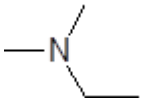
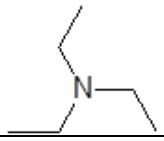
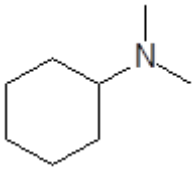
SIDS INITIAL ASSESSMENT PROFILE

[Category Name]	Tertiary Amines	
CAS No(s).	75-50-3 598-56-1 121-44-8 98-94-2	
Chemical Name(s)	Trimethylamine (**TMA**) Ethanamine, N, N-dimethyl- (**DMEA**) Triethylamine (**TEA**) Cyclohexylamine, N, N-dimethyl- (**DMCHA**)	
Structure(s)	75-50-3	
	598-56-1	
	121-44-8	
	98-94-2	

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The tertiary amines category is currently limited to the four sponsored substances mentioned above. The tertiary amines category is represented by R-N(R")-R'; with elemental compositions of only carbon, hydrogen and nitrogen. The structure has a single and tertiary amino-group, where R is an aliphatic hydrocarbon constituent that has no more than two linear carbon atoms or one cyclic group.

The nitrogen in an amine bears an unshared pair of electrons. The tendency to share these electrons underlies the chemical behavior of amines as a group. Furthermore, all category members have molecular weights of < 200 Daltons.

The category members demonstrate a consistent incremental change (trend) in number of carbon atoms, physical-chemical properties, and ecotoxicity and similar mammalian toxicity that correlate well with the structures of category members.

Specifically, the physical-chemical properties correlate well with structure, as an increase in side groups leads to an increase in melting point, boiling point and partition coefficient, and a decrease in vapor pressure and water solubility.

The aquatic toxicity of aliphatic amines is generally related to the length of the hydrophobic carbon chains (which mirrors octanol-water partition coefficient**);** the longer the chain the more toxic to aquatic organisms.

Observed corrosive properties, related to the alkaline properties of the compounds, are a general feature of the category and are the dominant effects for human health endpoints.

A read-across approach has been used for addressing the mammalian and ecotoxicity endpoints where no data were available on individual substances (as indicated in the table below).

	Mammalian toxicity endpoints			**Ecotoxicity**
Substance	Repeated dose toxicity	Effects on Fertility	Developmental toxicity	Algae
TMA	X	X	X	X
DMEA	READ ACROSS	READ ACROSS	READ ACROSS	X
TEA	X	READ ACROSS	READ ACROSS	READ ACROSS
DMCHA	X	X	X	X

Physical-chemical Properties

The physical-chemical properties correlate well with structure, as an increase in side groups leads to an increase in melting point, boiling point and partition coefficient, and a decrease in vapor pressure and water solubility. The substances are liquids except **TMA**, which is a gas, with melting points that range from -117 (**TMA**, measured) to <-77 °C (**DMCHA**, measured). The measured boiling points range from 2.9 °C at 1013 hPa (**TMA**) to 162.3 °C at 1013 hPa (**DMCHA**). Measured vapor pressures range from 3.17 hPa at 21.5 °C (**DMCHA**) to 1909 hPa at 20 °C (**TMA**). Water solubility correlates well with structure; longer chain or cyclic functionalities result in lower water solubility values. Water solubility values range from 13.4 g/L at 20 °C (**DMCHA**) to 409.6 g/L at 19 °C (**TMA**). Measured data on the log Kow are available for all members except **TEA**; modeling was used to fill this endpoint. The log Kow range from 0.245 at 25 °C (**TMA**) to 2.01 at 20 °C (**DMCHA**). The pKa values of the protonated forms of the tertiary amines in water (both measured and

estimated values) range between 9.91 and 10.75. In addition, due to the ionizing properties, water solutions of the category members are stable (substances remain in water) despite high vapor pressures. This is confirmed by pH-corrected Henry's Law constant values, which are below 1 Pa m^3/mol at pH 7. Hence, the transport of the substances from the water phase into the atmosphere is expected to be low.

