ISOPHTHALIC ACID

CAS N°: 121-91-5

SIDS Initial Assessment Report for 14th SIAM

(Paris, France, March 2002)

Chemical Name: ISOPHTHALIC ACID

CAS No: 121-91-5

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HISTORY: Documents were prepared and reviewed by industry prior to submission to sponsor country. Sponsor country conducted reviews of submitted data and offered comments to industry. Industry prepared and resubmitted documents for consideration at SIAM 14. Literature searches were conducted on Medline, PubMed, and Toxline. The following database sources were reviewed: Hazardous Substances Data Bank (HSDB); SRI 2000 Chemical Economics Handbook; SRC PhysProp Database; Registry of Toxic Effects of Chemical Substances; IUCLID Data Sheet; International Chemical Safety Cards; NIOSH Summary; International Occupational Safety and Health Information Centre; NTP Chemical Repository;

Testing: **No testing** **(X)**

Testing **( )**

COMMENTS:

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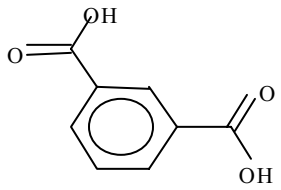
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	121-91-5
Chemical Name	Isophthalic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

For most SIDS endpoints, adequate data are available for isophthalic acid (IPA) to provide a characterization of its toxicity. Due to not having sufficient data for the endpoints of reproductive toxicity and *in vivo* genotoxicity with IPA, information on terephthalic acid (or TPA, CAS No. 100-21-0), an isomer of IPA was used as a surrogate. IPA and TPA are structural isomers, with carboxylic acid groups on the benzene ring at 1,3- and 1,4-carbons, respectively. Both IPA and TPA have similar physicochemical properties and show similar metabolic pathways and toxicological properties.

Human Health

In rats, both IPA and TPA are eliminated from the body unchanged primarily via urinary excretion. A steady state in blood is achieved fairly rapidly after inhalation exposure (on the first day) to IPA. One week after cessation of exposure, IPA was no longer detectable in the blood. Based on the Log Kow (2.34), IPA is not expected to accumulate appreciably in tissues and is likely to be readily excreted from the body.

IPA exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD50 has been reported from >5000 mg/kg (no deaths) to 13,000 mg/kg in rats. No mortality was observed in rats following acute inhalation exposures to 11,400 mg/m^3 or acute dermal doses in rabbits of 23,000 mg/kg. IPA is not a skin sensitizer as skin reactions were only seen in 10% of the animals. IPA has negligible skin irritation potential and was considered slightly irritating to the eyes.

In repeated dose studies, the target organ is the kidney. A NOAEL of 250 mg/kg-day for IPA for kidney effects (crystalluria, mild hydronephrosis, pelvic calcification) has been reported for rats following repeated oral exposures. No systemic effects were observed in rats following repeated inhalation exposures to 10 mg/m^3 of IPA. Evidence regarding the genotoxicity of IPA is mixed. While negative results have been consistently reported for IPA in studies that use mammalian cell systems, both positive and negative results have been reported in *S. typhimurium* at very high concentrations (5,000-10,000 µg/plate). No data is currently available for IPA in *in vivo* toxicity tests. As a result, data from TPA, indicates that IPA is not likely to be an *in vivo* genotoxicant. In TPA, results from an *in vivo* genotoxicity study (micronuclei formation in mice with doses of 200-800 mg/kg/day) were negative. In a two year bioassay, rats that were fed TPA (greater than 2%) 1000 mg/kg b.w./day developed bladder calculi, bladder hyperplasia and bladder tumors. Fetotoxicity was observed in an oral reproductive toxicity study for TPA (NOAEL (parental and F1 generation) = 240-307 mg/kg/day) with no effects on reproductive performance (NOAEL >2480 mg/kg/day). However, no signs of fetotoxicity or developmental effects were noted following inhalation exposures to IPA (NOAEL = 10 mg/m^3).

Environment

In its ionised form, IPA is a crystalline powder that has a melting point of 347 ^{0}C, sublimes, a vapor pressure of 3.5 x

10^{-6} Pa at 25 ^{0}C, a measured log K_{ow} of –2.34 and a water solubility of 5400 mg/L at 25 ^{0}C. In IPA's non-ionized form the log Kow is 1.76 and has a water solubility of 130 mg/L at 25 ^{0}C. IPA is not persistent in the environment and is not expected to bioaccumulate in food webs. The half-life of IPA in air is estimated to be 8 to 12 days due to direct reactions with photochemically generated hydroxyl radicals. IPA is readily biodegraded under aerobic and anaerobic conditions. Limited environmental monitoring data suggest that ambient levels of IPA in air are low with levels ranging from 1.3 – 3.4 ng/m^{3} in California and Japan (background levels were estimated to be 0.03 ng/m^{3}). Based on IPA's physical chemical properties, IPA will partition primarily to the water compartment, whether in its ionised or non-ionised form. Acute toxicity testing in fish, invertebrates, and algae indicate low toxicity with no effect concentrations of >895, >876 and >969 mg/l (the highest concentration tested for all test species), respectively.

Exposure

IPA is mainly used in the synthesis of resins, and in packaging fibers and plastics. In 1998, U.S. production was approximately 100,000 metric tonnes. Approximately 70% of the IPA produced is used in coatings and resins, while the remaining 30% is used in packaging fibers and fabrics. Exposures to workers may occur via inhalation and dermal contact. Because IPA present in consumer products is bound in a polymer matrix, the potential for exposures to consumers is low. Additionally, because IPA is not persistent in the environment, the potential for environmental exposures is low.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

SIDS FULL SUMMARY

CAS NO.: 121-91-5		SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMISTRY				
2.1	Melting Point		Measured	347° C 345-348° C 341-343° C
2.2	Boiling Point			Sublimes
2.3	Density		Measured	1.5 g/ml
2.4	Vapor Pressure		Measured Estimate MPBPWIM version 1.4	9 Pa at 100° C, 3.5 x 10-6 Pa at 25ºC
2.5	Partition Coefficient		OECD 107	Log Kow = -2.34 (at pH =7)
			Estimate	Log Kow = 1.66
			Estimate KOWWIN v1.66	Log Kow = 1.76
2.6	Water Solubility		Measured	130 mg/l at 25° C
	pKa			pKa1 = 3.70 pKa2 = 4.60
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Estimate AOPWIN	Half-life: 8.2 days
3.2	Monitoring Data		Measured	Detected in air: 2.1-3.4 ng/m^3
3.3	Environmental fate & distribution		Estimate Fugacity Level I Level II Level III	 Air – 0.00009% Water – 99.9% Soil - 0.00041% Air – 0.00009% Water – 99.9% Soil – 0.00041% Air – 0.000013% Water – 76.1% Soil – 23.8%
3.5	Biodegradation		Modified Sturm	>60% within 7 days
3.7	Bioaccumulation		Estimate	BCF = 2
ECOTOXICOLOGICAL DATA				
4.1	Acute Fish	Leuciscus idus melanotus	OECD 203	96-hour NOEC > 895 mg/l
4.2	Acute Daphnid	Daphnia magna	OECD 202	48-hour EC_0 > 876 mg/l
4.3	Acute Aquatic Plant	Scenedesmus subspicatus	OECD 201	96-hour NOEC >969 mg/l
4.4	Toxicity to Bacteria	Activated sludge	OECD 209	EC5 – 158.3 mg/l, EC25 – 353.3 mg/l, EC50 – 617 mg/l, EC75 – 1077 mg/l, EC95 – 2405 mg/l

CAS NO.: 121-91-5		SPECIES	PROTOCOL	RESULTS
MAMMALIAN TOXICOLOGICAL DATA				
5.1.1	Acute Oral	Rat	Acute Oral Toxicity	LD50 > 5,000 mg/kg LD50 13,000 mg/kg LD50 10,900 mg/kg LD50 10,400 mg/kg
5.1.2	Acute Inhalation	Rat	Acute Inhalation Toxicity	LC50 > 11.37 g/m3
5.1.3	Acute Dermal	Rabbit	Acute Dermal Toxicity	LD50 > 2000 mg/kg LD50 > 23,000 mg/kg
5.1.4	Acute Other Routes	Rat Mouse	LD50	i.p. LD50 13,000 mg/kg i.p. LD50 4200 mg/kg
5.2.1	Skin Irritation	Rabbit	Skin Irritation	Negative
5.2.2	Eye Irritation	Rabbit	Eye irritation	Negative
5.2.3	Skin Sensitization	Guinea Pig	Modified Buehler	Not a sensitizer
5.4	Repeated Dose	Rat Rat	13-feeding study 4-Week Inhalation study	13-week feeding study: Slight increase in the incidence of crystalluria (1/25 male, 2/25 female) and renal pathology (mild hydronephrosis, pelvic calcification 5/25 males). NOAEL = 0.5% or 250 mg/kg-day, LO AEL = 1.6% or 800 mg/kg-day. 4-week inhalation study– No significant effects up to 10 mg/m^3 6 hours per day 5 days per week. NOAEL > 10 mg/m^3.
5.5	Genetic Toxicity In Vitro			
A	Bacterial	Salmonella typhimurium Salmonella typhimurium Salmonella typhimurium	OECD 471 OECD 471 OECD 471	No mutagenic activity with or without metabolic activation. Dose dependent increase in the number of revertants with strains TA1537, TA1538, and TA98 in the presence and absence of metabolic activation. Positive response with tester strains TA98 and TA1538 in the presence of activation and with tester strains TA1538 in the absence of microsomal activation.
B	Non-Bacterial	Chinese Hamster Ovary cells Chinese Hamster Ovary cells Mouse lymphoma L5178Y cells	In vitro Chromosomal Aberration (OECD 473). In vitro HGPRT mutation (OECD 476). Mouse Lymphoma mutation (OECD 476)	Negative in the presence and absence of metabolic activation. Negative in the presence and absence of metabolic activation. No evidence of mutagenic activity in the presence and absence of metabolic activation.

5.6	Genetic Toxicity In vivo	Mouse	Chrom Aberration (OECD 474)	Negative for the structurally similar compound terephthalic acid (CAS NO. 100-21-0)
5.7	Carcinogenicity	Rat (Fischer 344)	2-year feeding study	For animals fed the structurally similar compound terephthalic acid (0, 20, 142 or 1000 mg/kg/day) there was a compound related increase in tumors, and hyperplasia of the urinary bladder at the highest dose tested and only in females.
5.8	Reproductive Toxicity	Rat (Wistar and CD)	90-day feeding study/1-gen reproductive assessment	For the structurally similar compound, terephthalic acid, no effects on fertility in a one-generation feeding study up to 5% in the diet (2499-2783 mgkg/d). Fetotoxic effects at 2% (930-1107 mg/kg/d) and 5% that included postnatal deaths, decreased survivability, high incidence of renal and bladder calculi and histopathological sequelae associated with presence of the calculi. NOEL for maternal and fetotoxic effects 0.5% (240-282 mg/kg/d).
5.9	Developmental Toxicity/Teratogenicity	Rat	Segment II Inhalation Teratology Study	No maternal or developmental toxicity at inhalation exposures up to 10 mg/m^3, days 6-15 of pregnancy.
5.10	Toxicokinetics	Rat Rat		Blood levels of IPA collected during a 13-week feeding study increased in a dose dependent manner. 24-hour urinary excretion data collected on days 7, 30, 60, 90 indicate that urinary excretion, presumably as the unchanged chemical, is the primary mechanism by which IPA is excreted. Blood levels of IPA were detected immediately following exposure to 10 mg/m^3, 6 hours per day. Serum levels were 5.3-9.3 ug/ml in females and 1.4-3.4 ug/ml for males. Data suggest that a steady state is achieved on first day of exposure. One week following exposure, IPA was not detected in the blood.

SIDS Initial Assessment Report (SIAR)

1.0 IDENTITY

Isophthalic acid (121-91-5) or IPA is a crystalline powder that possesses the following physical-chemical properties and characteristics:

Property	Value
Chemical Formula	$C_8H_6O_4$
Molecular Weight	166.13
Purity	99.9%
Impurities	Reaction intermediates (3-formylbenzoic acid and m-toluic acid); by-products (benzoic acid); and residual metals
Melting Point	347 °C
Boiling Point	Sublimes
Density	1.5 g/mL at 20 °C
Vapor Pressure Partition Coefficient (Log K_{ow})	3.5×10^{-6} Pa at 25 °C (calculated) -2.34* at pH 7 1.76 (neutral form)
Water Solubility	5400 mg/L at 25 °C 130 mg/L at 25 °C **
Synonyms	Benzene-1,3-dicarboxylic acid m-phthalic acid isophthalate m-benzenedicarboxylic acid

* Log Kow –2.34 is believed to be the most relevant value as IPA will be ionized under most environmental conditions.

** This value represents the solubility of of IPA without adjustment of pH. The pH of the water was not specifically stated though the pH of distilled water is typically between 6.0 and 7.0 depending on the amount of dissolved gas.

IPA is a dibasic acid (with two displaceable hydrogen atoms), and consequently has two dissociation constants (pKa1 = 3.70; pKa2 = 4.60 at 25 °C).

IPA is closely related in structure to terephthalic acid (TPA; CASRN=100-21-0). IPA and TPA are isomers, 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, metabolism pathways, and toxicological properties of IPA and TPA are very similar.

2.0 GENERAL INFORMATION ON EXPOSURE

The manufacture of IPA is accomplished using a continuous, enclosed process. Solvents, catalysts, and water used in the manufacture of IPA are recycled. Meta-xylene is used to synthesize crude IPA, in the form of an off-white powder. IPA is then purified to form a white powder, which is stored in silos and transferred using bulk trucks, railcars, or packaged in 1 metric tonne or 50 lb bags for sale. Waste streams are routed to an on-site wastewater treatment plant. Because manufacture occurs within a closed system, little to no IPA is expected to be released to the environment during production.

Estimated National Production or Import Volume

In 1998, U.S. production of IPA was approximately 100,000 tonnes (Personal Communication with BP Amoco, 2001). In the early- to mid-1970s, U.S. production of IPA typically ranged from 42 to 54 thousand tonnes (SRI, 1972, 1975). Production capacity in the U.S. in the 1980s was 250,000 tons/year (230,000 tonnes/year) (Gerhartz, 1985).

Although U.S. imports of IPA were negligible in the 1970s (SRI, 1972), significant amounts (41,000 tonnes/year) were imported during the 1980s (Bureau of the Census, 1984).

U.S. exports in the 1970s typically ranged from 1.3 to 4.4 thousand tonnes/year (SRI, 1972, 1975).

Uses and Functions

Of the IPA produced in the U.S. in 1998, approximately 70% was used in coatings and resins, while the remaining 30% was used in packaging fibers and fabrics (Personal Communication with BP Amoco, 2001). Approximately 54% of the IPA produced in the 1970s was reported to be used in the synthesis of isophthalic polyester resins, approximately 26% was used for alkyd resins production, approximately 1% as a chemical intermediate for the production of dioctyl isophthalate, and the remaining (approximately) 19% was used for other applications (SRI, 1972, 1975).

Form of Marketed Product

IPA forms part of a polymer matrix in a wide variety of products in the form of coatings, resins, packaging fibers, and fabrics.

Sources of Potential Release to the Environment

IPA is naturally occurring, with traces detected in lignite and in the rhizome of the iris plant (Bemis *et al.*, 1982). Additionally, IPA was found to be an oxidation product of Singletary Lake fulvic acid (Christman *et al.*, 1985). Data on natural sources are extremely limited, and a meaningful comparison with anthropogenic releases is not possible.

Isophthalic acid may be released to the environment in wastewater as a result of its production and use as a chemical intermediate for unsaturated polyester resins (Kramer, 1992), thermoplastic polyesters (Bruegging and Rueter, 1992), and alkyd resins (Lin, 1992).

Dicarboxylic acids produced by photooxidation of anthropogenic compounds during long-range transport are a source of IPA in atmospheric aerosols (Satsumabayashi *et al.*, 1990). There are also industrially important esters of IPA such as dimethyl isophthalate that may undergo chemical or enzymatic hydrolysis to yield IPA (Riemenschneider, 1987; NRCC, 1980; Wolfe *et al.*, 1980).

2.1 Environmental Exposure and Fate

Using default release estimates, predictions based on fugacity-based fate and transport models (Levels 1 and 2: Trent University, 1999) suggest that the majority of the IPA released to the environmental will partition primarily to the water compartment (99.9%), with negligible amounts found in the air, soil, and sediment compartments. Based on a Level 3 fugacity model (Trent University, 1999), the majority (76.1%) of IPA released is again predicted to partition to the water compartment. However, a larger percentage (23.8%) is predicted for soil, since this model level allows for continuous release to soil, with negligible amounts partitioning to air (<1%) and sediment (<1%).

Biodegradation IPA is readily biodegradable in screening tests using sewage sludge and may be expected to biodegrade in soil. Under aerobic conditions and following OECD guideline 301B, approximately 9%, 46%, 64%, and 77% of IPA contained in sludge was degraded after 2, 5, 7, and 12 days, respectively (Battelle, 1991). Similarly, IPA is degraded by aerobic microorganisms isolated from soil and marine sediment (Keyser *et al.*, 1976; Aftring *et al.*, 1981). Cultures isolated from marine sediments also degraded IPA under anaerobic conditions, although by a different metabolic pathway. After a 24-hour acclimation to an activated sludge inoculum, 84% of IPA was consumed in a respiratory test (Lund and Rodriguez, 1984). In another screening test, 95% of chemical oxygen demand (COD) was removed over five days using an acclimated activated sludge inoculum (Pitter, 1976). In a 2-week biodegradation-screening test using 100 ppm IPA and an activated sludge inoculum, 77.1% of BOD was removed (Japan Chemical Industry Report, 1992). Another investigator confirmed that IPA was significantly biodegradable using the screening test (Kitano, 1978). IPA was completely degraded in eight days using a soil inoculum (Alexander and Lustigman, 1966).

Terrestrial Fate

Based on its chemical-physical properties, IPA is expected to be highly mobile in soil (Meylan *et al.*, 1992; Swann *et al.*, 1983). In the environment, IPA is expected to be dissociated to form salts with cations in soil. Because IPA absorbs UV radiation >290 nm (Sadtler Research Laboratories, as cited in HSDB, 2001), it may photodegrade in surface soils.

Aquatic Fate

Based on its chemical structure, IPA is not expected to undergo abiotic hydrolysis in the environment. Under environmentally relevant conditions (pH) IPA is expected to partially dissociate resulting in the formation of isophthalic acid salts. In addition, based on its chemical-physical properties, IPA is not expected to adsorb to sediment and particulate matter in the water column. The very low Henry's Law constant estimated for IPA (4.4E-11 atm-m^3/mole [HENRYWIN USEPA EPI v3.10]) suggests that volatilization from surface water will be minimal. Since IPA is biodegradable in screening tests (Japan Chemical Industry Report, 1992; Pitter, 1976), it may also biodegrade in water. The absorption of UV radiation >290 nm (Sadtler Research Lab, 1990) suggests that IPA may also directly photodegrade in surface waters. A bioconcentration factor (BCF) value of 2 estimated for IPA (Lyman et al. 1982), suggests that IPA would not be expected to bioconcentrate in aquatic organisms.

Atmospheric Fate

IPA in the atmosphere exists in both the vapor and particulate phases (Cautreels and Cauwenberghe, 1978; Yokouchi and Ambe, 1986). IPA in the vapor-phase is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 12.3 days (Meylan and Howard, 1993). Similarly, a half-life of 8.2 days has been estimated for IPA based on

reaction with hydroxyl radicals using the AOPWIN software to assess its atmospheric oxidation potential (SRC, 2001). IPA in the particulate-phase may be physically removed from the air by wet and dry deposition processes.

