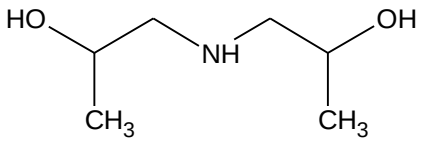
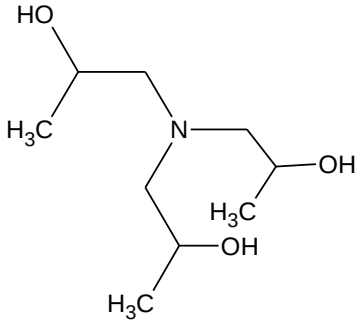
SIDS INITIAL ASSESSMENT PROFILE

Category Name	**Isopropanolamines category**
Chemical Names and CAS Nos.	**1,1'-Iminodipropan-2-ol (Diisopropanolamine, DIPA)** (CAS No. 110-97-4) **1,1',1"-Nitrilotripropan-2-ol (Triisopropanolamine, TIPA)** (CAS No. 122-20-3)
Structural Formulas	DIPA  TIPA 

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

DIPA and TIPA are the secondary and tertiary amine analogues, respectively, of the isopropanol amines series of compounds differing by a single, common substituent, isopropanol.

These chemicals can be included in a single category for several reasons. Both have similar chemical structures and exhibit physico-chemical properties that are either very similar or that reflect incremental changes expected for an alcoholic amines series. Environmental fate characteristics are also similar, with the exception of biodegradation. DIPA is considered readily biodegradable but TIPA is not; however, TIPA will biodegrade to different extents under various conditions. Regarding mammalian toxicity, both compounds are skin and eye irritants, both target the kidney in repeated-dose studies (with the larger molecule showing greater toxicity), and both exhibit similarly low toxicity for other endpoints.

Physical-Chemical Properties

DIPA is a solid with a measured melting point of 42 °C, a measured boiling point of 249 °C at 1013 hPa, a measured vapour pressure of 0.00107 hPa at 25 °C, and a dissociation constant (pKa) of 9.1 at 25 °C. The octanol-water partition coefficient (log K_{ow}) is -0.79, and the measured solubility is 870 g/L at 25 °C. TIPA is also a solid with the measured melting points range from 45-50 °C. Its measured boiling point is 305 °C at 1013 hPa, a measured vapour pressure of 0.000013 hPa at 25 °C, and a dissociation constant (pKa) of 8.06 at 25 °C. The octanol-water partition coefficient (log K_{ow})of TIPA is -0.15, and miscible with water at 25°C.

Human Health

The absorption, distribution, and excretion of DIPA have been studied in rats after dermal administration. A single dermal dose of 19 mg ^{14}C-DIPA/ kg bw was applied to the shaved skin on the back of rats for up to 48 hrs. Only 16.2% of the 14C-DIPA was absorbed representing an absorption rate of less than 0.3% of the dose per hour. The main route of

elimination was via the urine with minor amounts in the feces and no accumulation in the tissues. DIPA was also administered at 19 mg/kg intraveneously in rats where 96.8% of dose was excreted unchanged in the urine after 48 hrs.

Metabolism and excretion of TIPA was assessed in an OECD TG 417 oral study in male rats, in which single oral doses of 10.7 mg ^{14}C-TIPA/kg bw were administered. Radioactivity peaked in the plasma at 0.25 hrs post-dosing and rapidly declined. Approximately 80% of the dose was excreted in 24 hours in the urine as unchanged TIPA. Minor amounts were eliminated in the feces and in the expired air with less than 1% remaining in the tissues or carcass.

The most reliable study for acute oral toxicity indicates LD_{50} values between 2000 and 3980 mg/kg bw in rats for DIPA. For TIPA, two studies of acceptable quality indicate LD_{50} values in rats of 5994 and 6500 mg/kg bw. Rats administered TIPA showed signs of lethargy, and at the highest TIPA dose, rats had pale watery eyes and diarrhea. The dermal 24-h LD_{50} values in rabbits were 8000 mg/kg bw for DIPA and > 5000 mg/kg bw for TIPA.