Human Health

There is sufficient evidence from human and rat studies to conclude that these amines are extensively absorbed following ingestion or inhalation, and rapidly excreted, mainly in the urine, as either the parent compound and/or its N-oxide (**TMA**, **DMEA** and **TEA**). Some dealkylation may also occur. Metabolic routes for **DMCHA** were not located.

The acute 4-hour vapor inhalation LC_{50}s in rats was > 5.9 mg/L (**TMA)** and 10.9 mg/L (**TEA**) [most are equivalent or similar to OECD TG 403]. The acute 1-hour vapor inhalation LC_{50}s in rats ranged from >2.3 - <15.4 (**DMEA**) to 19.1 mg/L (**TMA**). The acute inhalation toxicity of the tertiary amines is generally characterized by local respiratory and ocular effects. **TEA** has an acute dermal LD_{50} of 580 mg/kg bw in rabbits. For rats, acute dermal toxicity ranged from 380 mg/kg bw (**DMCHA**) to > 5000 mg/kg bw (**TMA** as a 45% solution) [most are equivalent or similar to OECD TG 402]. The acute dermal toxicity of the tertiary amines is generally characterized by signs of acute systemic toxicity (such as effects on respiration, gait and posture, convulsions and ataxia, and lethargy) in moribund animals and localized signs of skin irritation or necrosis. The acute oral LD_{50}s for these substances in rats ranged from 272 – 289 mg/kg bw (**DMCHA**) to 1200 mg/kg bw (**TMA**) [most are equivalent or similar to OECD TG 401]. The acute oral toxicity of the tertiary amines is generally characterized by signs of acute systemic toxicity (such as effects on respiration, gait and posture, convulsions, tremors and ataxia, eye and nasal discharge, salivation and lethargy) in moribund animals and localized signs of gastrointestinal irritation.

The tertiary amines are generally corrosive to the skin [in studies with rabbits similar to OECD TG 404; patch tests] and eyes [in studies with rabbits similar to OECD TG 405 as well as in acute inhalation studies with rats] and are respiratory tract irritants in acute inhalation studies [in rats or mice in studies similar to OECD TG 403]. Workers who have been exposed to certain amine vapors have been known to experience a phenomenon known as "blue haze." Prominent effects on vision include dilated pupils, loss of accommodation, and corneal edema, which may result in hazy (looking through smoke) or blurry (out of focus) vision and halo perception. The exact mechanism is unknown. The visual symptoms are usually transient and rapidly decrease when removed from exposure to tertiary amine vapors.

DMEA and **DMCHA** were tested for skin sensitization in a guinea pig maximization test [similar to OECD TG 406], and **DMCHA** was tested in a mouse local lymph node assay [OECD TG 429]. These substances were negative in all of the tests. It is anticipated that the remaining tertiary amines also would not be sensitizing to the skin.

Repeated inhalation by rats (sex not specified) for 5 hrs/day for 7 months to **TMA** at 0, 0.025 or 0.075 mg/L resulted in severe lung effects and multiple effects in the liver, kidney and spleen at both doses, resulting in a systemic and local LOAEC of 0.025 mg/L. Male and female rats exposed to **TEA** via inhalation for 6 hrs/day, 5 days/week for 28 weeks did not exhibit significant effects at concentrations up to 1.02 mg/L (NOAEC); necrosis of nasal passages and squamous metaplasia in the trachea and mortality was observed in rats exposed to **TEA** for 10 days via inhalation to 4.3 mg/L (LOAEC). Male and female rats exposed to 0, 0.026, 0.10 or 0.39 mg/L **DMCHA** via whole-body inhalation for 9 exposures exhibited slight hyperplasia and hypertrophy of nasal mucosa at 0.39 mg/L and decreased body weights at all concentrations; the NOAEC was 0.104 mg/L.