2.2.1 Human Exposure

Information regarding potential occupational, consumer, and indirect exposures to IPA is provided below.

Occupational Exposure

Based on the manufacturing process, significant occupational exposure during normal operating procedures is not anticipated. Some potential for occupational exposure via the inhalation and dermal routes is possible during bag filling operations and while loading rail cars and trucks. Typical exposures for unit operators, baggers/loaders and forklift operators working in IPA manufacturing range from <0.04 to 2.92 mg/m^3 (personal communication BP Amoco) Engineering controls are employed to reduce employee exposure. In addition, appropriate personal protective equipment is generally available and may be worn to further reduce potential exposure. Information regarding downstream occupational exposures in not publicly available.

Occupational exposure limits (OELs) for IPA are listed below.

Exposure Limit (Country)	(mg/m^3)	(ppm)
Workplace environmental exposure level, 8-hr time-weighted average (U.S.)	10 (total) 5 (respirable)	1.5 0.74
STEL (Russia)	0.2 mg/m3	0.03

Consumer Exposure

Because IPA forms part of a polymer matrix in marketed products, the potential for consumer exposure to IPA is low. Some of these polymer matrices containing reacted isophthalic acid as a component have food contact applications. However, this accounts for less than 20 percent of the IPA use. Furthermore, result from measurements of residual IPA levels and migration into food simulant studies indicated that IPA residual levels were in the part per billion range and extraction into to food simulants were below detection limits (personal communication BP Amoco).

Indirect Exposure via the Environment

The ambient annual average concentrations of IPA in fine particle organic compounds at four sites in California on a west to east trajectory, West Los Angeles, downtown Los Angeles, Pasadena, and Rubidouc for 1982 were 2.1, 3.4, 2.9 and 2.1 ng/m^3, respectively (Rogge et al. 1993). The concentration of IPA at a background site on San Nicolas Island, west of Los Angeles, averaged <0.03 ng/m^3 from July to December (Rogge *et al.*, 1993).

A study was performed of the long-term transport of air pollution from large emission sources along the coastal areas in Japan to inland mountains (Satsumabayashi et al. 1990). The resulting mean concentrations of IPA in airborne aerosols in a plume at Takasaki (July 26-31, 1986) and Karuizawa (July 29-31, 1986) were 2.2 and 1.3 ng/m^3, respectively. The ratio of carboxylic acids to acetylene (which is believed to be derived from the same sources) increased during the day and decreased at night and averaged 72% at

Takasaki and 84% at Karuizawa. The authors proposed that IPA is almost entirely formed photochemically during long-term transport of airborne aerosols.

3.0 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

Information regarding the toxicity of IPA are summarized below. Where information on IPA is lacking, supplemental information for a structural isomer, terephthalic acid or TPA, (CAS:100-21-0) is provided. TPA is an isomer of IPA, differing only with respect to the positioning of the carboxylic acid groups on the benzene ring (1,3- for IPA; 1,4- for TPA). Both IPA and TPA are readily eliminated from the body, largely unchanged, via urinary excretion. The toxicities of these two isomers are also very similar with the formation of urinary calculi and subsequent inflammatory changes of the urinary tract being the only notable effect after repeated oral ingestion.

Toxicokinetics and Metabolism

Blood levels of IPA and TPA (determined as total mg phthalate/L) collected during a 13-week feeding study (in rats) were increased in a dose-dependent manner on days 7, 30, 60, and 90. IPA and TPA blood levels were generally highest during the first week of exposure and declined during the course of the study, suggesting either a change in feed consumption rates or some sort of adaptation resulting in increased clearance from the body. Results from 24-hour urines collected on days 7, 30, 60, and 90 indicate that urinary excretion, presumably as unchanged chemical, is the primary route of elimination for both IPA and TPA (Vogin, 1972).

Blood levels of IPA were detected immediately following exposure to rats at 10 mg/m^3 for six hours/day (IITRI, 1988). These levels remained elevated throughout the exposure period. Serum IPA concentrations detected in female rats (5.3-9.3 µg/mL) were consistently higher than the concentrations detected in male rats (1.4-3.4 µg/mL). The data suggest that steady state is achieved fairly rapidly (on the first day of exposure). One week following exposure, IPA was not detected in blood, indicating that clearance of IPA from the body occurs fairly rapidly. Based on a log K_{ow} value of –2.34, IPA is not expected to accumulate appreciably in tissues, and is likely to be readily excreted from the body.

In a similar study, rats were exposed via inhalation to an aerosol of 10 mg/m^3 TPA six hours per day for 25 consecutive days followed by a 28-day recovery period. Detectable blood concentrations of TPA were observed after 10 days of exposure and progressively increased over the remaining exposure period. The highest average blood concentration was 2.7 µg/mL after 25 days. Seven days after completion of the exposure period the blood concentration was less than 1 µg/mL (IITRI 1989).

Based on a molecular weight of 166 g/mol and a log Kow of –2.34, a dermal permeability coefficient (K_p) of 4.0x10^{-6} cm/hr was estimated for IPA (USEPA, 1992). This value suggests that the dermal absorption of IPA from an aqueous solution is relatively low.

IPA was reported to be a competitive inhibitor of hepatic glutamate dehydrogenase in cows (Boots *et al.*, 1976). This enzyme plays an important role in amino acid catabolism, amino acid synthesis, and nitrogen balance.

Acute Toxicity

Data available from laboratory animals exposed to IPA indicate that its acute toxicity is relatively low, regardless of the route of exposure.

- *Oral* – Acute oral LD50 ranging from values of 10,400 to 13,000 mg/kg for IPA have been reported in rats (Marhold, 1986; Industrial Bio-Test, 1958, 1975). Necropsy of animals that died revealed pale, discolored kidneys (Industrial Bio-Test, 1975). No deaths were reported in rats receiving a single oral dose of 5,000 mg/kg IPA (IITRI, 1990). Clinical signs (irritability, salivation, discoloration around nose and mouth, diarrhea, wet and/or discolored inguinal fur, discolored paws), which appeared within 24 hours after exposure, but generally resolved within 48 hours.
- *Inhalation* – No deaths or treatment-related effects were observed in rats exposed to 11,400 mg/m^3 IPA dust for four hours (Industrial Bio-Test, 1958).
- *Dermal* – In rabbits, no deaths were reported following a single dermal dose of 2000 mg/kg or 23,000 mg/kg IPA (IITRI, 1990; Industrial Bio-Test, 1958).
- *Other* – Following intraperitoneal injection, LD50 values of 4,200 and 13,000 mg/kg have been reported for IPA in mice and rats, respectively (Academie des Sciences, 1965; Calandra, 1975)

Irritation/Corrosiveness

IPA has negligible skin irritation potential and is only slightly irritating to eyes. No signs of dermal irritation (irritation score=0/8) was evident in rabbits receiving a single dermal dose of 500 mg IPA (IITRI, 1990). Mild dermal irritation (erythema) was observed in 4/10 immediately following dermal exposure to 2,000 mg/kg IPA (IITRI, 1990). Eye irritation scores ranging from 5.3/110 to 25.6/110 at 24 hours have been reported. In all cases signs of irritation were completely resolved by the end of the study.

Skin Sensitization

In guinea pigs dermally exposed to 0.3 mL of a 30% IPA solution once a week for three weeks, a positive erythema reaction (a score greater than or equal to 2) was observed in only 1/10 animals, and was not considered significant (IITRI, 1991). The authors concluded that repeated exposure to IPA did not produce dermal sensitization. Furthermore, no reports of human skin sensitization were located. The data suggest that IPA is unlikely to cause allergic skin reactions.

Repeated Dose Toxicity

Data available from laboratory animals exposed to IPA indicate that its subchronic toxicity is also relatively low, regardless of the route of exposure.

- *Oral* – In Wistar rats exposed to up to 0.5% IPA in feed (corresponding to a dose of approximately 250 mg/kg-day) for 13 weeks, no adverse effects were observed (Vogin, 1972). Levels of 1.6% (approximately 800 mg/kg-day) in feed produced small increases in the incidence of crystalluria (1/25 males, 2/25 females) and renal pathology (mild hydronephrosis, pelvic calcification, 5/25 males). This study identifies a NOAEL and LOAEL of 250 and 800 mg/kg-day, respectively, based on kidney effects in rats.
- *Inhalation* – Sprague-Dawley Rats were exposed to 1.0, 5.0 or 10 mg/m^3 IPA particulate 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 (IITRI, 1988). This study identifies a NOAEL of 10 mg/m^3 for subchronic inhalation exposures to IPA.

Genetic Toxicity

Although no studies regarding the *in vivo* genotoxicity of IPA were located, information collected for a structural isomer, TPA, is available. The number of micronuclei induced in the erythrocytes of mice exposed to a single i.p. dose of 200-800 mg/kg-day TPA was not increased (Bioreliance, 2001).

In mammalian cell systems, test results for the genetic toxicity of IPA are consistently negative. In Chinese hamster ovary cells, IPA concentrations up to 5000 ug/L, with and without metabolic activation, did not produce an increase in chromosomal aberrations (Microbiological Associates, 1990). Similar results were noted in this cell system when IPA concentrations up to 3,000 µg/L were evaluated for mutations at the HGPRT locus (Microbiological Associates, 1991). No increase in mutation frequency was reported in mouse lymphoma cells using test concentrations up to 950 µg/L (Riach and Willington, 1994).

Evidence regarding the genetic toxicity of IPA in bacteria cell systems is mixed. Three separate gene mutation studies with Salmonella typimurium were performed.. Each study was conducted both in the absence and presence of an exogenous metabolic activation system. The maximum dose of IPA investigated in two of the studies was 10,000 ug/plate, while the third study evaluated dose levels up to 5000 ug/plate. IPA-220 concentrations of up to 5000 µg/plate, with or without metabolic activation (rat liver S9), did not result in an increased mutation frequency in several strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, and TA100) (Huntingdon Research Centre, 1991). However, a small increase in mutation frequency was observed in two strains of *S. typhimurium*: TA98 (3-fold increase with activation) and TA1538 (9-fold increase with activation, and 6-fold increase without activation) using concentrations up to 10,000 µg/plate (Microbiological Associates, 1990). Precipitation of IPA was noted at concentrations higher than 5,000 µg/plate. No increase in mutation frequency was noted in these two strains at IPA concentrations less than or equal to 1,000 µg/plate, or in strains TA100 or TA1535 at IPA concentrations up to 10,000 ug/plate. In another experiment, concentrations up to 10,000 µg/plate resulted in an increased mutation frequency in several strains of *S. typhimurium,* including TA98 (7-fold increase with activation, 4-fold without activation), TA1537 (7-fold with and without activation), and TA1538 (10-fold with activation, 11-fold without activation) (Muller, 1991). No increase in mutation was observed in these test strains at IPA concentrations less than or equal to 500 µg/plate, or in strains TA100 or 1535 at IPA concentrations up to 10,000 µg/plate. It is noteworthy that both studies yielding positive responses evaluated dose-levels up to 10,000 ug/plate. At dose-levels of 5,000 ug/ml and above there is a clear indication in the report from one study that IPA visibly precipitated in the plates and the bacteria lawn was adversely affected.

The assays for gene mutation in bacteria produced inconsistent and equivocal results, though all three studies were considered valid. Thus the mutagenic potential of IPA in bacterial systems could not be determined definitively. In contrast, IPA elicited negative responses in assays investigating gene mutation in two different mammalian cell systems and chromosomal aberration in mammalian cells. In addition, IPA has no apparent structurally alerts. Furthermore, TPA (the structural analog of IPA) did not induce an increase in the mutation frequency of *Salmonella typhimurium*. Bacteria are relatively simple organisms, and a positive response in bacteria does not necessarily indicate that the compound will induce similar effects in animal cells or in intact mammals. Moreover when evaluating genetic toxicity assay results *in vivo* test results are considered to have greater weight than *in vitro* tests, tests in eukaryotes are considered to have greater weight than prokaryotes and tests using mammalian species are considered to have greater weight than tests using non-mammalian species. Therefore, the weight of evidence suggests that IPA is not mutagenic in mammalian cells and is unlikely to be active in a whole animal.

Carcinogenicity

No data regarding the carcinogenicity of IPA were located. However, a chronic dietary studies on the structural analog TPA are available. A two-year feeding study (0, 20, 142, or 1000 mg/kg/day) showed increase incidence of calculi, bladder hyperplasia and tumors in rats. These effects were seen only at the highest dose of 1000 mg/kg/day and only in females (CIIT 1983). In a similar study by Gross 1974 bladder and ureter tumors were reported for both males and females. The difference in male tumor response may be partially explained by the higher doses used in the Gross study (500, 1000, 2500 mg/kg/day). The induction of bladder tumors is believed to be a result of injury to the bladder epithelium from calculi formation.. Bladder calculi cannot occur unless the solubility of the stone components is exceeded. Based on urinary solubility of Ca-terephthalate, normal urine would become saturated with Ca-terephthalate at a terephthalic acid concentration of approximately 8 to 16 mM. Assuming that the average volume of urine excreted by humans is 1.5 liters/day, the amount of terepthalic acid that would have to be absorbed to produce the minimum saturating concentration of terephthalica acid is 2400 mg/day. It is unlikely that humans would ingest enough TPA to induce bladder calculi and therefore of low concern to human health. Based on similar findings from repeat dose studies with IPA and TPA (crystalluria) it is expected that IPA would respond similar to that of TPA with respect to carcinogenicity.

Reproductive Toxicity

Although no studies regarding the reproductive toxicity of IPA were located, information collected for a structural isomer, terephthalic acid (TPA), is available. In a one-generation reproductive toxicity test using two strains of rats (CD and Wistar), exposure to TPA in the diet at levels of 0, 0.03, 0.125, 0.5, 2 or 5% (approximately equivalent to: 0, 14, 59, 240, 930, 2499 mg/kg-day CD males; 0, 17, 67, 282, 1107, 2783 mg/kg/day CD females; 0, 14, 61, 249, 960, 2480 mg/kg/day Wistar males and; 0, 19, 78, 307, 1219, 3018 mg/kg/day Wistar females) began 90 days prior to mating, and continued through gestation and lactation (Gibson, 1982). Food intake and body weight gain were decreased in animals at the two highest dietary levels. Five deaths were reported in rats receiving the highest dietary level. Reproductive performance in parental animals was not affected by exposure (NOAEL 5.0% or 2480-3018 mg/kg/day). However, in the offspring, significant decreases in survival and body weight, and a significant increase in the incidence of renal/bladder calculi were observed at levels of 2% and 5%. Several large litters of pups were lost to dams suffering obvious signs of toxicity. Several of these dams did not allow the pups to nurse and did not attend the litters. This study identifies NOAEL and LOAEL values of 240-307 mg/kg/day (0.5%) and 930-1219 mg/kg-day (2.0%), respectively, for both maternal and fetotoxicity in rats.

Developmental Toxicity/Teratogenicity

No evidence of teratogenesis or fetotoxicity was observed in rats exposed to 0, 1, 5, or 10 mg/m^3 IPA particulate aerosol on gestation days 6 through 15 (IITRI, 1991). As summarized for the reproductive toxicity study above, oral doses of 930-1219 mg/kg-day of TPA administered in the diet for 90 days were fetotoxic (Gibson, 1982). The most likely route of potential exposure to IPA is via inhalation during manufacture and use. Therefore, the IPA inhalation study is likely more relevant than the oral TPA study for assessing fetotoxicity.

Human Cases

No data were located regarding human exposures or responses to IPA.

4.0 HAZARDS TO THE ENVIRONMENT

4.1 Acute Aquatic Effects

Data regarding the acute toxicity of IPA in aquatic species are summarized below.

- *Fish* - No signs of toxicity were observed in *Leuciscus idus melanotus* (Golden orfe) exposed to IPA at levels of up to 895 mg/L (measured) for 96 hours under static conditions (Battelle Europe, 1993).
- *Invertebrates* - No signs of toxicity in terms of mortality or immobilization were observed in *Daphnia magna* (water flea) exposed to IPA at levels of up to 876 mg/L (measured) for 48 hours under static conditions (Battelle Europe, 1993).
- *Plants* - No adverse effects on growth were observed in *Scenedesmus subspicatus* (green algae) exposed to IPA at levels of up to 969 mg/L (measured) for 96 hours under static conditions (Battelle Europe, 1993).
- *Bacteria* - In activated sewage sludge, toxicity to bacteria, as indicated by inhibition of oxygen consumption, was evident with a EC50 value of 617 mg/l (Battelle Europe, 1991).

Because IPA is an acid, adjustments were made to the testing systems in the studies above, to ensure that neutral pH is maintained. For this reason, the predominant form of the chemical tested was likely to be isophthalic sodium salt. In general, these data indicate low acute toxicity of IPA in aquatic species.

4.2 Terrestrial Effects

Although no data were located regarding the toxicity of IPA in terrestrial mammals, the low toxicity in laboratory animals suggests that its toxicity to mammals in general would also be low.

4.3 Other Environmental Effects

A bioconcentration factor (BCF) of 2 has been estimated for IPA, which suggests that IPA is not likely to concentrate in tissues or bioaccumulate in food webs.

5.0 CONCLUSIONS AND RECOMMENDATIONS

IPA is currently of low priority for further work.

Analog Jusitification
For most SIDS endpoints, adequate data are available for IPA to provide a characterization of its toxicity. Due to not having sufficient data for the endpoints of reproductive toxicity and in vivo genotoxicity with IPA, information on terephthalic acid (or TPA, CAS:100-21-0), an isomer of IPA was used as a surrogate. IPA and TPA are structural isomers, with carboxylic acid groups on the benzene ring at 1, 3- and 1,4-carbons, respectively. Both IPA and TPA have similar physicochemical properties and show similar metabolic pathways and toxicological properties.

Human Health
In rats, both IPA and TPA are eliminated from the body unchanged primarily via urinary excretion. A steady state in blood is achieved fairly rapidly after inhalation exposure (on the first day) to IPA. One week after cessation of exposure, IPA was no longer detectable in the blood. Based on the Log Kow (-2.34), IPA is not expected to accumulate appreciably in tissues and is likely to be readily excreted from the body.

IPA exhibits low acute toxicity by the oral, dermal, and inhalation routes. The oral LD50 has been reported from >5000 mg/kg (no deaths) to 13,000 mg/kg in rats. No mortality was observed in rats following acute inhalation exposures to 11,400 mg/m^3 or acute dermal doses in rabbits of 23,000 mg/kg. IPA is not a skin sensitizer as skin reactions were only seen in 10% of the animals. IPA has negligible skin irritation potential and was considered slightly irritating to the eyes.

In repeated dose studies, the target organ is the kidney. For IPA, a NOAEL of 250 mg/kg-day for kidney effects (crystalluria, mild hydronephrosis, pelvic calcification) has been reported for rats following repeated oral exposures. No systemic effects were observed in rats following repeated inhalation exposures to 10 mg/m^3 of IPA. Evidence regarding the genotoxicity of IPA is mixed. While negative results have been consistently reported for IPA in studies that use mammalian cell systems, both positive and negative results have been reported in *S. typhimurium* at very high concentrations (5,000-10,000 µg/plate). No data is currently available for IPA in *in vivo* toxicity tests. As a result, data from TPA, indicates that IPA is not likely to be an *in vivo* genotoxicant. In TPA, results from an *in vivo* genotoxicity study (micronuclei formation in mice with doses of200-800 mg/kg-day) were negative. In a two year bioassay, rats that were fed TPA (greater than 2%) 1000 mg/kg b.w./day developed bladder calculi, bladder hyperplasia and bladder tumors. Fetotoxicity was observed in an oral reproductive toxicity study for TPA (NOAEL (parental and F1 generation) = 240-307 mg/kg-day) with no effects on reproductive performance (NOAEL >2480 mg/kg-day). However, no signs of fetotoxicity or developmental effects were noted following inhalation exposures to IPA (NOAEL = 10 mg/m^3).