In an OECD TG 404 study, no skin irritancy was reported in rabbits in which undiluted DIPA was in semi-occluded contact with the intact skin for at least 4 hours, but after prolonged occluded exposure using 10% or undiluted DIPA on intact or abraded skin, hyperemia and necrosis or denaturation were seen in rabbits. In an OECD TG 404 study, undiluted TIPA was also not irritating to rabbits after a 4-h exposure using semiocclusive conditions. After prolonged covered contact of TIPA on rabbit skin, irritation (redness, swelling and scar formation) was observed. In separate OECD 405 guideline studies, undiluted DIPA and TIPA in the eyes of rabbits after exposure for 72 hours, resulted in irritation with severe effects in some animals.

No sensitisation potential was observed in screening tests involving repeated dermal applications of 50 % DIPA or 22% TIPA in guinea pigs.

Repeated dose studies have been conducted with DIPA in rats and TIPA in dogs and rats. In a repeat-dose oral toxicity study (OECD 408), rats (10/sex/dose) were administered DIPA at approximately 0, 100, 500 or 1000 mg/kg bw/day in their drinking water for 90 days. Another group (10/sex) was given untreated water for 28 days after the 90-day exposure to 1000 mg/kg-bw. Decreases in food and water consumption and body weight were observed at the highest dose and were associated with increased specific gravity and decreased volume of the urine. Serum cholesterol was increased and serum phosphorous was decreased at the highest dose, which were no longer seen at the end of the recovery period. Absolute and relative kidney weights were increased at 500 and 1000 mg/kg-bw without histopathological changes. The increased kidney weight was more pronounced in males than in females. The NOAELs were 100 mg/kg-bw/day for males and 500 mg/kg-bw/day for females. Rats (5/sex/dose) were also administered DIPA via drinking water at 100, 300, 600, 1200 and 3000 mg/kg bw/day for 14 days. At 1200 mg/kg bw/day, decreased body weights in males, slightly decreased food and water consumption, and increased relative kidney weights were observed. The NOAEL was 600 mg/kg-bw/day for male and female rats.

TIPA was administered to dogs (4/sex/dose) in their diet at 0, 500, 2000 or 7500 ppm (approximately 0, 16.8, 71.2 or 272 mg/kg bw/day in males or 0, 19.7, 78.3 or 288 mg/kg bw/day in females) for 100 days. Ophthalmology, hematology, serum chemistry, urinalysis, blood methemoglobin, macroscopic and microscopic examinations, and organ weight evaluations showed no treatment-related effects, resulting in a NOAEL of 272-288 mg/kg bw/day (the highest dose tested). Rats (5/sex/dose) were also administered TIPA via drinking water at 100, 300, 600, 1200 or 2000 mg/kg bw/day for 14 days. At 2000 mg/kg bw/day, decreased body weights, slightly decreased water consumption in females, and decreased protein and albumin were observed. At 1200 mg/kg bw/day, decreased protein and albumin were observed. Decreases in glucose were observed at 300 mg/kg bw/day and higher in males and 600 mg/kg bw/day and higher in females. Finally, increased relative kidney weights were observed at 300 mg/kg bw/day reaching statistical significance at 600 mg/kg bw/day in males. Increased relative kidney weights were observed in females starting at 300 mg/kg/day and became significant at 2000 mg/kg bw/day. The NOAEL was 100 mg/kg-bw/day for male and female rats.

Rats (5/sex/dose) were administered DIPA at 0, 100, 500 or 750 mg/kg-bw for 5 days/week for 28 days dermally. Moderate erythema, edema and scabs were noted at the application site but no systemic toxicity was observed, resulting in NOAELs for dermal irritation and systemic toxicity of 100 and 750 mg/kg bw/day, respectively. When TIPA was administered dermally at 0, 300, 1000 or 3000 mg/kg bw for 5 days/week for 28 days, rats exhibited minimal thickening of skin at the highest dose. Erythema and scabs were seen in one animal each at the mid- and high-doses. The NOAEL for systemic toxicity was 3000 mg/kg bw/day and the NOAEL for local effects was 300 mg/kg bw/day.