Repeated oral (gavage) exposure of male and female rats to **TMA** resulted primarily in local (site of contact) effects in the gastrointestinal tract (and decreased body weight/protein levels in males) at 200 mg/kg bw/day with a NOAEL 40 mg/kg bw/day [OECD TG 422]. When **TMA** was administered in the diet as the hydrochloride salt to male rats for 90 days, the NOAEL was 79 mg/kg bw/day for **TMA** [administered as ca. 130 mg/kg bw/day as **TMA-HCl**]; site of contact effects were not observed [guideline not specified], which is expected from administration of the salt and from the fact that the substance was administered via diet and not

via gavage. At the highest dose of **TMA-HCl** (500 mg/kg bw/day), reduced size of the seminal vesicles and effects on the prostate were seen**.** Repeated dietary administration of **DMCHA** to male and female rats for $\geq$ 28 days did not produce systemic or local toxicity up to the highest dose tested [OECD TG 422]. The NOAEL was 1500 ppm (equivalent to 91-104 and 85-147 mg/kg bw/day for males and females, respectively).

Repeated dose toxicity data were not located for **DMEA**. Read across from category members **TMA** and **TEA** suggests both systemic toxicity as well as effects at the site of contact (respiratory tract or gastrointestinal tract) are expected.

Negative results are available for bacteria [similar to OECD TG 471; all category members], *in vitro* mammalian gene mutation assays (OECD 476; **TEA** and **DMEA**), *in vitro* mammalian chromosomal aberration assays [similar to OECD TG 473; **TMA**, **DMEA** and **DMCHA**], *in vitro* sister chromatid exchange [no guideline specified; **TEA**], *in vitro* DNA Damage and Repair - Unscheduled DNA Synthesis [similar to EU Method B.18; **DMCHA**] and *in vivo* micronucleus tests [OECD TG 474] (**TEA**). Based on these studies, the tertiary amines are not considered genotoxic.

No data are available for the carcinogenicity of the tertiary amines category members.

TMA [OECD TG 422], **TEA** [similar to OECD TG 413], and **DMCHA** [OECD TG 422] have been tested for effects on fertility and/or developmental toxicity. When administered orally by gavage, **TMA** had no effects on fertility or developmental parameters, and the NOAEL was 200 mg/kg bw/day (the highest dose tested) for F1 offspring. The parental NOAEL for **TMA** was 40 mg/kg bw/day, based on systemic toxicity at 200 mg/kg bw/day. At the highest dose of **TMA-HCl** (administered at 500 mg/kg-bw/day) in the 90 day dietary study in male rats, reduced size of the seminal vesicles and effects on the prostate were seen**.** Groups of male and female rats were exposed to **TEA** by whole body vapor inhalation at concentrations of 0, 0.10 or 1.02 mg/L (nominal) for 6 hours/day, 5 days/week for 28 weeks; there were no gross or microscopic findings in reproductive organs up to the highest concentration tested. Following dietary administration of **DMCHA**, the NOAEL for reproductive toxicity and parental systemic toxicity was 1500 ppm (highest dose tested, equivalent to 91-104 and 85-147 mg/kg bw/day for males and females, respectively; nominal). The NOAEL for developmental toxicity from the study was 150 ppm (8.5-15 mg/kg bw/day) based on decreased pup weights at 500 and 1500 ppm (28-49 and 85-147 mg/kg bw/day).

The tertiary amines category members possess properties indicating a hazard for human health (acute toxicity for some of the tertiary amines; corrosive to skin, eyes, respiratory tract, and/or the site of contact; some systemic toxicity at higher doses following repeated exposure of TMA and by read-across to DMEA; developmental toxicity of DMCHA limited to decreased pup weights); based on read-across, TEA and DMEA may also cause similar developmental effects by the oral route.). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

These substances are expected to be hydrolytically stable in the natural environment. The majority of the tertiary amines will likely exist as cations in water at environmentally relevant pH. It should be noted, however, that EPISuite predicts certain environmental fate endpoints in their uncharged forms. Therefore, there will be some differences between predicted and actual results.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is estimated (one measurement for **TEA**) to occur with a half-life of <1 day. Based on absorbance properties, photodegradation is expected to be negligible. Biodegradation data for all the tertiary amines category members indicate that they are readily biodegradable in standard ready biodegradation tests [OECD TGs 301A, 301C and 301D].