Environment
In its ionised form, IPA is a crystalline powder that has a melting point of 347^{0}C, sublimes, a vapor pressure of 3.5 x 10^{-6} Pa at 25^{0}C, a measured log K_{ow} of –2.34 and a water solubility of 5400 mg/L at 25^{0}C. In IPA's non-ionized form the log Kow is 1.76 and has a water solubility of 130 mg/L at 25^{0}C IPA is not persistent in the environment and is not expected to bioaccumulate in food webs. The half-life of IPA in air is estimated to be 8 to 12 days due to direct reactions with photochemically generated hydroxyl radicals. IPA is readily biodegraded under aerobic and anaerobic conditions. Limited environmental monitoring data suggest that ambient levels of IPA in air are low with levels ranging from 1.3 – 3.4 ng/m^3 in

California and Japan (background levels were estimated to be (0.03 ng/m^3.) Based on IPA's physical chemical properties, IPA will partition primarily to the water compartment, whether in its ionised or non-ionised form. Acute toxicity testing in fish, invertebrates, and algae indicate low toxicity with no effect concentrations of
>895, >876 and >969 mg/l (the highest concentration tested for all test species), respectively.

Exposure
IPA is mainly used in the synthesis of resins, and in packaging fibers and plastics. In 1998, U.S. production was approximately 100,000 metric tonnes. Approximately 70% of the IPA produced is used in coatings and resins, while the remaining 30% is used in packaging fibers and fabrics. Exposures to workers may occur via inhalation and dermal contact. Because IPA present in consumer products is bound in a polymer matrix, the potential for exposures to consumers is low. Additionally, because IPA is not persistent in the environment, the potential for environmental exposures is low.

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SIDS DOSSIER
ISOPHTHALIC ACID

.....

CAS No. 121-91-5

Sponsor Country: U.S.A.

DATE: January, 2002

CONTENTS

Note: ; Data elements in the SIDS
; Data elements specially required for inorganic chemicals

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. **CAS-Number** 121-91-5

B. **Name** *(IUPAC name)* Isophthalic Acid

C. **Name** *(OECD name)*

D. **CAS Descriptor**

E. **EINECS-Number** 204-506-4

F. **Molecular Formula** C8-H6-O4

G. **Structural Formula** C8H6O4

H. **Substance Group**

I. **Substance Remark**

J. **Molecular Weight** 166.13

1.02 OECD INFORMATION

A. **Sponsor Country:** U.S.A.

B. **Lead Organisation:**

Name of Lead Organisation: BP Chemicals
Contact person: David Dutton
Address:

U.S.A.
Tel:
Fax:

1.1 GENERAL SUBSTANCE INFORMATION

A. **Type of Substance** element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometalic [ ]; petroleum product [ ]

B. **Physical State** *(at 20°C and 1.013 hPa)*
gaseous [ ]; liquid [ ]; solid [X]

C. **Purity** *(indicate the percentage by weight/weight)* 99.9%

1.2 SYNONYMS benzene 1,3-dicarboxylic acid;
m-phthalic acid
isophthalate
m-benzenedicarboxylic acid

1.3 IMPURITIES Reaction intermediates: 3-formalbenzoic acid, m-toluic acid; by-products: benzoic acid; and residual metals

1.4 ADDITIVES None

1.5 QUANTITY In 1998 U.S. production of IPA was approximately 100,000 tonnes. (Personal communication BP Amoco 2001)

1.6 LABELLING AND CLASSIFICATION

Labelling
Type:
Specific limits:
Symbols:
Nota:
R-phrases: None
S-phrases: None
Text of S-phrases:
Remarks:

Classification
Type:
Category of danger:
R-phrases:
Remarks:

1.7 USE PATTERN

A. General

Type of Use: Approximately 70% of Isophthalic acid is used in coatings and resins while the remaining 30% is used in packaging fibers and fabrics

Category: Non dispersive use: Chemical industry use as an intermediate.

Remarks:
Reference: BP Amoco Personal communication 2001

B. Uses in Consumer Products

	Function	Amount Present	Physical State

Remarks: IPA forms part of a polymer matrix in a wide variety of products in the form of coatings, resins, packaging fibers, and fabrics.

Reference:

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Exposure limit value

Type:	WEEL, 8-hr time-weighted average (U.S.)
Value:	10 mg/m3 (total); 5 mg/m3 (respirable)

Type:	STEL (Russia)
Value:	0.2 mg/m3 (skin)

Short term exposure limit value

Value:
Length of exposure period:
Frequency:
Remarks:
Reference:

1.9 SOURCES OF EXPOSURE

(a)
Media of release:
Source:
Remarks:
Reference:

1.10 ADDITIONAL REMARKS

A. Options for disposal

Remarks:
Reference:

B. Other remarks

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a)
Value: 347°C
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Sublimation: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Remarks:
Reference: Lide, D.R. (ed.) CRC Handbook of Chemistry and Physics. 75th edition. Boca Raton, FL: CRC Press, Inc., 1994-1995. HSDB, 2001

(b)
Value: 345-348°C
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Sublimation: Yes [ ] No [ ] Ambiguous [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [X]
Remarks:
Reference: Merck, 9th Edition.

(c)
Value: 341-343°C
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Sublimation: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Remarks:
Reference: Aldrich, 1992-93.

2.2 BOILING POINT

(a)
Value: 100°C
Pressure: 0.068 mm Hg (9 Pa)
Decomposition: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [X]
Remarks: IPA sublimes which brings into question the reliability of this reference.
Reference: SRC PhysProp Database, 2000

(b)
Value: Not applicable, IPA sublimes
Pressure:
Decomposition Yes[] No [] Ambiguous []
Method:
GLP: Yes [] No [x] ? []
Remarks:

Reference: Lide, D.R. (ed.) CRC Handbook of Chemistry and Physics. 75th edition. Boca Raton, FL: CRC Press, Inc., 1994-1995. HSDB, 2001

2.3 DENSITY

(a)

Type:	Bulk density [ ]; Density [x]; Relative Density [ ]
Value:	1.5 g/mL
Temperature:	20 °C
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	
Reference:	Kirk-Othmer (1978-1984), Reported in HSDB 2001.

2.4 VAPOUR PRESSURE

(a)

Value:	9 Pa (0.068 mm Hg)
Temperature:	100°C
Method:	calculated [ ]; measured [ ] Year:
GLP:	Yes [ ] No [ ] ? []
Remarks:	
Reference:	Daubert and Danner (1989), as cited in HSDB (2001)

(b)

Value:	3.5 $x10^{-6}$ Pa
Temperature:	25° C
Method:	Calculated[x]; measured[] Year:
GLP:	Yes []; No[x]
Remarks:	
Reference:	MPBPWIN version 1.40 (USEPA EPIWIN Suite Software)

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

(a)

Log Pow:	-2.34
Temperature:	22 °C
Method:	calculated [ ]; measured [X]
GLP:	Yes [X] No [ ] ? [ ]
Remarks:	Value was measured in pH = 7 buffer, which is believed to be environmentally more relevant.
Test Substance	isophthalic acid
Reference:	IIT Research Institute, 1992.

(b)

Log Pow:	1.66
Temperature:	
Method:	calculated [X]; measured [ ]
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	This value is likely an estimate for the neutral form.
Test Substance	isophthalic acid
Reference:	Hansch and Leo, 1981

(c)

Log Pow	1.76
Temperature:	
Method:	Calculated [X] measured []
GLP:	yes [] No [X]
Remarks:	This calculated value represents the Kow for the neutral form.
Test Substance	..... Isophthalic acid
Reference:	KOWWIN v1.66 (EPIWIN Suite)

2.6 WATER SOLUBILITY

A. Solubility

(a)

Value:	$0.54x10^4$ mg/L
Temperature:	14^oC
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	Other
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	This value most likely represents the solubility after adjustment of the pH, forming the more water soluble isophthalic acid salt.
Reference:	Towle et al., 1968.

(b)

Value:	130 mg/L
Temperature:	25^oC
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	Other
GLP:	Yes [ ] No [ ] ? [X]
	Remarks: This value represents the solubility of IPA without adjustment of pH. The pH of the water was not specifically stated though the pH of distilled water is typically between 6.0 and 7.0 depending on the amount of dissolved gas.
Reference:	Bemis et al., 1982

2.7 FLASH POINT *(liquids)*

(a)

Value:	
Type of test:	Closed cup [ ]; Open cup []; Other [ ]
Method:	Other
GLP:	Yes [ ] No [ ] ? []
Remarks:	
Reference:	

2.8 AUTO FLAMMABILITY *(solid/gases)*

(a)
Value:
Pressure:
Method:
GLP: Yes [ ] No [ ] ? [ ]
Remarks:
Reference:

2.9 FLAMMABILITY

Results: Extremely flammable [ ]; Extremely flammable - liquefied gas [ ]; Highly Flammable [ ]; Flammable [ ]; Non flammable [ ]; Spontaneously flammable in air [ ]; Contact with water liberates highly flammable gases [ ]; Other [ ]
Method:
GLP: Yes [ ] No [ ] ? [ ]
Remarks:
Reference:

2.10 EXPLOSIVE PROPERTIES

Results: Explosive under influence of a flame[ ];
More sensitive to friction than m-dinitrobenzene [ ];
More sensitive to shock than m-dinitrobenzene [ ]; Not explosive [ ];
Other [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks:
Reference:

2.11 OXIDIZING PROPERTIES

Results: Maximum burning rate equal or higher than reference mixture [ ];
Vigorous reaction in preliminary test [ ];
No oxidizing properties [ ]; Other [ ]
Method: Other
GLP: Yes [ ] No [ ] ? [ ]
Remarks:
Reference:

2.12 ADDITIONAL REMARKS

Remarks: No additional remarks

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Value:
Method:
GLP:
Remarks: No studies located

Reference:

B. Other data

Results: No studies located
Remarks:
Reference:

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(a)
Type: Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source: Sun light [ ]; Xenon lamp [ ]; Other [ ]
Light spectrum:
Relative intensity:
Concentration of Substance:
Temperature:
Direct photolysis:
Half life: 8.2 days
Degradation:
Quantum yield:
Method: calculated [x]; measured [ ]
Other
GLP: Yes [ ] No [x] ? [ ]
Test substance:
Remarks:
Result: Reaction rate constant with hydroxyl radicals=1.3x10^{-12} cm^3/mol-sec
Reference: AOPWIN (SRC, 2001)

3.1.2 STABILITY IN WATER

Type:
Half life:
Degradation:
GLP: Yes [ ] No [ ] ? [ ]
Test substance:
Remarks: Based on its chemical structure, isophthalic acid is not expected to undergo abiotic hydrolysis in the environment
Reference:

3.1.3 STABILITY IN SOIL

(a)
Type: Field trial [ ]; Laboratory [ ]; Other [ ]
Radiolabel: Yes [ ] No [ ] ? [ ]
Concentration:
Soil temperature:
Soil humidity:
Soil classification: DIN19863 [ ]; NF X31-107 [ ]; USDA [ ]; Other [ ]
Year:
Content of clay etc.:
Organic Carbon:
Soil pH:
Cation exchange capacity:
Microbial biomass:
Dissipation time: DT 50:

DT 90:

Method:
GLP: Yes [ ] No [ ] ? [ ]
Test substance:
Remarks:
Reference:

3.2 MONITORING DATA (ENVIRONMENT)

Type of Measurement: Ambient annual average concentration
Media: Airborne Particulates
Results: 2.1, 3.4, 2.9 and 2.1 ng/m3
Remarks : Samples collected from west Los Angeles, downtown Los Angeles, Pasadena, and Rubidouc for 1982
Reference: Rogge WF et al. 1993. Atmos Environ 27A:1309-30

Type of Measurement: ..... Background concentrations
Media: Air
Results: A study was performed of the long-term transport of air pollution from large emission sources along the coastal areas in Japan to inland mountains. The resulting mean concentrations of IPA in airborne aerosols in a plume at Takasaki (July 26-31, 1986) and Karuizawa (July 29-31, 1986) were 2.2 and 1.3 ng/m^3, respectively. The ratio of carboxylic acids to acetylene (which is believed to be derived from the same sources) increased during the day and decreased at night and averaged 72% at Takasaki and 84% at Karuizawa. The authors proposed that IPA is almost entirely formed photochemically during long-term transport of airborne aerosols.
Reference: Satsumabayashi et al. (1990). Atmos, Environ. 24A: 1443-50

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type: Adsorption [ ]: Desorption [ ]; Volatility [ ]: Other [ ]
Media:
Method:
Remarks:
Reference:

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-biota [ ]; Air-biota-sediment-soil-water [x]; Soil-biota [ ]; Water-air [ ]; Water-biota [ ]; Water-soil [ ]; Other [ ]
Method: Fugacity level I [x]; Fugacity level II [x]; Fugacity level III [x]; Fugacity level IV [ ]; Other (calculation) [ ]; Other (measurement)[ ]
Results:

Media	Level I	Level II	Level III
Air	0.000090%	0.000090%	0.000013%
Water	99.9995%	99.9995%	76.1%

Soil	0.00041%	0.00041%	23.8%
Sediment	0.000009%	0.000009%	0.03%

Remarks: Predicted concentrations are not provided since default release estimates were used.
Reference: Trent University. 1991. Fugacity-based Environmental Equilibrium Partitioning Model. Version 2.17. Environmental Modeling Centre, Trent University, Peterborough, Ontario.

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Results:
Remarks:
Reference:

3.5 BIODEGRADATION

(a)
Type: aerobic [X]; anaerobic [ ]
Inoculum: adapted [ ]; non-adapted [ ]; ? [ ]; sewage [X]
Concentration: 10.17 mg/l related to COD [ ]; DOC [ ]; Test substance [ ];
Medium: water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation: >60% within 7 days
Results: Readily biodeg. [X]; Inherently biodeg. [ ]; under test condition no biodegradation observed [ ], Other [ ]
Method: OECD Guideline 301 B, Modified Sturm-Test
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: From the data obtained in the test, the test substance may be regarded as "readily biodegradable".
Reference: Battelle Europe, 1991

3.6 BOD_5,COD OR RATIO BOD_5/COD

BOD_5
Method:
Concentration:
Value:
GLP: Yes [ ] No [ ] ? [ ]

COD
Method: Other
Value:
GLP: Yes [ ] No [ ] ? [ ]

Ratio BOD_5/COD:

Remarks:
Result:
Reference:

3.7 BIOACCUMULATION

Species:	
Exposure period:	
Temperature:	
Concentration:	
BCF:	2
Elimination:	
Method:	Estimation
Type of test:	
GLP:	Yes [ ] No [x] ? [ ]
Test substance:	
Remarks:	
Reference:	Lyman W.J. et. al. Handbook of Chemical Property Estimation Methods. Chap 5,15 (1982)

3.8 ADDITIONAL REMARKS

A. Sewage Treatment

Remarks: No additional remarks

B. **Other**

Remarks:

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static [X]; semi-static [ ]; flow-through [ ]; other [ ]; open-system [ ]; closed-system [ ]
Species:	*Leuciscus idus melanotus*
Exposure period:	96 hours
Results:	Based on nominal concentrations: LC_0 (96 hr): >1000 mg/L IPA and Isophthalic Sodium Salt (ISS) LC_{50} (96 hr): could not be determined NOEC (96 hr): = 1000 mg/L IPA and ISS Based on the measured average concentration of the highest concentration level tested: NOEC (96 hr): > 895 mg/L IPA and ISS
Analytical monitoring:	Yes [X] No [ ] ? [ ]
Method:	OECD Guideline No. 203 "Fish, Acute Toxicity Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Isophthalic Acid (Purity 99.9%)
Remarks:	The authors commented that IPA was ionized under test conditions. Therefore, it was believed that under test conditions and after pH adjustment, IPA and Isophthalic Sodium Salt were test materials investigated in this study.
Reference:	Battelle Europe, 1993.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a)

Type of test:	static [x]; semi-static [ ]; flow-through [ ]; other [ ]; open-system [ ]; closed-system [ ]
Species:	*Daphnia magna* (Straus)
Exposure period:	48 hours
Results:	Based on nominal concentrations: EC_0: 1000 mg/L IPA and Isophthalic Sodium Salt (ISS) EC_{50}: could not be determined NOEC: = 1000 mg/L IPA and ISS Based on measured average concentration of the highest concentration tested: EC_0 >876 mg/L IPA and isophthalic sodium salt
Analytical monitoring:	Yes [X] No [ ] ? [ ]
Method:	OECD Guideline 202, Part I, 1984.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Isophthalic Acid (Purity 99.9%)
Remarks:	The authors commented that IPA was ionized under test conditions. Therefore, it was believed that under test conditions and after pH adjustment, IPA and Isophthalic Sodium Salt were test materials investigated in this study.
Reference:	Battelle Europe, 1993.

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

(a)

Species:	Algae (*Scenedesmus subspicatus*)
End-point:	Biomass [ ]; Growth rate [X]; Other [ ]
Exposure period:	96 hour
Results:	Based on nominal concentrations: NOEC = 1000 mg/L IPA and Isopthalic Sodium Salt. Based on the measured average concentration of the highest concentration level tested: NOEC = 969 mg/L IPA and Isophthalic Sodium Salt.
Analytical monitoring:	Yes [X] No [ ] ? [X]
Method:	OECD No. 201 "Alga, Growth Inhibition Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Isophthalic Acid (purity 99.9%)
Remarks:	The authors commented that IPA was ionized under test conditions. Therefore, it was believed that under test conditions and after pH adjustment, IPA and Isophthalic Sodium Salt were test materials investigated in this study.
Reference:	Battelle Europe, 1993.

4.4 TOXICITY TO BACTERIA

(a)

Type:	Aquatic [ ]; Field [ ]; Soil [ ]; Other [X]
Species:	activated sludge
Exposure Period:	3 hr.
Results:	EC_5: 158.3 mg/L EC_{25}: 353.3 mg/L EC_{50}: 617.1 mg/L EC_{75}: 1077.9 mg/L EC_{95}: 2405.4 mg/l
Analytical monitoring:	Yes [ ] No [ ] ? [X]
Method:	OECD-Test Guideline 209: "Activated Sludge, Respiration Inhibition Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Isophthalic Acid (99.9% pure)
Test Condition:	Activated sludge was added to the test solution and was aerated with compressed air for 3 hr. After the contact time, the solutions were poured into an oxygen-bottle and oxygen consumption was recorded for 10 minutes to determine respiration rates.
Reference:	Batelle Europe, 1991

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4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1. CHRONIC TOXICITY TO FISH

No studies located

4.5.2. CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

No studies located

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No studies located

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Type of test:	Growth inhibition
Species:	Rice seedlings
Results:	Concentrations of 10 or 100 ppm had slight to no inhibition on plant growth
Remarks:	Inadequate detail to assess overall quality therefore not included in SIAR.
Reference:	Isogai et al. 1972. SCI PAP COLL GEN EDUC, UNIV TOKYO 22 (2): 129

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No studies located

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

Results: No studies located

4.8 BIOTRANSFORMATION AND KINETICS

No studies located

4.9 ADDITIONAL REMARKS

No additional remarks

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley rats
Value:	>5 g/kg
Method:	
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	isophthalic acid
Remarks:	Ten rats (5 male and 5 female) were administered 5 g/kg body weight IPA at a dosing volume of 15 ml/kg. Mean body weights increased during the study and gross necropsy findings were within normal limits for all animals. No deaths occurred during the study. Therefore, the median acute lethal oral dose of IPA was determined to be greater than 5 g/kg.
Reference:	IIT Research Institute, 1990.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Albino Rat
Value:	13,000 mg/kg
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	isophthalic acid - 110
Remarks:	Ten rats (5 male and 5 female) were studied at each dose level. Rats were administered IPA in the form of either a 40% suspension in corn oil. A 95% confidence limit of 10,526-16,055 mg/kg was reported for the LD50. The authors concluded that IPA was practically non-toxic. Necropsy of the animals that died revealed pale, discolored kidneys.
Reference:	Industrial BIO-TEST Laboratories, Inc., 1975.