DIPA and TIPA did not cause gene mutations in a bacterial reverse mutation assay in several strains of *Salmonella typhimurium* or in Chinese hamster ovary cells. Neither substance resulted in chromosomal aberrations in rat lymphocytes. All the studies examined activity both in the presence and absence of metabolic activation. These chemicals are not

considered to be genotoxic *in vitro*.

The carcinogenic potential of DIPA and TIPA has been investigated in two oral studies. In one study, DIPA was administered via the diet to 20 males/dose at 0 or 1% DIPA (approximately 392 to 843 mg/kg bw/day) for 94 weeks. Sixteen of twenty animals survived. There were no significant differences between tumour incidence in controls or treated groups. A 104-week dietary study with 2% TIPA in the feed of male Wistar rats did not show any histological evidence of increased liver foci. Data from these studies combined with generally negative results from *in vitro* genotoxicity assays have indicated no evidence of a carcinogenic potential of these chemicals alone. However, the studies were limited in their ability to detect tumours because they used small numbers of males only and a single dose level.

The reproductive toxicity of TIPA was investigated in a one-generation study in rats in which the test substance was administered via the diet to 25 rats/sex/dose at approximately 0, 39.7, 160 or 609 mg/kg bw/day (males) or 0, 43.7, 182 or 700 mg/kg bw/day (females) for 5 weeks prior to mating, during mating, gestation and lactation. Twenty offspring/sex/dose were also given the same doses for 90 days post-weaning. No effects were reported and the reproductive NOAEL was 609/700 mg/kg bw/day (highest doses tested). In an OECD TG 414 developmental toxicity study, pregnant female rats were administered DIPA via oral gavage at 1000 mg/kg-bw/day on gestation days 6 to 20. The maternal and developmental NOAEL was 1000 mg/kg bw/day (highest dose tested). Based on these results, DIPA and TIPA are not expected to have the potential for reproductive or developmental toxicity.

DIPA and TIPA possess properties indicating a hazard for human health (skin and eye irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

DIPA and TIPA do not possess a molecular structure that contains functional groups subject to hydrolysis under neutral ambient conditions. Based on the dissociation constants, these chemicals are expected to be largely in the protonated amine forms (conjugate acids) at pH 7. The compounds absorb light >290 nm, and therefore direct photolysis is possible. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals for DIPA is predicted to have a half-life of approximately 1.262 hours and for TIPA is predicted to be 1.035 hours when evaluated using the AOPWIN model. DIPA passed the test for ready biodegradation (OECD 301F assay). A 94% degradation of DIPA was observed within 28 days in the presence of activated sludge. TIPA, however, did not pass the test for ready biodegradation (OECD 301F assay), as it exhibited an average of 0% biodegradation based on oxygen consumption after 28 days. However, TIPA is susceptible to degradation in the environment. An aerobic metabolism study resulted in a half-life of 14.3 days with 39% mineralization in 30 days and 64% mineralization in 60 days. Another aerobic soil metabolism study resulted in a half-life of approximately 2 days with complete mineralization by 20 days.

A level III fugacity model with equal and continuous distribution to the air, water and soil compartments suggests that DIPA and TIPA will distribute mainly to the soil (62.2 and 69.4%) and water (37.8 and 30.6%) compartments, respectively, with negligible amount in the air (<0.1%) and sediment (<0.1%) compartments for both chemicals. When they are released only to water, they will distribute mainly to water (99.8%) with 0.2% to sediment and 0 % to air and soil.