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Albino Rat
Value:	10,900 mg/kg
Method:	
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	isophthalic acid - 85
Remarks:	Ten rats (5 male and 5 female) were studied at each dose level. Rats were administered IPA in the form of either a 40% suspension in corn oil. A 95% confidence limit of 8,862-13,407 mg/kg was reported for the LD50. The authors concluded that IPA was practically non-toxic. Necropsy of the animals that died revealed pale, discolored kidneys.
Reference:	Industrial BIO-TEST Laboratories, Inc., 1975.

(d)

Type	LD0 []; LD100 []; LD50 [X]; LD lo []; Other []
Species/strain:	Rat
Value:	12,200 mg/kg

Method:
GLP: Yes [] No [X] ? []
Test Substance: Isophthalic acid
Remarks: Ten rats (5 male, 5 female) were studies at each dose level. Rats were administered IPA in the form of either a 20% or 40% suspension in a 10% aqueous gum Arabic solution. Rats were monitored for 14 days. Mortality data were statistically analysed according to the method of Litchfield and Wilcoxon and the acute lethal dose was calculated. A 95% Confidence limit of 10.0 to 14.9 g/kg was reported for the LD50. Necropsy of the animals that died did not reveal any gross pathological alterations attributable to ingestion of test material.
Reference: Industrial BIO-TEST Laboratories, Inc 1958

(d)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 10,400 mg/kg
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: isophthalic acid
Remarks:
Reference: Marhold, 1986.

5.1.2 ACUTE INHALATION TOXICITY

a)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [X]
Species/strain: Albino Rats
Exposure time: 4 hours
Value: --
Method: Ten rats were exposed to11.37 g/m3 isophthalic acid (particle size: 1-5 microns). The animals were placed into specially designed chambers that were equipped with a Wright Dust Feed Mechanism which introduced the IPA in the form of a fine dust. The animals were exposed to the test material continuously for 4 hours. Observation of the animals after exposure was conducted for 16 days.
GLP: Yes [] No [ ] ? [X]
Test substance: isophthalic acid
Remarks: All test animals survived the acute inhalation exposures and were not observed to exhibit any adverse reactions during or after exposure.
Reference: Industrial BIO-Test Laboratories, Inc., 1958

5.1.3 ACUTE DERMAL TOXICITY

(a)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [ ]
Species/strain: Rabbits (New Zealand albino)
Value: >2,000 mg/kg body weight
Method: Single dose applied to the clipped back of each animal for 24 hours.
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: 5 male and 5 female rabbits received a single dermal dose of 2,000 mg/kg, applied for 24 hours. Animals were observed for 14 days following exposure.

No deaths were observed during the study. The authors concluded that the acute dermal LD50 value for IPA exceeds 2,000 mg/kg. Mild dermal irritation was observed in four animals immediately following unwrapping. No adverse treatment-related clinical signs were observed and no gross pathological lesions due to treatment were evident in any of the animals at necropsy. Mean body weights increased during the study.

Reference: ITTRI, 1990

(b)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain: Albino Rabbits
Value: The acute mean lethal dose is greater than 23,000 mg/kg
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: isophthalic acid
Remarks: Rabbits were clipped with electronic clippers 24 hours prior to testing. The test material was applied to the exposure sites in the form of an aqueous paste. The exposure sites were covered with an impervious plastic sheeting that was firmly taped to the animal. Four animals at each of the four dose levels (4000, 8000, 16000, and 23000 mg/kg) were tested.
Reference: Industrial BIO-TEST Laboratories, Inc., 1958

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [ ]
LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Charles River Albino Rats
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Exposure time:
Value: 13,000 mg/kg
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Isophthalic Acid-110
Remarks: 95% Confidence Limits of LD50 = 10,526 –16,055
Reference: Calandra, 1975

(b)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [ ]
LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: mouse
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; infusion [ ]; s.c. [ ]; other [ ]
Value: 4200 mg/kg
GLP: Yes [ ] No [ ] ? [X]
Test substance: Isophthalic Acid-110
Remarks:
Reference: Academie des Sciences, 1835-1965.

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)

Species/strain: Rabbits (New Zealand white rabbits)
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ];
Not irritating [X]
Method: A 500 mg dose of undiluted IPA was applied to skin that was previously clipped. The treated site was covered by adhesive dressing and the entire midsection of the rabbit was wrapped in a lint-free cloth towel and secured by an adhesive bandage.
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: The irritation score was 0.0/8.0 at all time points following unwrapping. The Primary Dermal Irritation Score for IPA was 0.0. No signs of dermal irritation or corrosivity were seen.
Reference: IITRI, 1990.

(b)

Species/strain: Rabbits (albino)
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ];
Not irritating [X]
Method: A 500 mg dose of undiluted IPA was applied for 24 hours to abraded or unabraded skin that was previously clipped. The treated site was occluded.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Isophthalic Acid
Remarks: With intact skin, mild erythema was noted in 1/6 animals at 24 hours (score=0.2/8), and 0/6 animals at 72 hours (score=0/8). With abraded skin, mild erythema was noted in 3/6 animals at 24 hours (score=0.5/8) and 0/6 animals at 72 hours (score=0/8). No edema was observed. The authors concluded that IPA is not an irritant.
Reference: Industrial Bio-Test Laboratories, 1975.

(c)

Species/strain: Rabbits (albino)
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ];
Not irritating [X]
Method: A 500 mg dose of undiluted IPA was applied for 24 hours to abraded or unabraded skin that was previously clipped. The treated site was occluded.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Isophthalic Acid
Remarks: With intact skin, mild erythema was noted in 1/6 animals at 24 hours (score=0.3/8), and 0/6 animals at 72 hours (score=0/8). With abraded skin, mild erythema was noted in 3/6 animals at 24 hours (score=0.7/8) and 3/6 animals at 72 hours (score=0.5/8). No edema was observed. The authors concluded that IPA is not an irritant.
Reference: Industrial Bio-Test Laboratories, 1975.

5.2.2 EYE IRRITATION/CORROSION

(a)

Species/strain: New Zealand Albino Rabbit
Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [];

Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X];
Not irritating [ ]

Classification: Irritating []; Not irritating [ ]; Risk of serious damage to eyes [ ]

Method: 100 mg of IPA was instilled into an eye of 6 rabbits. Irritation scores were recorded at 1, 2, 3, 4, 7 and 14 days following test article application.

GLP: Yes [X] No [ ] ? [ ]

Test substance: isophthalic acid-99

Remarks: The maximum irritation score of 5.3/110.0 was obtained 1 day after administration of the test article. Ocular irritation was seen in all rabbits during the study, but only three rabbits exhibited positive reactions. Complete recovery from all signs of ocular irritation was evident in two rabbits by the 2nd day, in five rabbits by the 4th day, and in all rabbits by the final scoring interval.

Reference: IIT Research Institute, 1985.

(b)

Species/strain: New Zealand Albino Rabbit

Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X];
Not irritating [ ]

Classification: Irritating []; Not irritating [ ]; Risk of serious damage to eyes [ ]

Method: 100 mg of IPA was instilled into an eye of 6 rabbits. Irritation scores were recorded at 1, 24, 48, 72, and 168 hours.

GLP: Yes [ ] No [ ] ? [X]

Test substance: isophthalic acid-85

Remarks: An irritation score of 26.7/110 was reported at 1 hour, which diminished to 13.1/110 at 24 hours. Signs of irritation were completed resolved at 48 hours through 1 week. The authors concluded that IPA is not an eye irritant.

Reference: Industrial BIO-TEST Laboratories, Inc., 1975.

(c)

Species/strain: New Zealand Albino Rabbit

Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X];
Not irritating [ ]

Classification: Irritating []; Not irritating [ ]; Risk of serious damage to eyes [ ]

Method: 100 mg of IPA was instilled into an eye of 6 rabbits. Irritation scores were recorded at 1, 24, 48, 72, and 168 hours.

GLP: Yes [ ] No [ ] ? [X]

Test substance: isophthalic acid-110

Remarks: An irritation score of 19/110 was reported at 1 hour, which increased slightly to 25.6/110 at 24 hours. Signs of irritation were completed resolved at 48 hours through 1 week. The authors concluded that IPA is not an eye irritant.

Reference: Industrial BIO-TEST Laboratories, Inc., 1975.

(d)

Species/strain: rabbit

Results: Highly corrosive [ ]; Corrosive [ ]; Highly irritating [];
Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ];
Not irritating [ ]

Classification: Irritating []; Not irritating [ ]; Risk of serious damage to eyes [ ]

Method: Standard Draize Test

GLP: Yes [ ] No [ ] ? [X]

Test substance: isophthalic acid
Remarks: Mild reaction
Reference: Prehled Prumyslove Toxikologie, 1986.

5.3 SENSITISATION

(a)
Type: Dermal Sensitzation
Species/strain: Guinea Pig
Results: Sensitizing [ ]; Not sensitizing [X]; ambiguous [ ]
Number of animals with respective erythema scores

Group	Induction										Challenge									
	24 hours					48 hours					24 hours					48 hours				
	Erythema Score					Erythema Score					Erythema Score					Erythema Score				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Treated		9	1			6	4				2	7	1			3	7			
Vehicle control	1	3	6			2	3	3			3	7				8	2			
Sham Control	10					10					3	7				4	6			

Classification: Sensitizing [ ]; Not sensitizing [ ]
Method: Modified Buehler Method. A dose of 0.3 mL of a 30% solution of IPA in dimethyl sulfoxide (DMSO) was applied to the shaved backs of 10 male guinea pigs once a week for 3 weeks during the induction period. The 30% solution was the maximum concentration to cause mild irritation (Driaze score of 2 or less). Another group of 10 guinea pigs served as a vehicle control and was similarly dosed with 0.3 ml of undiluted DMSO. A third group of 10 sham control animals was handled in the same way but was not treated with vehicle or test article. Two weeks following the last induction dose, the treated and sham control animals received a challenge dose of 0.3 mL of a 30% solution of IPA; the vehicle control received a 0.3 ml of a 70% aqueous DMSO solution.. Using a body weight of 0.6 kg, the treatment corresponds to a dose of approximately 15,000 mg/kg.
GLP: Yes [X] No [ ] ? [ ]
Test substance: isophthalic acid
Remarks: A positive erythema response (score> or = 2) was elicited in 1/10 animals. The primary effect of treatment (treated vs. control) and the secondary effect of time of scoring (24 vs 48 hours) were not statistically significant. The authors concluded that IPA is not a dermal sensitizer. The same concentration (30%) was used for both the induction and challenge phase which represents a slight deviation from standard protocol. However, because conditions were more stringent and results were still negative it is not believed to affect the conclusion.
Reference: IIT Research Institute, 1991.

5.4 REPEATED DOSE TOXICITY

(a)
Species/strain: rats (Wistar-derived stock)
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: oral
Exposure period: 13 weeks
Frequency of treatment: once/day
Post exposure observation period:
Dose: 0.5, 1.6, 5.0% of a normal diet (250, 800, 2500 mg/kg/day)
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL: 0.5% (approximately 250 mg/kg-day)
LOEL: 1.6% (approximately 800 mg/kg-day)
Method: subchronic feeding study
GLP: Yes [ ] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remark: Following the first week of the study, the weight gains of the rats were examined. It was concluded that the 5% dose level would not permit growth

or even survival of the animals. Therefore, the doses were reduced to 3%. Levels of 1.6% (approximately 800 mg/kg-day) in feed produced small increases in the incidence of crystalluria (1/25 males, 2/25 females) and renal pathology (5/25 males). This study identifies a NOAEL and LOAEL of 250 and 800 mg/kg-day, respectively, based on kidney effects in rats.

Reference: Vogin, 1972

(b)

Species/strain: Wistar and CD Rats
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: dietary
Exposure period: 90 day
Frequency of treatment: once per day
Post exposure observation period:
Dose: 0, 0.03, 0.125, 0.5, 2.0, or 5% teraphthalic acid
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL:
LOEL:
Method:
GLP: Yes [ ] No [ ] ? [X]
Test substance: Teraphthalic Acid, an isomer of IPA
Remark: Dose-related decreases in food consumption, body weight, and weight gain were found in both male and female Wistar and CD rats. Statistically significant decreases were confined mainly to the two highest dietary levels of TPA.
Reference: Gibson, 1982

(c)

Species/strain: Sprague-Dawley rats
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: inhalation
Exposure period: 4 weeks
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period:
3 weeks (5 rats/sex/group in the control group and the high dose level groups designated for pre-exposure, single exposure, and weekly serum analysis)
Dose: 1.0, 5.0, and 10.0 mg/m3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL: 10 mg/m3
LOEL: --
Method: subchronic inhalation of particulate aerosol
GLP: Yes [ ] No [ ] ? [X]
Test substance: isophthalic acid
Remark: The dosing groups contained 10 male and 10 female rats each. In addition, 5 rats/sex were designated for pre-exposure, single exposure, and weekly serum analysis. These rats were included in the control group and the high exposure groups. There were no statistically significant effects of treatment on any body weight or organ weights in the exposed rats. In addition, there were no significant differences in hematology or clinical chemistry parameters between the exposed groups and control group.
Reference: IIT Research Institute, 1988.

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL IN VITRO TEST

(a)

Type: Mutagenicity, Bacterial Reverse Mutation Assay
System of testing: *Salmonella typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, and TA 100)
Concentration: 5, 50, 500, or 5000 ug/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc:
Precipitation conc: --
Genotoxic effects:

	+	?	--
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: Salmonella/Mammalian-Microsome Reverse Mutation Test (OECD 471)
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid 220
Remarks: Isophthalic acid 220 showed no evidence of mutagenic activity when tested in this bacterial system.
Reference: Huntingdon Research Centre, 1991

(b)

Type: Mutagenicity/ Bacterial Reverse Mutation Assay
System of testing: *Salmonella typhimurium* (TA98, TA100, TA1535, TA1538)
Concentration: 0, 667, 1000, 3333, 6667, or 10000 ug/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc:
Precipitation conc:
Genotoxic effects:

	+	?	--
With metabolic activation:	[X]	[ ]	[ ]
Without metabolic activation:	[X]	[ ]	[ ]

Method: Salmonella/Mammalian-Microsome Reverse Mutation Test (OECD 471)
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: Under the conditions of this assay, IPA did cause reproducible positive responses in various strains in the presence and absence of microsomal enzymes.
Reference: Microbiological Associates, Inc. 1990.

(c)

Type: Mutagenicity/ Bacterial Reverse Mutation Assay
System of testing: *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537, and TA 1538)
Concentration: 0, 4, 20, 100, 500, 2500, and 10000 ug/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc:
Precipitation conc: --
Genotoxic effects:

	+	?	--
With metabolic activation:	[X]	[ ]	[ ]

Without metabolic activation: [X] [ ] [ ]
Method: Salmonella/Mammalian-Microsome Reverse Mutation Test (OECD 471)
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: Isophthalic acid was found to be not toxic to the bacterial strains. The test compound was found to be mutagenic with and without exogenous metabolic activation.
Reference: Muller, 1991.

B. NON-BACTERIAL IN VITRO TEST

(a)
Type: Chromosomal Aberration
System of testing: Chinese hamster ovary cells
Concentration: 625, 1250, 2500, and 5000 ug/ml
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc: --
Precipitation conc: --
Genotoxic effects:

	+	?	--
Without metabolic activation:	[ ]	[ ]	[X]

Method: OECD 473
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: No increase in chromosome aberrations was observed in either the non-activated or S-9 activated test system. IPA was concluded to be negative in the cytogenetics assay.
Reference: Microbiological Associates, Inc.1991.

(b)
Type: Mammalian Cell Gene Mutation/HGPRT Mutation Assay
System of testing: Chinese hamster ovary cells
Concentration: 125, 250, 500, 1500, 2000, and 3000 ug/ml (non-activated); 250, 500, 1000, 1500, 2000, and 3000 ug/ml (activated).
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:
Cytotoxicity conc:
Precipitation conc: --
Genotoxic effects:

	+	?	--
Without metabolic activation:	[ ]	[ ]	[X]
With metabolic activation:	[ ]	[ ]	[X]

Method: OECD 476
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: Isophthalic acid was found to be negative in the CHO/HGPRT mutation assay both in the absence and presence of exogenous metabolic activation.
Reference: Microbiological Associates, 1991

(c)
Type: Mammalian Cell Gene Mutation/Lymphoma Assay
System of testing: Mouse lymphoma L5178Y cells
Concentration: 150, 300, 450, 600, 650, 700, 750, 800, 850, 900 and 950 ug/ml.
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results:
Cytotoxicity conc:
Precipitation conc: --
Genotoxic effects:

	+	?	--
Without metabolic activation:	[ ]	[ ]	[X]
With metabolic activation:	[ ]	[ ]	[X]

Method: Mouse Lymphoma Mutation Assay (OECD 476)
GLP: Yes [X] No [ ] ? [ ]
Test substance: Isophthalic Acid
Remarks: Based on the results of this study, there is no conclusive evidence of mutagenic activity attributable to isophthalic acid in mouse lymphoma cells.
Reference: Riach and Willington, 1994.

5.6 GENETIC TOXICITY IN VIVO

(a)
Type: Micronuclei Formation
Species: Mouse
Strain: ICR
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Concentration: 200, 400, 800 mg/kg
Route of Administration: i.p.
Frequency of treatment: once
Sampling frequency: once, 24 hours post-exposure
Results: Negative. Mortality was observed in 1/15 male mice that had been treated with 800 mg/kg TPA. One mouse from the replacement group was used in place of the animal that died. Clinical signs following treatment with either dose of TPA included lethargy and piloerection. Negative and positive control animals appeared normal during the course of the study. The total number of micronuclei observed per 20000 PCE in animals treated with vehicle, 200, 400 or 800 mg/kg for 24 hours was 4, 8, 5, and 4, respectively. The incidence of micronuclei in animals treated with 800 mg/kg also did not differ from the vehicle control at 48 hours (2/20000 vs. 8/20000, respectively). There was no difference between males and females. TPA was negative in the test. The test was valid, as the incidence of micronuclei in the vehicle control was not greater than 5/1000 PCE and the number of micronucleated cells in the positive controls (382/20000) was significantly different ($p < 0.05$) from the vehicle control. Reductions (up to 9%) in the ratio of polychromatic erythrocytes to total erythrocytes were observed in some of the treated groups relative to the vehicle control, suggesting that the test article did not inhibit erythropoiesis. Greater reductions in this ratio were observed in animals treated with cyclophosphamide (25-29%).
Toxic concentration: 800 mg/kg
Remarks: Criteria for a valid test: The mean incidence of micronucleated polychromatic erythrocytes must not exceed 5/1000 polychromatic erythrocytes (0.5%) in the negative control vehicle. The incidence rate in the positive control group must be significantly increased relative to the negative control ($p<0.05$, Kastenbaum-Bowman Tables).
Method: OECD 474
GLP: Yes [X] No [ ] ? [ ]
Test substance: Terephthalic acid (an isomer of IPA)
Reference: Bioreliance, 2001

5.7 CARCINOGENICITY

Although no data were located regarding the carcinogenicity of IPA, some information is available for its isomer, TPA.

(a)

Species:	Rat
Sex:	Male/female
Strain:	Fischer 344
Route of admin.:	Oral feed
Exposure period:	Lifetime (2 years)
Frequency of treatment:	Daily
Post. obs. period:	
Doses:	0, 20, 142, 1000 mg/kg/day
Control Group:	Yes, concurrent no treatment
Method:	Other
Year:	1983
GLP:	Unknown
Test substance:	TPA
Remark:	Terephthalic acid induced bladder stones were seen in 13/126 females in the high dose group. At the scheduled 6 and 12 month sacrifices, no bladder calculi were detected. At the 18 month sacrifice sand like particle or bladder calculi were only seen in two of the high dose females. There were 18/118 females with what was described as transitional cell adenomas by one pathology laboratory and epithelial hyperplasia by another. Two of these were detected in high dose females after 18 months (2/27), 15 were seen in seen in high dose females at the end of the study (15/79), and one was seen in a control female at the end of the study. None were found in the males, nor at any other dose level. It was believed that rats fed high concentrations of terephthalic acid in the diet develop bladder calculi which appear to cause chronic inflammation of the bladder epithelium, bladder hyperplasia and subsequently bladder tumours. An apparent threshold effect exists because animals exposed to lower concentrations for their lifetime do not form bladder calculi or tumors. The high dose group in this study (1000 mg/kg/day) corresponds to an approximate dietary concentration of 2.0% to 2.8% in adult Fisher rats.
Reference:	CIIT (1983) Chronic Dietary Administration of Terephthalic Acid. CIIT Docket 20124

(b)

Species:	Rat
Sex:	Male/female
Strain:	Wistar
Route of admin.:	Oral feed
Exposure period:	2 years
Frequency of treatment:	Daily
Post. obs. period:	
Doses:	1% (500 mg/kg/day) & 2% (1000 mg), 5% (2500 mg)
Control Group:	Unknown
Method:	
Year:	1974

GLP: Unknown
Test substance: As prescribed in 1.1 - 1.4
Remark: Reduced body weight gain occurred at in the 5% dose level (males and females) and in the 2% dose level (males). At 1%, reduced relative liver weight in females and reduced relative kidney size in males and females. At 2%, reduced liver, kidney, and heart weights (females only). At 5%, there was increased kidney weight in males, and increased adrenal weights in males and females; as well as increased mortality, mainly as a result of increased incidence of bladder stones (at 5%: males, 42/47; females, 39/42; at 1%: females, 1/48). There was increased incidence of bladder and ureter tumors (at 5%: males, 21/37; females, 21/34; at 2%: males, 1/48; females, 2/48; at 1%: males, 1/43.). There was increased incidence of bladder and ureter tumors.
Reference: Gross J. (1974) The effects of prolonged feeding of terephthalic acid (TPA) to rats. Project FG-IS-175. Submitted to US Dept. of Agriculture, Agriculture Research Service, Washington D.C.

(c)
Species: Mouse
Sex: Female
Strain: C3H
Route of admin.: Oral feed
Exposure period: 12 months
Frequency of treatment: Daily
Post. obs. period:
Doses: 5%
Control Group: Unknown
Method:
Year: 1973
GLP: Unknown
Test substance: No data
Remark: Reduced number of mammary tumours. At 12 months, mammary tumours occurred in 78% of controls and in 50% of treated mice.
Reference: Nagasawa H, Fujimoto M. (1973) Experimentia 29, 89. Cited in BIBRA Toxicity Profile
1995

5.8 TOXICITY TO REPRODUCTION

Although no data were located regarding the toxicity to reproduction of IPA, some information is available for its isomer, Terephthalic acid.

(a)
Type: Fertility [ ]; One generation study [X]; Two generation study [ ]; Other [ ]
Species/strain: Wistar and CD Rats
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: dietary
Exposure period: Parental: 90 days prior to breeding and throughout mating gestation, lactation, and postweaning periods, Offspring: 51 days birth through lactation, 30 days post-weaning
Frequency of treatment: *ad libitum*

Postexposure observation period:
Premating exposure period: male: 90 days female: 90 days
Duration of the test:

Doses:	diets containing 0, 0.03, 0.125, 0.5, 2.0, and 5.0% terephthalic acid (TPA)
Control group:	Yes [X]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL Parental:	0.5% CD rats (approximately 240-282 mg/kg-day), 2.0% Wistar rats (approximately 960-1219 mg/kg-day)
LOEL Parental:	2.0% CD rats (approximately 930-1107 mg/kg-day), 5.0% Wistar rats (approximately 2480-3018 mg/kg-day)
NOEL F1 Offspring:	0.5% (both strains, approximately 240-307 mg/kg-day)
LOEL F1 Offspring:	2% (both strains, approximately 930-1219 mg/kg-day)
NOEL F2 Offspring:	--
LOEL F2 Offspring:	--
Results:	Parental Effects: Following 90 days of exposure to TPA, statistically significant decreases in food consumption were observed in CD females treated with 2% and 5%, and in both sexes of Wistars treated with 5%. Body weights were statistically decreased after 13 weeks in both sexes of CD rats on 2% and 5% TPA diets, and in males exposed to 0.03%. This effect occurred in Wistars (both sexes) only at the 5% level. There were 5 deaths (3 CD females, 1 Wistar/sex) reported during weeks 4-13 in animals given 5% TPA in the diet. During the one-generation component of the study 3 CD (1 male at 2.0%, 1/sex at 5.0%) and 4 Wistar female (2 at 5.0% and 2 at 0.03%) rats died. There was no effect of treatment on fertility index and litter size. Offspring Effects: There were no effects of treatment on litter size, sex ratio, or total number of offspring. While no control offspring were found dead on Day 0, 17 Wistar pups (1 at 0.03%, 2 at 0.125%, 1 at 0.5%, 12 at 2.0% (2 from one dam and 10 from another)) and 23 CD pups (1 at 0.5%, 7 at 2.0% (3 dams) and 15 at 5.0% (3 dams; with 11 from one of them)) were found dead. No statistical differences were noted in viability on Days 0, 1, or 21 in either strain. In CD rats, survivability on Day 21 was reduced in both sexes of offspring whose parents had been exposed to 5% TPA in the diet. In Wistar rats, body weights of both sexes of offspring from dams given 5.0% were reduced at Day 1. On Day 21, body weight was reduced in both strains of offspring from dams that ingested 5% TPA in the diet. Increased postnatal deaths on Day 1 and decreased survivability to Day 21 were noted in the 2% and 5% groups. At these dose levels, several large litters of pups were lost to dams suffering obvious signs of toxicity. Several of these dams did not allow the pups to nurse or attend to the litters. These pups were noted not to have milk in their stomachs and presented clinically as being very weak. These dams were consuming dietary levels of TPA known to cause reduced feed consumption, diarrhea and gastric trichobezoars (hairballs) and induce the formation of renal and bladder calculi. Unscheduled deaths during the postweaning period (Day 21-51) were confined to the 5% TPA group (18 Wistar and 16 CD) and were associated with a very high incidence of renal and bladder calculi. Renal and bladder calculi were noted in all animals exposed to 5% that were necropsied at Day 21. Day 51 necropsy findings also reported a very high incidence of renal and bladder calculi and the histological sequelae of the presence of the calculi.
Method:	One generation reproductive toxicity test
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	.....Terephthalic Acid (TPA), an isomer of IPA
Reference:	Gibson, 1982

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a)

Species/strain: Sprague-Dawley rats
Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration: inhalation
Duration of the test: 7 days/week , for a total of 10 consecutive exposures.
Exposure period: Gestation days 6 through 15
Frequency of treatment: 6 hours/day, 7 days/week
Doses: 0, 1.0. 5.0, and 10.0 mg/m3
Control group: Yes [X]; No [ ]; No data [ ];
Concurrent no treatment [ ]; Concurrent vehicle [X]; Historic al [ ]
NOEL Maternal Toxicity:
NOEL Fetotoxicity:
NOEL Teratogenicity -- >10 mg/m3
Results: Exposure to IPA during the major organogenesis period did not result in any significant toxic or teratogenic effects in the dam or fetus.
Method:
GLP: Yes [X] No [ ] ? [ ]
Test substance: isophthalic acid
Remarks: IPA was administered to four groups of 16-18 timed-pregnant primiparous rats. The incidences of clinical signs in the IPA-exposed rats and the control rats were similar. No deaths occurred during the study.
Reference: IIT Research Institute, 1991.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type:
Results:
Remarks:
Reference:

B. Toxicodynamics, toxicokinetics

(a)

Type: Subchronic feeding study
Species/Strain Rat/Wistar
Results:
Remarks: Blood levels of IPA and TPA (determined as total mg phthalate/L) collected during a 13-week feeding study were increased in a dose-dependent manner on days 7, 30, 60, and 90. IPA and TPA levels were generally highest during the first week of exposure and declined during the course of the study, suggesting either a change in feed consumption rates or some sort of adaptation resulting in increased clearance of IPA. 24-Hour urinary excretion data collected on days 7, 30, 60, and 90 indicate that urinary excretion, presumably as unchanged chemical, is the primary mechanism by which IPA and TPA are eliminated from the body.
References: Vogin, E.E. 1972. Subacute feeding studies (13-week) in rats with

demethylterepthalate (DMT), isophthalic acid (IA), and terephthalic acid (TA). Food and Drug Research Laboratories, Incorporated, Laboratory No. 0411.

(b)
Type: Subchronic inhalation study
Species/Strain Rat/Wistar
Results:
Remarks: Blood levels of IPA were detected immediately following exposure in rats exposed to 10 mg/m^3 for 6 hours/day. Levels remained elevated during the exposure period. Serum concentrations detected in female rats (5.3-9.3 ug/mL) were consistently higher than the concentrations detected in male rats (1.4-3.4 ug/mL). The data suggest that steady state is achieved fairly rapidly (on the first day of exposure). One week following exposure, IPA was not detected in blood, indicating that clearance of IPA from the body occurs fairly rapidly. Based on a log Kow value of –2.34, IPA is not expected to accumulate appreciably in tissues, and is likely to be readily excreted from the body.
References: IITRI 1988

(c)
Type: Subchronic inhalation study
Species/Strain Rat/Sprague-Dawley
Results: Sprague-Dawley rats were exposed by inhalation to a particulate aerosol of 10 mg/m^3 terephthalic acid. Exposure was 6 hours per day for 25 consecutive days, followed by a 28-day post-exposure recovery period. Blood and urine samples were collected one day prior to exposure and after 1, 5, 10, 15, 25 days of exposure and every 7 days during the 28 day recovery period. Terephthalic acid was not detected in the blood after the first 5 days of exposure. Detectable blood concentrations of terephthalic acid were observed after 10 consecutive days of exposure and progressively increased over the remaining exposure period. The highest mean blood concentration was 2.7 ug/ml after 25 days. Seven days after completion of the exposure period, the blood concentration of terephthalic acid was less than 1 ug/ml. However, the presence of trace levels of terephthalic acid was detected in the blood throughout the post-exposure recovery period.
Reference: IIT Research Institute 1989. Time Course Analysis of Terephthalic Acid Concentration in Blood and Urine of Rats Following Inhalation Exposures. Study IITRI Study #1448A

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(a)
Results:
Remarks:
Reference:

6. REFERENCES

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Robust Study Summaries
ISOPHTHALIC ACID

.....

CAS No. 121-91-5

Sponsor Country: U.S.A.

DATE: January, 2002

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE
- Isophthalic Acid (IPA)

METHOD
- Method/guideline:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Melting point: 347 °C
- Decomposition:
- Sublimation:
- Remarks:

CONCLUSIONS
- The melting point for IPA is 347 °C

DATA QUALITY

REMARK
- The CRC Handbook of Chemistry and Physics reference for the melting point was considered more reliable because it reported a specific melting point rather than a range, though all reported values were very similar.

REFERENCES
- Lide, D.R. (ed.) CRC Handbook of Chemistry and Physics. 75th ed. Boca Raton, Fl: CRC Press, Inc., 1994-1995. IN HSDB, 2001.

OTHER
- 345-348ºC Merck, 9th Edition; 314-343 ºC Aldrich.

BOILING POINT

TEST SUBSTANCE
- Isophthalic Acid (IPA)

METHOD
- Method:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Boiling point: sublimes
- Pressure:
- Pressure unit:
- Decomposition (yes/no/ambiguous)
- Remarks:

CONCLUSIONS
- IPA has been found to sublime.

DATA QUALITY

REFERENCES
- Lide, D.R. (ed.) CRC Handbook of Chemistry and Physics. 75th ed. Boca Raton, Fl: CRC Press, Inc., 1994-1995. IN HSDB, 2001.

OTHER

VAPOUR PRESSURE

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks:

METHOD
- Method:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Vapor Pressure: 9 Pa (0.068 mm Hg)
- Temperature: 100 °C
- Decomposition:
- Remarks:

CONCLUSIONS
- The vapor pressure for IPA is 9 Pa at 100°C and is approximately 2.25 Pa at 25°C.

DATA QUALITY

REFERENCES
- Dauber, T.E., R.P. Danner. Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, D.C.: Taylor and Francis, 1989. IN HSDB, 2001.

OTHER
- Sublimation may have influenced the high-temperature measurement. The extrapolation from high temperature to environmentally relevant temperature (e.g. 25ºC) may be inaccurate.

VAPOUR PRESSURE

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks:

METHOD
- Method: MPBPWIN version 1.40 (Model)
- GLP: No
- Year (study performed):
- Remarks:

RESULTS
- Vapor Pressure: 3.5×10^{-6} Pa (2.6×10^{-8} mm Hg)
- Temperature:
- Decomposition:
- Remarks: Modified Grain Method selected.

CONCLUSIONS
- The vapor pressure for IPA is estimated to be 3.5×10^{-6} Pa.

DATA QUALITY
- (2) Reliable with restrictions. Value is an estimate by an accepted method.

REFERENCES
- MPBPWIN version 1.40 (US EPA EPIWIN Suite Software)

OTHER
- Other QSAR estimates ranged from 1.57×10^{-7} mm Hg using the Mackay method to $1.19\ 10^{-8}$ mm Hg using the Antoine method. The Modified Grain method was selected by the software.
- Because the QSAR model provides estimates at the environmentally relevant temperature, it was preferred to the estimate derived by an extrapolation from a measurement at a high temperature.

PARTITION COEFFICIENT

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: Purity 99.9%

METHOD
- Method: OECD 107 "Partition Coefficient (n-octanol/water)"
- GLP: Yes
- Year (study performed): 1991
- Remarks: The water phase was buffered to pH 7 because of the possibility of ionization. Buffer was prepared by diluting 200 ml of 1M sodium hydroxide to 700 ml with water, adjusting to pH 7 with glacial acetic acid, and adjusting the final volume to one liter. Solvents (octanol and buffer) were presaturated by shaking at room temperature. Test sample was added to each of three test conditions consisting of varying ratios of octanol to buffered water. Solutions were mixed for 30 minute then centrifuged at 1500 rpm for 5 minutes to separate the two phases. Three replicate samples were prepared from each of three test conditions.

RESULTS
- Log P_{ow}: -2.34
- Temperature: 22°C
- Remarks: Chemical analyses conducted by high performance liquid chromatography (HPLC). Recoveries ranging from 92.6-98.1% were reported. The mean recovery was 95.4 percent. There was no trend in the partition coefficient with varying amounts of water.

CONCLUSIONS
- The Log Pow value for IPA is –2.34.

DATA QUALITY
- (1) Reliable without restrictions

REMARKS
- The Log Pow of the ionized form of isophthalic acid (value determined a pH 7) is believed to be the most relevant as this is the form most likely encountered in the environment.

REFERENCES
- ITT Research Institute. 1992. Determination of the Octanol/Water Partition Coefficient of Isophthalic Acid (IPA). Study No. 1705.

OTHER
- Log Pow: 1.66 (Hansch and Leo, 1981) This value may represent to Log Pow of the neutral form which w ould explain the difference between this value and the measured value above. In sufficient documentation of methods to assess. Log Pow 1.76 (KOWWIN in USEPA EPIWIN Suite software.

WATER SOLUBILITY

TEST SUBSTANCE
- Identity: Isophthalic Acid (IPA)

METHOD
- Method:
- GLP: ?
- Year (study performed):
- Remarks:

RESULTS
- Value: 0.013 g/100 g at 25°C
- Description of solubility:
- pH value and concentration at temperature °C:
- pKa value at 25 °C:
- Remarks: .

CONCLUSIONS
- The water solubility of IPA is 0.013 g/100 mL (130 mg/L).

DATA QUALITY

REFERENCES
- Bemis, A.G., Dindorf, J.A., Horwood, B., Samans, C. 1982 Phthalic acids and other benzenepolycarboxylic acids. In: Kirk-Othmer encycl. Chem Tech 3Rd Ed. 17: 732-77.

OTHER
- 40 mg/L at 1°C; 130 mg/L at 25°C; 300 mg/L at 50°C; 2400 mg/L at 100°C (Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed. Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984, p V17 759). Reported in HSDB 2001.

ENVIRONMENTAL FATE ELEMENTS AND PATHWAYS

PHOTODEGRADATION

TEST SUBSTANCE
- Isophthalic Acid

METHOD
- Method/guideline: Estimated - AOPWIN
- Type (test type): Estimated
- GLP:
- Year (study performed): 2001
- Remark: Assumptions molecular weight 166, water solubility 130 mg/L, vapor pressure 3.5 x 10^{-6} Pa at 25º C, Log Kow = -2.34.

RESULTS
- Direct photolysis:
- Half-life t ½ : 8.2 days
- Remarks: Overall OH Rate Constant: 1.3E-12 cm^3/molecule-sec at 25 degrees C, Concentration of OH radical is 1.5E 6 OH/cm^3, 12 hour day

CONCLUSIONS

DATA QUALITY
- (2) Reliable with restrictions. Value is an estimate by an accepted method.

REFERENCES
- SRC. 2001. Atmospheric Oxidation Program for Microsoft Windows (AOPWIN). Syracuse Research Center.

OTHER
- IPA in the vapor-phase is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 12.3 days (Meylan and Howard, 1993).

STABILITY IN WATER

TEST SUBSTANCE

METHOD

- Method/guideline:
- Type (test type):
- GLP:
- Year (study performed):
- Remarks:
- Duration:
- Positive Controls:
- Negative Controls:
- Analytical procedures:

RESULTS

- Measured value:
- Degradation:
- Breakdown products:
- Remarks: Based on the chemical structure, isophthalic acid is not expected to undergo abiotic hydrolysis in the environment.

CONCLUSIONS

DATA QUALITY

REFERENCES

OTHER

- IPA is biodegradable in screening tests (Japan Chemical Industry Report, 1992; Pitter, 1976), it may also biodegrade in water. The absorption of UV radiation >290 nm (Sadtler Research Lab, 19??) suggests that IPA may directly photodegrade in surface waters.

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE

- Isophthalic Acid

METHOD

- Test (test type): Calculated
- Method: Level I, II, and III Fugacity
- Year (study performed): 2001
- Remarks: Chemical Assumptions: Molecular weight=166 g/mol; water solubility=130 g/m^3; Vapor pressure=3.5 x 10^{-6} Pa; Log Kow=-2.34; Melting Point=347ºC; Temperature=25ºC; Half life in air=288 hr. Default values for release estimates were assumed for Level 1 (single release of 100,000 kg), Level 2 (continuous release of 1,000 kg/hr), and Level 3 (continuous release of 1,000 kg/hr each to air, water, and soil). All environmental parameters were default values.