Henry law's constant values for DIPA and TIPA of 6.91×10^{-11} atm-m^3/mole (7.00×10^{-6} Pa-m^3/mole) and 9.77×10^{-12} atm-m^3/mole (9.90×10^{-7} Pa-m^3/mole), respectively, at 25 °C suggests that volatilization of these chemicals from the water phase is expected to be low. The bioaccumulation potential of DIPA and TIPA is considered to be low based on log Kow values of -0.79 and -0.15, respectively, and supported by an estimated BCF value of 3 for both chemicals (BCFBAF Program (v3.00); USEPA, 2009).

The following acute toxicity test results have been determined for aquatic species:

DIPA

Fish [*Brachydanio rerio*(new name:*Danio rerio*]	96 h LC_{50} ≥1000 -≤2200 mg/L (nominal)
Invertebrate [*Daphnia magna*]	48 h LC_{50} = 277.7 mg/L (nominal)
Algae [*Scenedesmus subspicatus*]	72 h ErC_{50} = 270 mg/L(growth rate, nominal)

TIPA

Fish [*Cyprinus carpio*]	96 h LC_{50} >1000 mg/L (nominal)
Invertebrate [*Daphnia magna*]	48 h LC_{50} = 857 mg/L (nominal)

Algae [*Scenedesmus subspicatus*]	72 h ErC_{50} = 710 mg/L (growth rate, nominal)
	72 h E_bC_{50} = 50 mg/L (biomass, nominal)
	72-h NOEC = 0.64 mg/L (biomass, nominal)

The chemicals in the isopropanolamines category possess properties indicating a hazard for the environment (acute aquatic toxicity to algae (biomass) between 0.1 and 100 mg/L for TIPA). DIPA is readily biodegradable but TIPA is not readily biodegradable. The bioaccumulation potential of DIPA and TIPA is considered to be low. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

DIPA had a production and/or import volume (aggregated across companies) in the United States between 4,540 to < 22,700 tonnes during 2005 as reported to the U.S. Environmental Protection Agency through Inventory Update Reporting (IUR). Four companies reported manufacturing or importing DIPA in quantities greater than 11.35 tonnes. The number of manufacturing, processing and use sites is between 100 and 999.

DIPA and TIPA are widely used as emulsifiers, stabilizers, surfactants and chemical intermediates. Major uses of DIPA include: 1) natural gas purification as a scavenger of carbon dioxide and hydrogen sulfide, 2) personal care products such as soaps and detergents as a pH adjuster or to form emulsifiers, foam stabilizers or viscosity modifiers, and 3) industrial metalworking as a corrosion inhibitor, and lubrication enhancer to reduce friction. The major applications of TIPA include: 1) coatings as a cross-linker, acid neutralizer to improve product stability and 2) pesticides as a neutralizer and to improve product stability.

The most likely routes of occupational exposure to DIPA and TIPA are the dermal route, or by inhalation exposure to aerosols. DIPA and TIPA are both manufactured in closed systems using engineering controls that prevent the escape of liquid or vapours and minimize release to the environment. Workers who produce DIPA or TIPA, and those using it as a chemical intermediate or in product formulations, could be exposed during maintenance, sampling, testing or other procedures. The potential for exposure is reduced by engineering controls and personal protective equipment.

Because DIPA and TIPA, or DIPA- and TIPA-derived fatty acid soaps and salts may be used in a wide variety of personal care products, the most likely route of consumer exposure to DIPA and TIPA in these products would be via the dermal route although some inhalation exposure may also be possible. These chemicals are also used in herbicide/pesticide formulations and coatings formulations, which may also introduce the possibility of dermal or inhalation exposure to DIPA and TIPA. There may also be low levels of DIPA and TIPA present in process waters from manufacturing and processing sites, which are discharged to a waste water treatment system.

The chemical is stored in closed tanks, and transported in bulk tank cars or trucks, intermediate bulk containers, as well as in drum quantities. Environmental release during transport is possible in the event of a transportation accident. Releases to water or as waste may occur as a result of consumer uses. At environmental pHs (typically pH 8) they are highly water soluble.