RESULTS

- Media: Air, soil, water, and sediment concentrations

	Level I	Level II	Level III
Air	0.000090%	0.000090%	0.000013%
Water	99.9995%	99.9995%	76.1%
Soil	0.00041%	0.00041%	23.8%
Sediment	0.0000090%	0.0000090%	0.03%

- Remarks: Predicted concentrations are not provided since default release estimates were used. Ionization of IPA would increase the water solubility, but use of a higher water solubility (2300 mg/L) had no significant effect on predicted distributions.

- Remarks: IPA was modeled as a Type 1 chemical using the Trent University software, i.e., it was assumed capable of partitioning into all media. A more correct approach would have been to model IPA as a Type 2 chemical with a Z value of zero or near-zero in air, and an initial estimate of Z in water of 1.0. This partitioning model would be calculated using the equivalence approach instead of the fugacity calculation. However, the required partition coefficients for Type 2 models are not those used for Type 1 chemicals, and were not available. In the absence of data, errors and uncertainties from using estimated parameters would be likely to counteract any improved accuracy from using a better model. The fugacity model did indicate zero or near-zero amounts in air. Consequently, more detailed modeling would be unlikely to significantly affect the prediction of environmental distribution.

CONCLUSIONS

- A majority of the IPA released to the environment is predicted to partition to the water compartment with lesser amounts partitioning to air and soil, depending upon the media to which IPA is directly released.

DATA QUALITY

- (2) Reliable with restrictions. Values are estimates using accepted methods.

REFERENCES

- Trent University. 1991. Fugacity-based Environmental Equilibrium Partitioning Model. Version 2.17. Environmental Modeling Centre, Trent University, Peterborough, Ontario.

OTHER

BIODEGRADATION

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9% pure

METHOD
- Method/guideline: OECD 301B and Directive 79/831/EEC Annex V
- Test Type: Modified Sturm Test (aerobic)
- GLP: Yes
- Year (study performed): 1991
- Contact time (units): 16 days
- Innoculum: sewage
- Remarks field for Test Conditions:

RESULTS
- Degradation % after time: >60% degradation within 7 days
- For each time period %: 9% up to day 2; 46% up to day 5; 64% up to day 7; 77% up to day 12.
- Breakdown products: None specified.
- Remarks field for Results:

CONCLUSIONS
- IPA is readily biodegradable under aerobic conditions, with a half-life near 5-6 days.

DATA QUALITY
- (1) Reliable without restrictions

REMARKS
- While other studies reported conclusions similar to the Battelle study the Battelle study was considered key because it was a GLP study following OECD test guidelines.

REFERENCES
- Battelle Europe. 1991. Study on the "Ready Biodegradability" (Modified Sturm Test) of Isophthalic Acid. Study No: BE-EA-128-91-01-STT-02.

OTHER
- IPA is degraded by aerobic microorganisms isolated from soil and marine sediment (Keyser et al., 1976; Aftring et al., 1981). Cultures isolated from marine sediments also degraded IPA under anaerobic conditions, although by a different metabolic pathway. After an acclimation to an activated sludge inoculum over a 24-day period, 84% of IPA was consumed in a respiratory test (Lund and Rodriguez, 1984). In another screening test, 95% of COD was removed in 5 days using an acclimated activated sludge inoculum (Pitter, 1976). In a 2-week biodegradation-screening test (MITI test) using 100 ppm IPA and an activated sludge inoculum, 77.1% of BOD was removed (Japan Chemical Industry Report, 1992). Another investigator confirmed that IPA was significantly biodegradable using the MITI test (Kitano, 1978). IPA was completely degraded in eight days using a soil inoculum (Alexander and Lustigman, 1966).

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9% pure

METHOD
- Method/guideline: OECD 203
- Type (test type): acute toxicity test - fish
- GLP: yes
- Year (study performed): 1991
- Species/Strain/Supplier: *Leuciscus idus melanotus*
- Analytical monitoring: High performance liquid chromatography (HPLC)
- Exposure period (unit): 96 hours
- Statistical methods: descriptive
- Details of test: static
- Remarks: Fish were exposed to test substance added to water at a range of concentrations for 96 hours. Mortalities were recorded at 24 hour intervals. The pH of the stock solution was adjusted to the required physiological value (7.8) using sodium hydroxide prior to the start of the study and was monitored daily thereafter. Adjustment of the stock solution increased the solubility of the test material. The authors believe that after pH adjustment isophthalic sodium salt was the test material investigated. The conductivity and alkalinity of the solutions were measured in addition to other parameters because addition of sodium hydroxide altered the physico-chemical properties of the test solution. A "salinity control" was added to the study to determine if the altered physico-chemical properties could cause any effect.

RESULTS
- Nominal concentrations: 130, 220, 350, 600, and 1000 mg/L
- Measured concentrations: The analytically determined actual concentrations of the test material at the beginning of the study ranged from 91 to 98% (average of 94.2%) of the nominal concentration. The analytically determined stability after 96 hours of exposure, were found to be within the range of 28% to 92% (average of 59%) of the nominal values.
- Element value: LC0 value exceeds 1,000 mg/L, LC50 (96 hr) could not be determined, NOEC (96 hr) > 895 mg/L based on the 96-hour average measured concentration for the highest concentration level tested.
- Statistical results:
- Remarks: The pH values during the study ranged from 7.0 to 7.8 (average 7.47).

CONCLUSIONS
- IPA has low toxicity to *Leuciscus idus melanotus*.

DATA QUALITY
- Reliability: Klimisch Code= 1.

REFERENCES
- Battelle Europe. 1993. A study of the Acute Toxicity to Fish (*Leuciscus idus melanotus*) of Isophthalic Acid.

OTHER

TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9% pure

METHOD
- Method/guideline: OECD 201
- Test type (static/other): static, algal growth inhibition test
- GLP: Yes
- Year (study performed): 1992
- Species/strain # and source: *Scenedesmus subspicatus* (Chodat, SAG 86.81); green alta; Supplier: Institu fur Pflanzenphysiologie.
- Element basis: Determination of cell number: THOMA Counting Chamber.
- Exposure period, date of start and end of the test [Duration]: 96 hours
- Analytical monitoring: HPTLC System
- Statistical methods: ANOVA with Bonferroni Multiple Range Test
- Remarks: The pH of the stock solution was adjusted prior to study initiation to 8.2 using sodium hydroxide. The authors believe that after pH adjustment Isophthalic Sodium Salt was the test material investigated..

RESULTS
- Nominal concentrations: 62.5, 125, 250, 500, and 1000 mg/L
- Measured concentrations: The analytically determined actual concentrations of the test material at the beginning of the study ranged from 102 – 121% (average of 110.38%) of the nominal concentration. After 96 hours of exposure, analyzed concentrations of the test material were relatively unchanged from measurements at 0 hours. Values were found to be within the range of 83% to 103% (average of 92.5%) of the nominal values.
- Unit: mg/L
- Element value: .
- NOEC, LOEC, or NOEL, LOEL: NOEC = ?1000 mg/L based on nominal concentrations; NOEC ? 969 mg/L based on the 96-hour average measured concentration of the highest concentration level tested.
- Was control response satisfactory: Yes
- Statistical results: Effects of IPA on cell growth were not statistically significant.
- Remarks: The pH of the test media range from 8.0 to 10.2 throughout the test period. The author concluded that the relatively high pH values at the end of the test (10.2 for control) were probably caused by the algal growth.

CONCLUSIONS
- Effects of IPA on algal cell growth were not statistically significant. Toxicity of IPA in algae is low.

DATA QUALITY
- Reliability: Klimisch Code= 1

REFERENCES
- Battelle Europe. 1993. A Study of the Toxicity to Algae (*Scenedesmus subspicatus*) of Isophthalic Acid. Study Number BE-EA-128-91-02-ALG-2.

OTHER

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (E.G., DAPHNIA)

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: 99.9% Pure

METHOD

- Method/guideline: OECD No. 202
- Test type: Acute Immobilisation Test
- GLP: Yes
- Year (study performed): 1991
- Species/Strain: *Daphnia magna* (straus) water flea
- Test details: static
- Statistical methods: descriptive
- Exposure period: 48 hours
- Remarks: Daphnids were exposed to the test substance added to water at a range of concentrations for 48 hours. The effect measured was immobilization of the daphnids. Animals were considered to be immobile if they were not able to swim 15 seconds after gentle agitation of the test container. Immobilization was recorded at 24 and 48 hours. Four replicates, each containing 5 daphnids, were run per test substance concentration. The pH of the stock solution containing test material (1000 mg/L nominal) was 4.1 before addition of base. Enough sodium hydroxide was added to bring the final pH to 7.8. The pH of test solutions was monitored at the beginning and end of the study. Values ranged from 7.7 to 7.9. The authors believe that after pH adjustment isophthalic acid and isophthalic sodium salt were the test materials investigated.

RESULTS

- Nominal concentrations: 80, 130, 220, 350, 600, and 1000 mg/L
- Measured concentrations: The analytically determined actual concentrations of the test material at the beginning of the study ranged from 91 – 105% (average of 97.8%) of the nominal concentration. After 48 hours of exposure, analyzed concentrations of the test material were relatively unchanged from measurements at 0 hours. Values were found to be within the range of 77% to 92% (average of 84.5%) of the nominal values.

Exposure time	Nominal concentration	Average Measured concentration
0	80	74.4
0	350	340
0	1000	1022
48	80	67
48	350	286
48	1000	876

- Unit: mg/L
- EC_{50}, EL_{50}, LC_0, LL_0, at 48 hours: EC0(48 hr) = 1000 mg/L, EC50 (48 hr) = could not be determined, NOEC > = 1000 mg/L based on nominal concentrations. EC0 (48 hr) = >876 mg/L based on the 48 hour average measured concentration of the highest concentration level tested.
- Statistical results:
- Remarks:

CONCLUSIONS

- The acute toxicity of IPA to *Daphnia magna* is low.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- Battelle Europe. 1993. A Study of the Acute Immobilisation to DAPHNIA of Isophthalic Acid.

OTHER

TOXICITY TO BACTERIA

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9% pure

METHOD
- Method/guideline: OECD 209
- Test Type: activated Sludge, Respiration Inhibition Test
- GLP: Yes
- Year (study performed): 1991
- Innoculum: Activated sludge from a sewage plant
- Remarks : Test substance and positive control were tested at different concentration in the the test solution containing 16 ml of sewage feed, 200 ml of inoculum and deionized water to give a final volume of 500 ml. IPA was tested at 0, 1, 10, 100, 500, 1000, 2000, and 4000 mg/l . Test solutions were aerated with compressed air for 3 hours. After 3 hours test solutions were poured into an oxygen bottle and oxygen consumption was measured for 10 minutes.

RESULTS.
- EC_5: 158.3 mg/l
  EC_{25}: 353.3 mg/l
  EC_{50}: 617.1 mg/l
  EC_{75}: 1077.9 mg/l
  EC_{95}: 2405.4 mg/l
- Remarks: Respiration rates were not inhibited at concentrations in the range of water solubility of the test material (130 mg/l). Bacteria were inhibited beginning at 158.3 mg/l (EC_5). This inhibition may be due to pH shift in the solution. Positive control substance (3,5-dichlorphenol) exhibited an EC50 of 11.0 mg/l.

CONCLUSIONS
- The EC50 for for IPA was 617.1 with a 95% confidence interval: 525.2 – 725 mg/l.

DATA QUALITY
- (1) Reliable without restrictions

REMARKS

REFERENCES
- Battelle Europe. 1991. Study on the "Toxicity of Isophthalic Acid towards Bacteria According to OECD-Test Guideline 209 (Activated Sludge, Respiration Inhibition Test. Study No: BE-EA-128-91-01-BHT-02.

OTHER

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD
- Method/guideline: Acute oral toxicty
- Type (test type): Acute oral toxicity study
- GLP: Yes
- Year (study performed): 1990
- Species/Strain: Sprague-Dawley Rats
- Sex: male/female
- No. of animals per sex per dose: 5 males and 5 females/group
- Vehicle: water (reverse osmosis-purified)
- Route of administration: oral (gavage)
- Concentrations: A 33% (W/V) aqueous suspension of the test article was administered by oral gavage at a dosing volume of 15 ml/kg of body weight.
- Remarks: Limited gross necropsy was performed on all animals.

RESULTS
- LD50 Value: > 5000 mg/kg of body weight
- Number of deaths at each dose level: 0
- Remarks: No deaths occurred during the study. Signs observed within 24 hours following test article administration included irritability, salivation, redness around the nose, discoloration around the mouth, diarrhea, wet and/or discolored inguinal fur and discolored paws. All clinical signs observed were minor in nature and mostof the rats appeared normal 48 hours following test article administration.

Observations	Incidence	
	Males	Females
Irritability	0	1
Salivation	1	0
Diarrhea	5	5
Redness around the nose	5	3
Discoloration around the mouth	3	0
Wet inguinal fur	2	0
Discolored inguinal fur	5	1
Discolored paws	2	0

CONCLUSIONS
- The acute oral toxicity of IPA is relatively low.

DATA QUALITY
- Reliability: Klimisch Code= 1

REMARK
- Multiple acute toxicity studies were available for isophthalic acid all of which indicate the IPA has a relatively low acute toxicity. This study was chosen as the key study because it is the most current oral GLP study available. The oral route was chosen over the routes because it allows for the highest potential internal dose.

REFERENCES

- IIT Research Institute. 1990. Acute Oral Toxicity Study of Isophthalic Acid in Rats. Study No. 1553.

OTHER

- Oral LD50 (albino rat) = 12,200 mg/kg (Industrial BIO-TES T Laboratories, Inc., 1958).
- Oral LD50 (rat) = 13,000 mg/kg (Industrial BIO-TEST Laboratories, Inc., 1975).
- Oral LD 50 (rat = 10,900 mg/kg (Industrial BIO-TEST Laboratories, Inc., 1975).
- Oral LD50 (rat) = 10,400 mg/kg Marhold 1986
- 4-Hour Acute inhalation LC50 > 11,400 mg/m3 (Industrial BIO-TEST Laboratories, Inc., 1958).
- Acute Dermal LD50 > 2000 mg/kg IITRI 1990
- Acute Dermal LD50 >23,000 mg/kg (Industrial BIO-TEST Laboratories, Inc., 1958).

HEALTH ELEMENTS

ACUTE TOXICITY

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD

- Method/guideline: Primary Eye Irritation
- Type (test type): Eye irritation
- GLP: Pre GLP
- Year (study performed): 1985
- Species/Strain: New Zealand Albino rabbit
- Sex: male/female
- No. of animals per sex per dose: 3 males and 3 females
- Vehicle: none
- Concentrations: 0.1 grams of undiluted IPA
- Remarks: IPA was administered undiluted at a dose of 0.1 grams into one eye of each of six rabbits, with the other eye serving as the untreated control. The treated eye was scored for irritation at 1, 2, 3, 4, 7, and 14 days following test article administration. Irritation was scored using the Draize method. A reaction was considered positive if at any observation period, the test article produced ulceration or opacity of the cornea (cornea score > than 0), inflammation or slight circumcorneal injection of blood vessels of the iris (iris score > 0), any obvious conjunctival swelling with partial eversion of the lids (chemosis score 2 or greater), or conjunctival erythema of diffuse crimson red (erythema score 2 or greater) with individual vessels not easily discernable

RESULTS

- Slight ocular irritation was seen in all rabbits during the study, but only three rabbits exhibited positive reactions. All scores for cornea and iris were zero.

Conjunctiva scores (A=erythema, B=chemosis, C=discharge)

Sex	Day 1			Day 2			Day 3			Day 4			Day 7			Day 14		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
M	1	2	1	1	1	0	0	0	0	0	0	0		0	0	0	0	0
M	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
F	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
F	2	2	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0
F	2	1	0	1	1	0	0	1	0	0	1	0	0	0	0	0	0	0

The maximum eye irritation score of 5.3/110 was obtained 1 day after administration of test article. Complete recover was evident by the final scoring.

CONCLUSIONS

- IPA is slightly irritating to eyes.

DATA QUALITY

- Reliability: Klimisch Code= 1

REMARK

- Multiple eye irritation studies were available for isophthalic acid. This study was choosen as the key study because it is the most current, detailed study available.

REFERENCES

- IIT Research Institute. 1985. Primary Eye Irritation Study of IPA in Rabbits. Study No. 869

OTHER

ACUTE TOXICITY

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD
- Method/guideline: Abbreviated Dermal Irritancy/Corrosivity Study
- Type (test type): skin irritation
- GLP:
- Year (study performed): 1990
- Species/Strain: New Zealand White rabbit
- Sex: male/female
- No. of animals per sex per dose: 2 males and 1 females
- Vehicle: none
- Concentrations: 0.5 grams of undiluted IPA
- Remarks: IPA was administered undiluted at a dose of 0.5 grams to the shaved backs of three rabbits. The application site was covered with an adhesive dressing. After 4 hours the dressings were removed, the application site was rinsed with 0.9% saline and dried. The skin of the animal was scored for irritation at 30-60 minutes, 24, 48, and 72 hours following removal of the wrappings. Skin reactions were graded according to the Draize method.

RESULTS
- There was no evidence of edema, erythema and or eschar formation in any of the test animals at any of the time points. The irritation score was 0.0/8.0 at all time points, the primary dermal irritation score was 0.0.

CONCLUSIONS
- IPA is not a skin irritant.

DATA QUALITY
- Reliability: Klimisch Code= 1

REMARK
- Multiply irritation studies were available for IPA all of which showed similar findings. This study was chosen as the key study because it was the most recent and follows current protocols.

REFERENCES
- IIT Research Institute. 1990. Abbreviated Acute Dermal Irritancy/Corrosivity Study of Isophthalic acid in Rabbits. Study No. 1552

OTHER

REPEATED DOSE TOXICITY

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remark: Purity not stated in the report though purity was generally greater than 98.5% at the time of the study.

METHOD

- Method/guideline followed: Subacute feeding study
- Test type: Oral repeated-dose toxicity study
- GLP (Y/N): Pre-GLP
- Year (study performed): 1972
- Species: Rat
- Strain: Wistar-derived stock
- Route of administration: oral (diet)
- Duration of test: 13 weeks
- Doses/concentration levels: 0, 0.5, 1.6, and 5.0%
- Sex: male & female
- Exposure period: 13 weeks
- Frequency of treatment: daily
- Control group and treatment: feed
- Post exposure observation period: 0
- Statistical methods: descriptive
- Remarks field for Test Conditions. Assumes a default food intake of 0.05 kg/kg body weight-day for rats, the feed concentrations correspond to doses of 0, 250, 800, and 2500 mg IPA/kg body weight-day, respectively. Following the first week of the study the weight gains of the rats were examined. It was concluded that the 5% dose level would not permit growth. Therefore the high dose was reduced to 3% or approximately 1500 mg/kg.
- Test Subjects
  - Age at study initiation: 28 days
  - No. of animals per sex per dose: 450 rats total, 25 males and 25 females in both control groups, the remainder equally distributed across test groups.
- Study Design
  - Vehicle: feed
  - Clinical observations performed and frequency: daily
  - Organs examined at necropsy: Liver, spleen, stomach, small intestine, large intestine, pancreas, kidneys, ureters, urinary bladder, adrenals, gonads, thyroids, pituitary, thymus, salivary gland, lymph nodes, heart, lungs, bone marrow, skin, skeletal muscle, and brain.

RESULTS

- NOAEL (NOEL): 250 mg/kg-day
- LOAEL (LOEL): 800 mg/kg-day
- Toxic response/effects by dose level:

	Incidence			
Approximate Dose (mg/kg-day)	**Renal Pathology**		**Crystalluria***	
	Male	**Female**	**Male**	**Female**
0	1/25	4/25	0/5	0/5
250	1/25	5/25	0/5	0/5
800	5/25	4/25	1/5	2/5
2500/1500	4/25	7/25	3/5	3/5

* Only five animals per test group were evaluated for crystalluria.

Levels of 1.6% (approximately 800 mg/kg-day) in the feed produced small increases in the incidence of crystalluria (1/5 males, 2/5 females) and renal pathology (mild hydronephrosis and pelvic calcification) 5/25 males 4/25 females.

CONCLUSIONS

- No adverse responses associated with the ingestion of IPA on total or differential leukocyte counts, total erythrocyte counts, hemoglobin, or hematocrit levels were noted. In addition, no adverse effects were noted on blood urea nitrogen, fasting blood glucose, serum glutamic pyrumic transaminase, or serum alkaline phophatase levels. Examination of organs at necropsy revealed no effect of treatment. This study identifies a NOAEL of 250 mg/kg-day and a LOAEL of 800 mg/kg-day based on a small increase in the incidence of kidney effects and crystalluria.

DATA QUALITY

- Reliability: (1) valid without restriction

REMARK

- Only one other repeat dose study was available for isophthalic acid, which was a 4-week inhalation study (IITRI 1988). Both this study and the inhalation study were considered valid though this study was considered key for the repeat dose endpoint because it was of longer duration (13 weeks versus 4 weeks). The 4-week inhalation robust summary is included under the toxicokinetics heading.

REFERENCES

- Vogin, E.E. 1972 . Subacute Feeding Studies (13-week) in Rats with Dimethylterephthalate (DMT), Isophthalic Acid (LA), and Terephthalic Acid (TA). Food and Drug Research Laboratories. Incorporated, Laboratory No.0411

GENETIC TOXICITY ELEMENTS

GENETIC TOXICITY IN VITRO (Mammalian Cell Gene Mutations)

TEST SUBSTANCE

- Isophthalic Acid (IPA) Remarks: 99.9 % pure

METHOD

- Method/guideline: CHO/HGPRT Mutation Assay with Confirmation (Machanoff, et al., 1981; O'Neill et al., 1977) (OECD 476)
- Type (test type): In vitro mammalian mutation assay
- GLP: Yes
- Year (study performed): 1991
- Cells: Chinese Hamster Ovary
- Concentration levels: Initial assay - 125 (only in non-activated study), 250, 500, 1500, 2000, 3000 ug/l. Confirmatory assay – 500, 1000, 2000, 3000, 3200, 3500, 4000 ug/ml in the absence and presence of activation
- Exposure period: 5 hours
- Statistical methods: descriptive
- Remarks: Doses were selected based on a preliminary cytotoxicity test. Cells were exposed to concentrations of test article ranging from 0.5 to 5000 ug/ml in the presence and absence of activation system. Significant cytotoxicity was noted at the 5000 ug/ml concentration as indicated by the cloning efficiency (0% and 13% in the absence and presence of activation)
- Control groups: ethyl methanesulfonate, benzo(a)pyrene, DMSO
- Criteria for evaluating results: Positive in the event of a dose-dependant increase in mutant frequencies with at least two consecutive doses showing mutant frequencies which are elevated above 40 mutants per 10^6 clonable cells.
- Criteria for determination of a valid test: Cloning efficiency of the solvent an untreated controls must be greater than 50%. The spontaneous mutant frequency in the solvent an untreated controls must fall within the range of 0-25 mutants per 10^6 clonable cells. The positive control must induce a mutant frequency at least three times that of the solvent control.

RESULTS

- Cytotoxicity:

Cytotoxicity as measured by cloning efficiency relative to solvent control

Concentration (ug/ml)	**Initial Assay**		**Concentration (ug/ml)**	**Confirmatory Assay**	
	-	+		-	+
125	95	-	**500**	108	108
250	105	123	**1000**	117	112
500	102	102	**2000**	105	99
1000	-	106	**3000**	101	98
1500	107	98	**3200**	96	95
2000	111	90	**3500**	110	111
3000	87	69	**4000**	87	89

- = without activation

+ = with activation

- With metabolic activation: negative
- Without metabolic activation: negative

- Chromosomal Aberrations
  Mutant Frequency (mutants/10^6 clonable cells)

Concentration (ug/ml)	Initial Assay		Concentration (ug/ml)	Confirmatory Assay	
	-	+		-	+
Untreated	2	3.4	**Untreated**	<0.5	<0.6
Solvent	<0.5	11.9	**Solvent**	5.8	1.6
125	1.5	--	**500**	0.5	1.5
250	6.2	7.0	**1000**	7.6	2.0
500	3.8	11.6	**2000**	8.2	4.1
1000	--	7.6	**3000**	4.3	2.1
1500	4.3	0.5	**3200**	10.3	2.6
2000	20.8	2.8	**3500**	<0.5	1.5
3000	5.7	7.7	**4000**	<1	16.1
Ethyl methansulfonate	256	-	**Ethyl methansulfonate**	189	--
Benzo(a)pyrene	--	93	**Benzo(a)pyrene**	--	165

- = without activation
+ = with activation

- With metabolic activation: negative
- Without metabolic activation: negative

CONCLUSIONS

- Under the conditions of this assay, IPA was found to be negative in the CHO/HGPRT mutation assay.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- Microbiological Associates, Inc. 1991. CHO/HGPRT Mutation Assay with Confirmation. Laboratory Study Number T9410.332001.

OTHER

GENETIC TOXICITY IN VITRO (mammalian cell chromosomal aberrations)

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD

- Method/guideline: Chromosomal abberation (Preston, et al., 1981; Perry and Wolff, 1974) (OECD 473)
- Type (test type): chromosomal aberration
- GLP: Yes
- Year (study performed): 1990
- Cells: Chinese Hamster Ovary
- With and without metabolic activation.
- Concentration levels: 625, 1250, 2500, 5000 ug/ml.
- Exposure period: 12 hours (non-activated study); 10 hours (activated study)
- Statistical methods: Analysis of the percent aberrant cells was performed using the Fisher's exact test. The Fisher's exact test was used to compare pairwise the percent aberrant cells of each treatment group with that of the solvent control. In the event of a positive Fisher's test at any test article dose level, the Cochran-Armitage test was used to measure dose-responsiveness.
- Remarks: Dose levels for the chromosome aberration assay were selected following a preliminary toxicity test based on the reduction in mitotic index after treatment relative to solvent control.
- Control groups: triethylenemelamine, cylcophosphamide, DMSO
- Criteria for evaluating results: The test article was considered to induce a positive response when the percentages of cells with aberrations are increased in a dose responsive manner with one or more concentrations being statistically elevated relative to the solvent control group ($p \leq 0.05$). A significant increase at the high dose only with no dose response was considered suspect. A significant increase at one dose level other than the high dose with no dose response was considered equivocal.

RESULTS

Treatment	S-9 Activation	Mitotic Index	% Cells with Aberrations
Untreated	-	4.7	2
DMSO	-	4.9	0
625	-	3.8	0
1250	-	3.2	0
2500	-	2.7	2
5000	-	4.2	1
Triethylenemelamine	-	2.4	18
Untreated	+	8.6	0
DMSO	+	8.9	2
625	+	8.7	1
1250	+	9.5	0
2500	+	8.9	0
5000	+	9.6	2
Cylcophosphamide	+	2.4	14

- Cytotoxicity:
  - With metabolic activation: negative
  - Without metabolic activation: negative
- Chromosomal Aberrations
  - With metabolic activation: negative
  - Without metabolic activation: negative

CONCLUSIONS

- Under the conditions of this assay, IPA was found to be negative in the CHO cytogenics assay.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- Microbiological Associates, Inc. 1990. Chromosome Aberrations in Chinese Hamster Ovary (CHO) cells. Laboratory Study Number T9410.337.

OTHER

GENETIC TOXICITY IN VITRO (bacterial gene mutations)

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD

- Method/guideline: Salmonella/Mammalian-Microsome Plate Incorporation Assay with Confirmation (Ames Assay) (Ames et al., 1975; Maron and Ames, 1983) (OECD 471)
- Type: mutagenicity assay
- System of testing: Bacterial
- GLP: Yes
- Year (study performed): 1990
- Cell line: Salmonella typhimurium TA98, TA1537, TA1538, TA100; Escherichia coli WP2uvrA
- Metabolic activation: Liver S-9
- Species: Rat
- Concentrations tested: 0, 667, 1000, 3333, 6667, 10000 ug/plate
- Statistical Methods: descriptive
- Number of replicates: 3
- Positive and negative control groups and treatment: 2-aminofluorene, sodium azide, 2-nitrofluorene, DMSO
- Criteria for evaluating results (e.g. cell evaluated per dose group): For IPA to be evaluated positive, it must cause a reproducible dose-related increase in the mean revertants per plate of at least one tester strain with a minimum of two increasing concentrations of test article. For strains TA1535, TA1537, TA1538 data sets were considered positive if an increase in the mean revertants at the peak of the dose response is equal to or greater than three times the mean vehicle control value. Data sets for strains TA98 and TA100 were judged positive if the increase in mean revertants at the peak of the dose response is equal to or greater than two times the mean vehicle control value.

RESULTS

- Genotoxic effects
  - With metabolic activation: positive (TA98 and TA1538)
  - Without metabolic activation: positive (TA1538)

	Average Revertants				
Dose ug/plate	**TA98**	**TA100**	**TA1535**	**TA1537**	**TA1538**
0 +	20 / 28	120 / 177	9 / 14	10 / 7	6 / 9
-	26 / 23	151 / 131	15 / 8	8 / 7	11 / 7
667 +	26 / 39	125 / 173	9 / 10	9 / 7	10 / 13
-	37 / 19	150 / 136	11 / 10	11 / 9	10 / 8
1000 +	24 / 31	132 / 171	11 / 11	11 / 9	14 / 10
-	32 / 21	147 / 146	10 / 13	10 / 9	12 / 6
3333 +	30 / 51	131 / 192	9 / 14	17 / 17	23 / 20
-	44 / 25	150 / 142	9 / 9	11 / 16	28 / 17
6667 +	53 / 62	139 / 226	12 / 12	23 / 28	37 / 39
-	54 / 24	159 / 163	11 / 11	15 / 26	60 / 41
10000 +	57 / 93	147 / 246	8 / 8	26 / 40	52 / 75
-	79 / 28	167 / 159	11 / 10	20 / 31	65 / 44

CONCLUSIONS

- IPA did cause reproducible positive responses with tester strains TA98 and TA1538 in the presence of microsomal enzymes and with tester strain TA1538 in the absence of microsomal enzymes.

DATA QUALITY

- Reliability – Klimish Code= 1.

REFERENCES

- Microbiological Associates, Inc. 1990. Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay. Study Number: T9410.501014.

OTHER

GENETIC TOXICITY IN VITRO (Bacterial gene mutations)

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: >99.5 % pure

METHOD

- Method/guideline: Salmonella/Mammalian-Microsome Mutagenicity Test, OECD No. 471 (Ames Test) (Ames et al., 1973; Ames et al., 1975)
- Type: mutagenicity assay
- System of testing: Bacterial
- GLP: Yes
- Year (study performed): 1991
- Cell line: Salmonella typhimurium TA98, TA1535, TA1537, TA1538, TA100
- Metabolic activation: Liver S-9
- Species: Rat
- Concentrations tested: 0, 4, 20, 100, 500, 2500, 10,000 ug/plate
- Statistical Methods: descriptive
- Number of replicates: 3
- Positive and negative control groups and treatment: 2-aminofluorene, sodium azide, 2-nitrofluorene, 9-aminoacridine, benzo(a)pyrene
- Criteria for evaluating results: A dose dependent 2-fold increase in revertant colonies was considered positive.

RESULTS

- Genotoxic effects
  - With metabolic activation: positive - TA1537, TA1538, TA98
  - Without metabolic activation: positive – TA1537, TA1538, TA98

	Average Revertants				
Dose ug/plate	**TA1537**	**TA100**	**TA1535**	**TA1538**	**TA98**
0 +	7	92	5	15	22
-	8	122	6	11	22
4 +	7	106	7	13	20
-	11	137	12	8	24
20 +	7	107	6	14	23
-	7	124	7	14	24
100 +	9	99	6	14	20
-	7	127	8	13	23
500 +	13	120	7	23	19
-	10	118	6	15	25
2500 +	22	137	7	52	70
-	20	124	6	25	27
10000 +	48	218	8	151	151
-	57	188	10	133	79

CONCLUSIONS

- IPA gave a dose-dependant increase in the number of revertant colonies with the bacterial strains TA1537, TA1538, and TA98 in the absence and presence of activation.

DATA QUALITY

- Reliability – Klimish Code= 1.

REFERENCES

- Muller, W. 1991. Isophthalsaure. Study of the Mutagenic Potential in Strains of Salmonella Typhimurium (Ames Test); Study No. 91.0006.

OTHER

GENETIC TOXICITY IN VITRO (Bacterial gene mutations)

TEST SUBSTANCE
- Isophthalic Acid (IPA)
- Remarks: 99.9% pure

METHOD
- Method/guideline: OECD No. 471: Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay
- Type: reverse mutation assay
- System of testing: Bacterial
- GLP: Yes
- Year (study performed): 1991
- Cell line: Salmonella typhimurium TA98, TA1535, TA1537, TA1538, TA100
- Metabolic activation: Liver S-9
- Species: Rat
- Concentrations tested: 50, 150, 500, 1500, 5000 ug/plate
- Statistical Methods: descriptive
- Number of replicates: 3
- Positive and negative control groups and treatment: 2-aminofluorene, sodium azide, 2-nitrofluorene, dimethyle sulfoxide(DMSO), 9-aminoacridine, N-ethyl-N'-nitro-N-nitroguanidine
- Criteria for evaluating results (e.g. cell evaluated per dose group): If treatment with a test material produces an increase in revertant colony numbers of at least twice the concurrent solvent controls, with some evidence of a positive dose-relationship, in two separate experiments, with any bacterial strain either in the presence or absence of S-9 mix, it is considered to show evidence of mutagenic activity in this test system.

RESULTS
- Genotoxic effects
  - With metabolic activation: negative
  - Without metabolic activation: negative

CONCLUSIONS
- No evidence of mutagenic activity was seen at any dose level in either mutation test.

DATA QUALITY
- Reliability – Klimish Code= 1.

REFERENCES
- Huntingdon Research Centre. 1991. Amoco Isophthalic Acid 220: Bacterial Mutation Assay. AOM 2/91617.

OTHER

GENETIC TOXICITY IN VITRO (Mammalian Cell Gene Mutations)

TEST SUBSTANCE

- P.I.A. Purified Isophthalic Acid (IPA)\
- Remarks: 99.9 % pure

METHOD

- Method/guideline: Mouse Lymphoma Mutation Assay, OECD Guideline No. 476
- Type (test type): mutation assay
- GLP: Yes
- Year (study performed): 1994
- Cells: mouse lymphoma L5178Y cells
- Concentration levels: 7.5, 25, 75, 250, 750, and 2500 ug/ml (toxicity test); 150, 300, 450, 600, 750, 900, and 950 ug/ml (mutation assays)
- Exposure period: cells were incubated for 2 days following exposure
- Statistical methods:
- Remarks:
- Control groups: ethyl methanesulphonate and 3-methylcholanthrene (positive controls); DMSO (vehicle control)
- Criteria for evaluating results: A negative response was recorded if responses form the test substance were not higher than those of the vehicle control and the chemical had been tested to preset limits that included either a reduction of relative total growth to 20%, or precipitation of the test compound, or a maximum acceptable dose of 5 mg/ml.

RESULTS

- No indication of mutagenic activity was obtained in both assays (with and without S9 activation).

CONCLUSIONS

- The results of this study provide no conclusive evidence of mutagenic activity attributable to P.I.A. Purified Isophthalic Acid in mouse lymphoma L5178Y cells.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- Inversk Research International Limited. 1994. P.I.A. Purified Isophthalic Acid Mouse Lymphoma Mutation Assay. IRI Project No. 755466.

OTHER

GENETIC TOXICITY IN VIVO

TEST SUBSTANCE

- In the absence of an in vivo genotoxicity study for IPA, it is believed that terephthalic acid (TPA), an isomer of IPA, may be used as a reasonable surrogate.

METHOD

- Type: Mammalian Erythrocyte Micronucleus assay (OECD 474)
- Species: Mouse
- Strain: ICR
- Sex: male and female
- Route of admin.: single intraperitoneal (ip) injection
- Exposure period: 24 and 48 hours
- Doses: 200, 400, 800 mg/kg
- Year : 2001
- GLP : Yes
- Remark: Terephthalic acid was supplied by the BP Amoco Chemicals Corporation. Purity was not noted but typically exceeds 99%. Animals were about 6-8 weeks of age at study initiation. Animals (5/sex/group) were dosed ip with vehicle (negative control), 200, 400 or 800 mg/kg TPA, or 50 mg/kg cyclophosphamide (positive control) in corn oil in a volume of 20 ml/kg body weight and were sacrificed at 24 hours. Additional animals (5/sex/group) were treated with vehicle or 800 mg/kg TPA and sacrificed at 48 hours. An additional group of 5 males and 5 females were dosed with 800 mg/kg TPA as a replacement group in case of mortality. Bone marrow samples from animals sacrificed at 24 and 48 hours were scored under oil immersion (2000 polychromatic erythrocytes (PCE) per animal) for the presence of micronuclei. The number of micronucleated normocytes per 2000 PCE was also assessed. The proportion of PCE to total erythrocytes was also recorded on a per 1000 erythrocyte basis. Statistical significance for the incidence of micronucleated polychromatic erythrocytes was determined using Kastenbaum-Bowman Tables. Criteria for a valid test: The mean incidence of micronucleated polychromatic erythrocytes must not exceed 5/1000 polychromatic erythrocytes (0.5%) in the negative control vehicle. The incidence rate in the positive control group must be significantly increased relative to the negative control ($p<0.05$, Kastenbaum-Bowman Tables).

RESULTS

- Negative. Mortality was observed in 1/15 male mice that had been treated with 800 mg/kg TPA. One mouse from the replacement group was used in place of the animal that died. Clinical signs following treatment with either dose of TPA included lethargy and piloerection. Negative and positive control animals appeared normal during the course of the study. The total number of micronuclei observed per 20000 PCE in animals treated with vehicle, 200, 400 or 800 mg/kg for 24 hours was 4, 8, 5, and 4, respectively. The incidence of micronuclei in animals treated with 800 mg/kg also did not differ from the vehicle control at 48 hours (2/20000 vs. 8/20000, respectively). There was no difference between males and females. TPA was negative in the test. The test was valid, as the incidence of micronuclei in the vehicle control was not greater than 5/1000 PCE and the number of micronucleated cells in the positive controls (382/20000) was significantly different ($p < 0.05$) from the vehicle control. Reductions (up to 9%) in the ratio of polychromatic erythrocytes to total erythrocytes were observed in some of the treated groups relative to the vehicle control, suggesting that the test article did not inhibit erythropoiesis. Greater reductions in this ratio were observed in animals treated with cyclophosphamide (25-29%).

DATA QUALITY

- Reliability: (1) valid without restriction

REFERENCES

- Bioreliance. 2001. Mammalian erythrocyte micronucleus test. Study No. AA41MJ.123.BTL for BP Amoco.

CARCINOGENICITY

TEST SUBSTANCE
- Terephthalic Acid (TPA)

METHOD
- Method/guideline followed: Two-year oral feeding study
- GLP (Y/N): Unknown
- Year study performed: 1983
- Species: Rat
- Strain: Fischer 344
- Route of Administration: Oral feed
- Duration of test: Lifetime (2 years)
- Doses/concentration levels: 0. 20, 142, 1000 mg/kg/day
- Sex: Male and Female
- Exposure period: Lifetime
- Frequency of treatment: Daily
- Control group: Yes concurrent no treatment
- Post exposure period: None

RESULTS :
- Terephthalic acid induced bladder stones were seen in 13/126 females in the high dose group. At the scheduled 6 and 12 month sacrifices, no bladder calculi were detected. At the 18 month sacrifice sand like particle or bladder calculi were only seen in two of the high dose females. There were 18/118 females with what was described as transitional cell adenomas by one pathology laboratory and epithelial hyperplasia by another. Two of these were detected in high dose females after 18 months (2/27), 15 were seen in seen in high dose females at the end of the study (15/79), and one was seen in a control female at the end of the study. None were found in the males, nor at any other dose level. It was believed that rats fed high concentrations of terephthalic acid in the diet develop bladder calculi which appear to cause chronic inflammation of the bladder epithelium, bladder hyperplasia and subsequently bladder tumours. An apparent threshold effect exists because animals exposed to lower concentrations for their lifetime do not form bladder calculi or tumors. The high dose group in this study (1000 mg/kg/day) corresponds to an approximate dietary concentration of 2.0% to 2.8% in adult Fisher rats.

CONCLUSION:
- Chronic dietary exposure to TPA resulted in an increase incidence of calculi, bladder hyperplasia, and bladder tumors at the highest dose tested (1000 mg/kg). The induction of bladder tumors is believed to be a result of injury to the bladder epithelium from the calculi formation.

DATA QUALITY
- Reliability: (1) Reliable without restrictions

REMARK
- Two carcinogenicity studies were available for TPA (the structural analog of IPA). This 1983 CIIT study was considered key because the report contained considerably more detail than did the 1974 study by Gross. However, it is important to note that both studies reported consistent results.

REFERENCE:
- CIIT (1983) Chronic Dietary Administration of Terephthalic Acid. CIIT Docket 20124

TOXICITY TO REPRODUCTION

TEST SUBSTANCE

- In the absence of a reproductive toxicity study for isophthalic acid (IPA), it is believed that a reproductive toxicity study of terephthalic acid (TPA), an isomer of IPA, is a reasonable surrogate for the effects of IPA.

METHOD

- Method/guideline followed: Reproductive toxicity study
- Test type: One generation
- GLP (Y/N): Y
- Year (study performed): 1982
- Species: Rat
- Strain: Wistar and CD
- Route of administration: oral (feed)
- Doses/concentration levels: 0, 0.03, 0.125, 0.5, 2.0, or 5% TPA in diet
- Sex: male and female
- Control group and treatment: feed
- Frequency of treatment: daily
- Duration of test: Throughout mating, gestation, lactation, and post weaning
- Premating exposure period for males: 90 days
- Premating exposure period for females: 90 days
- Statistical methods: descriptive
  Remarks: This study contrasted the toxicity of TPA in two different strains of rats. Experimental conditions were identical for both. Rats 15-17 weeks of age (n=30) were grouped housed 3/cage for the first 90 days of exposure. Body weight and feed intake were determined weekly during this time period. On Day 91, breeding pairs (n=10/sex) were housed together for 2 weeks prior to being separated. On Day 0 (delivery) the number and viability of offspring were evaluated and grossly examined. Offspring were recounted, sexed, and weighed on Day 1. These measurements were repeated at weaning on Day 21. After weaning the litters were reduced to 2/sex/dose from each of 5 litters (20 pups/dose/strain) and maintained on test diets for 30 more days (Day 51) prior to sacrifice. There were only 9 pairs of CD strain rats at the 5% diet level. Remaining animals were necropsied within a few days post weaning. At termination offspring were grossly examined and necropsied. Parental and F1 generation animals were observed 2x/day for clinical signs. Body weight gain and standard reproductive indices were assessed and statistically compared using ANOVA and Dunnett's-t-test using SAS statistical programs. Parameters evaluated consisted of: fertility index, number of offspring born per dam; number and proportion of each sex born; number (Day 0, 1, and 21) and proportion (Day 1 and 21) of each sex alive; average weight at Day 1 and 21 of all offspring and of each sex. The approximated mg/kg doses based on average feed consumption and body weight during the 90 day pre-mating period were: CD(M): 14, 59, 240, 930, 2499; CD(F): 17, 67, 282, 1107, 2783; Wistar(M): 14, 61, 249, 960, 2480; Wistar(F): 19, 78, 307, 1219, 3018.

RESULTS

- Parental Effects: Following 90 days of exposure to TPA, statistically significant decreases in food consumption were observed in CD females treated with 2% and 5%, and in both sexes of Wistars treated with 5%. Body weights were statistically decreased after 13 weeks in both sexes of CD rats on 2% and 5% TPA diets, and in males exposed to 0.03%. This effect occurred in Wistars (both sexes) only at the 5% level. There were 5 deaths (3 CD females, 1 Wistar/sex) reported during weeks 4-13 in animals given 5% TPA in the diet. During the one-generation component of the study 3 CD (1 male at 2.0%, 1/sex at 5.0%) and 4 Wistar female (2 at 5.0% and 2 at 0.03%) rats died. There was no effect of treatment on fertility index and litter size.

- Offspring Effects: There were no effects of treatment on litter size, sex ratio, or total number of offspring. While no control offspring were found dead on Day 0, 17 Wistar pups (1 at 0.03%, 2 at 0.125%, 1 at 0.5%, 12 at 2.0% (2 from one dam and 10 from another)) and 23 CD pups (1 at 0.5%, 7 at 2.0% (3 dams) and 15 at 5.0% (3 dams; with 11 from one of them)) were found dead. No statistical differences were noted in viability on Days 0, 1, or 21 in either strain. In CD rats, survivability on Day 21 was reduced in both sexes of offspring whose parents had been exposed to 5% TPA in the diet. In Wistar rats, body weights of both sexes of offspring from dams given 5.0% were reduced at Day 1. On Day 21, body weight was reduced in both strains of offspring from dams that ingested 5% TPA in the diet. Increased postnatal deaths on Day 1 and decreased survivability to Day 21 were noted in the 2% and 5% groups. At these dose levels, several large litters of pups were lost to dams suffering obvious signs of toxicity. Several of these dams did not allow the pups to nurse or attend to the litters. These pups were noted not to have milk in their stomachs and presented clinically as being very weak. These dams were consuming dietary levels of TPA known to cause reduced feed consumption, diarrhea and gastric trichobezoars (hairballs) and induce the formation of renal and bladder calculi. Unscheduled deaths during the postweaning period (Day 21-51) were confined to the 5% TPA group (18 Wistar and 16 CD) and were associated with a very high incidence of renal and bladder calculi. Renal and bladder calculi were noted in all animals exposed to 5% that were necropsied at Day 21. Day 51 necropsy findings also reported a very high incidence of renal and bladder calculi and the histological sequelae of the presence of the calculi.

	Response – CD Rats		
Percent in diet	**Viability of Offspring - # alive/litter – 21 days**	**Average weight (g), male and female combined – day 21**	**Renal and Bladder Calculi in offspring**
0	9.6	58.1	0
0.03	10.1	50.7	0
0.125	11.2	55.1	0
0.5	10.3	52.2	0
2.0	7.8	45.4	1m, 1f
5.0	5.8	25.2	5m, 9f

REMARK

- Other studies have demonstrated an increased incidence of renal and bladder calculi formation in weanling animals when compared to adults consuming the same dietary level of TPA. This apparent increase in sensitivity can be explained by the large amount of feed consumed in relation to body weight for young animals experiencing their growth spurt. Weanling animals are not more sensitive to TPA when the results are expressed on a mg/kg basis.

CONCLUSIONS

- The NOAEL for reproductive toxicity was >5% in the diet (approximately 2480-3018 mg/kg-day). Whereas, the NOAEL for parental and F1 generation toxicity was 0.5% (approximately 240-307 mg/kg-day) TPA in the diet.

DATA QUALITY

- (1) reliable without restriction

REMARK

- This study was chosen as the key study because it was the most extensive/detailed reproductive study available (90-day repeat dose one generation repro study in two strains of rat).

REFERENCES

- Gibson, J.E., 1982. A Ninety Day Study of Terephthalic -Induced Urolithiasis and Reproductive Performance in Wistar and CD Rats. Research Triangle Institute Experimental Pathology Laboratories Inc. Chemical Industry Institute of Toxicology.

OTHER

DEVELOPMENTAL TOXICITY/TERATOGENICITY

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD

- Method/guideline: Segment II Inhalation Teratology Study
- GLP: yes
- Year (study performed): 1991
- Species: Rat
- Strain: Sprague-Dawley
- Route of administration: inhalation (particulate aerosol)
- Doses/concentration levels: 0, 1.0, 5.0, and 10.0 mg/m^3
- Sex: Female
- Number of pregnant females per dose: Control-16; 1.0–18; 5.0–18; 10.0–18.
- Exposure period: Gestation days 6-15
- Frequency of treatment: 6 hr/day, 7 days/week
- Control group and treatment: Filtered Air
- Duration of test: 10 consecutive exposures
- Statistical methods: Descriptive
- Remarks: All dams were subjected to a Cesarian section and gross necropsy. The uterine horns, fetuses and ovaries were removed intact trimmed and weighed. Ovaries were removed and the corpora letea were counted. Fetuses were individually weighed after the total number and disposition of each implant was recorded. Each fetus received a gross external morphological examination. One-half of each litter was randomly assigned to receive either a skeletal or a wet visceral examination.

RESULTS

- Clinical Observations: Salivation, hair loss and the forelimbs and red material around the nose/eyes/face were evident in all groups, with the incidence of these observations being similar in all groups. Discolored paws was more prominent in the exposure groups, however, the etiology of this is unknown, One dam in the $1mg/m^3$ group exhibited signs of aborting on gestation days 11-19. This observation was not considered treatment related since it was confined to only one rat in the low dose group. All other clinical signs were sporadic in nature and of similar incidence in the exposed and control dams.
- Maternal toxicity: 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.
- Developmental toxicity: 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

Parameter	Study Group Isophthalic Acid mg/m^3			
	Control	1	5	10
Average Litter size	11.6	11.2	13.4	10.7
Male : female ratio	0.8:1	0.9:1	0.9:1	0.9:1
Mean resorptions	1.12	1.12	0.83	1.17

- Remarks: The gravimetrically determined time-weighted average concentrations corrected for respirability, were 0, 0.98, 4.23, and 9.07 mg/m^3 for control, low medium and high dose, respectively. UV spectrophotometric corrected TWA concentrations were 0, 0.99, 4.35, and 9.14 mg/m^3,

respectively. The mass median aerodynamic diameter was 4.52, 5.02, and 5.59 microns for the low, medium and high dose, respectively. NOAEC = 10 mg/m^3; LOAEC = none identified.

CONCLUSIONS

- Inhalation exposure of pregnant rats to IPA during the major organogenesis period did not result in any significant toxic or teratogenic effects in the dam or fetus.

DATA QUALITY

- Reliability: Klimisch Code= 1

REFERENCES

- ITT Research Institute. 1991. A Segment II Inhalation Teratology Study of Isophthahlic Acid (IPA) in Rats. Study No. 1463.

OTHER

HEALTH ELEMENTS

REPEAT DOSE/TOXICOKINETICS

TEST SUBSTANCE

- Isophthalic Acid (IPA)
- Remarks: 99.9 % pure

METHOD

- Method/guideline: Subchronic Inhalation
- Type (test type): Subchronic Inhalation
- GLP: No
- Year (study performed): 1988
- Species/Strain: Sprague-Dawley Rats
- Sex: male/female
- No. of animals per sex per dose: 10 males and 10 females/group
- Exposure period: 4 weeks
- Frequency of Treatment: 6 hours/day 5 days per week
- Route of administration: Inhalation
- Dose/Concentrations: 1.0, 5.0, and 10 mg/m^3
- Control group Treatment: Filtered air
- Post exposure observation period: 3 weeks; 5 rats per sex designated for pre-exposure, single exposure, and weekly serum analysis for IPA were included in the control and high exposure groups. These animals were retained for 3 weeks after the last exposure to monitor diminishing serum levels of IPA.
- Statistical methods: Means and standard deviations were calculated for all quantitative parameters. Data were log transformed and statistically analyzed using both multivariate and univariate two-factor fixed effects analysis of variance (ANOVA). Body weights were evaluated using a multivariate repeated-measures analysis of variance to determine the shape of the dose response relationship over time.
- Remarks: Serum samples were collected immediately pre exposure, immediately after the first exposure, and weekly thereafter for the duration of the exposure (4 weekly samples). Samples were collected one week after the last exposure and were found to have returned to zero so no additional samples were collected.
- Study Design
  - Clinical Observations performed and frequency: Daily
  - Organs examined: Liver, spleen, duodenum, jejunum, ileum, cecum, colon,, pancreas, kidneys, urinary bladder, adrenals, gonads, epididymides, eyes, esophagus, thyroids, pituitary, thymus, salivary gland, lymph nodes (mandibular, respiratory, and mesenteric), mammary gland, nasal turbinates, prostate and seminal vesicles, sciatic nerve, spinal chord, sternum, stomach, tongue, trachea, uterus, ear, heart, lungs, femur and bone marrow (smear), skin, skeletal muscle, and brain.

RESULTS

- NOAEL (NOEL): 10 mg/m^3
- Remarks: The analytical time weighted average concentrations were 0, 0.96, 4.59, and 9.59 mg/m3. The average particle size was 5.04, 5.59, and 5.74 microns for the low, medium, and high group respectively. The proportion of respirable size particles (</= 10 microns) averaged 87.9% overall and 91.6%, 87.4%, 84.6% in the low medium and high exposure chambers, respectively. There were no treatment related deaths in any exposure group. Redness around the nose/eyes was increased in the exposed rats, but other minor adverse clinical signs were evenly distributed across all groups. No statistically significant differences between control and test article treated groups were detected with regard to body weight, clinical chemistry, hematology, absolute or relative organ weights or lung volumes. There were no significant difference between control and treated groups with respect to histopathology.

Blood level of IPA were detected immediately following exposure in rats exposed to 10 mg/m^3 for 6 hours/day. Levels remained elevated during the exposure period. Serum concentrations detected in female rats (5.3-9.3 ug/ml) were consistently higher than the concentrations detected in male rats (1.4-3.4 ug/ml). One week following exposure, IPA was not detected in the blood. IPA was not detected in the serum of any untreated rats.

IPA Serum Levels (ug/ml) for 10 mg/m^3 exposure group

Number of exposures	0	1	6	11	16	20	1-week post exposure
Male	0	2.9	2.9	3.4	2.7	1.4	0
Female	0	5.5	5.3	9.3	7.5	7.3	0

CONCLUSIONS

- The NOAEL for this study was 10 mg/m^3, the highest dose tested. IPA blood levels were detected immediately following the first exposure to 10 mg/m^3 and remained elevated during the exposure period. The data suggest that a steady state is achieved fairly rapidly (on the first day of exposure) and clearance is complete within one week.

DATA QUALITY

- Reliability: Klimisch Code= 1

REMARK.

REFERENCES

- IIT Research Institute. 1988. Four-Week Inhalation Toxicity Study of Isophthalic acid in Rats. Study No. 1301.

OTHER

- Food and Drug Research Laboratories. 1972. Subacute Feeding Studies (13-week) in Rats with Dimethylterephthalate (DMT), Isophthalic Acid (LA), and Terephthalic Acid (TA).

TOXICODYNAMICS

TEST SUBSTANCE

- Isophthalic Acid (IPA)/Terephthalic acid
- Remark: Purity not stated in the report though purity was generally greater than 98.5% at the time of the study.

METHOD

- Method/guideline followed: Subacute feeding study
- Test type: Oral repeated-dose toxicity study
- GLP (Y/N): Pre-GLP
- Year (study performed): 1972
- Species: Rat
- Strain: Wistar-derived stock
- Route of administration: oral (diet)
- Duration of test: 13 weeks
- Doses/concentration levels: 0, 0.5, 1.6, and 5.0% IPA, TPA 5.0%
- Sex: male & female
- Exposure period: 13 weeks
- Frequency of treatment: daily
- Control group and treatment: feed
- Post exposure observation period: 0
- Statistical methods: descriptive
- Remarks field for Test Conditions. Assumes a default food intake of 0.05 kg/kg body weight-day for rats, the feed concentrations correspond to doses of 0, 250, 800, and 2500 mg IPA/kg body weight-day, respectively. The corresponding dose for TPA was 2500 mg/kg body weight. Following the first week of the study the weight gains of the rats were examined. It was concluded that the 5% dose level would not permit growth. Therefore the high dose was reduced to 3% or approximately 1500 mg/kg. Blood and urine samples were collected from rats in each group at 7, 30, 60, and 90 days after initiation of the test feeding.
- Analytical Method: Samples were diluted in water and pH adjusted to 9.5 with NaOH. Samples were dehydrated. Samples were then trans-esterified with trimethylphosphate in pyridine, and esters were extracted with chloroform. Samples were analyzed by gas chromotoraphy and results compared to a standard curve
- Test Subjects
  - Age at study initiation: 28 days
  - No. of animals per sex per dose: 5 rats per sex per group for days 7 and 90 and 3 rats per sex per group for days 30 and 60..
  - Vehicle: feed

RESULTS

IPA and TPA blood levels (micrograms/ml)

Level	7-Day		30-Day		60-Day		90-Day	
	M	F	M	F	M	F	M	F
IPA 0.5%	-	-	8.75	7.51	26	27.1	3.4	ND
IPA 1.6%	29	37.1	16.3	25.3	9.6	24.6	17.5	21.3
IPA 5%/3%	97	114	32	30	17.9	31.2	26.3	40.8
TPA 5%/3%	75	54	13.7	14.2	3.1	trace	15.3	7.5

(Limit of detection (5.0 micrograms/ml)

24 Hour Urine excretion of IPA and TPA (mg/24 hours)

Level	7-Days		30-Days		60-Days		90-Days	
	M	F	M	F	M	F	M	F
IPA 0.5%	40	65	33	18	62	73	64	69
IPA 1.6%	114	110	178	87	162	153	103	95
IPA 5%/3%	200	347	162	50	177	243	159	198
TPA 5%/3%	100	54	57	61	73	188	209	270

(Limit of detection 2 micrograms/ml)

CONCLUSIONS

- Blood levels of IPA and TPA (determined as total mg phthalate/ml) increased in a dose dependant manner on days 7, 30, 60, and 90. IPA and TPA levels were generally highest during the first week of exposure and declined during the course of the study, suggesting either a change in feed consumption rates or some sort of adaptation resulting in increased clearance. 24-hour urinary excretion data collected on day 7, 30, 60, and 90 indicate that urinary excretion, presumably as unchanged chemical is the primary pathway by which IPA and TPA are eliminated from the body.

DATA QUALITY

- Reliability: (1) valid without restriction

REMARK

REFERENCES

- Vogin, E.E., 1972 Subacute Feeding Studies (13-week) in Rats with Dimethylterephthalate (DMT), Isophthalic Acid (LA), and Terephthalic Acid (TA). , Food and Drug Research Laboratories, Incorporated, Laboratory No. 0411.