For the tertiary amines, EPIWIN Level III fugacity modeling predicts that, when distributed equally to air, water and soil, for most of the amines (except **TMA**), the substances will partition more towards the soil compartment

relative to the water compartment; the favored distribution towards soil increases proportionally with molecular weight of the primary amine. **TMA** will partition more towards the water compartment relative to the soil compartment. Minimal to negligible tertiary amines are predicted to partition to the air and sediment compartments. Measured BCF values for **TEA** were <0.5-5 (0.5 mg/L) and <4.9 (0.05 mg/L) [OECD TG 305C]. Estimated BCF values were <1 (**TMA**), 3.16 (**DMEA**) and 19.84-35.66 (**DMCHA**). The tertiary amine category members are not expected to bioaccumulate.

The following acute toxicity test results have been determined for aquatic species; most tests were conducted in un-neutralized conditions although a few results are available for neutralized conditions. The un-neutralized tests conditions can be considered as worst case. In those tests where the OECD guideline recommended pH limits for fish [6.0 – 8.5] and *Daphnia* [6.0 – 9.0] were exceeded at the higher test concentrations, it is possible that the observed adverse effects may have been caused by a pH shift of the test medium.

Fish

Substance	Species	96 hr LC_{50} (mg/L)	Remark
TMA	*Leuciscus idus*	48 h LC_{50} = 610	nominal; not specified; neutralized pH 7.0
	Leuciscus idus	48 h LC_{50} = 25	nominal; not specified; not neutralized pH 10.2
	Oryzias latipes	48 h LC_{50} = 1000	nominal; static; pH not specified
DMEA	*Leuciscus idus*	>100	nominal; static; neutralized pH 8
	Leuciscus idus	38.3	nominal; static; not neutralized; pH at test start: 7.9-9.5; pH at test end: 7.7-7.8
TEA	*Oncorhynchus mykiss*	36	measured; flow-through; not neutralized pH 7.2-7.3
	Danio rerio	7 d, LC_{50} = 180; $EC_{50(\text{total embrytoxicity})}$ = 53; $LOEC_{(\text{mortality})}$ = 320; $LOEC_{(\text{total embryotoxicity})}$ = 100 [note: total embryotoxicity = lethality and malformations]	nominal; flow-through; not specified
DMCHA	*Leuciscus idus*	>100	nominal; static; neutralized pH 7.8-7.9
	Leuciscus idus	31.6	nominal; static; not neutralized; pH at test start: 8.3-10.0; pH at test end: 7.9-8.0, with pH not measured at two highest concentrations due to 100% mortality
	Oncorhynchus mykiss	28	measured; static; not neutralized pH 7.2-10

Invertebrates

Substance	Species	48 hr EC_{50} (mg/L)	Remark
TMA	*Daphnia magna*	139.95	nominal; static; not neutralized; pH at test start: 8.75-10.49; pH at test end: 8.11-9.33
DMEA	*Daphnia magna*	39.23	nominal; static; not neutralized; pH at test start: 8.89-10.57; pH at test end: 8.23-9.45
TEA	*Ceriodaphnia dubia*	17	measured; semi-static; not neutralized: pH at test start 8; pH at test end > 8.5 at 3 highest concentrations (out of 5)
	Daphnia magna	200	nominal; static; not neutralized; pH not specified
	Ceriodaphnia dubia	7 d, NOEC = 7.1 mg/L	measured, semi-static; not neutralized pH 8
DMCHA	*Daphnia magna*	75	measured; static; not neutralized pH 7.6-9.4

Algae

Substance	Species	72 hr EC_{50} (mg/L)	Remark
TMA	*Desmodesmus subspicatus*	ErC_{50} = 150; EbC_{50} = 90.6	nominal; not neutralized; pH at test start: 8.1-9.7; pH at test end (uninoculated) 8.2-8.5; pH at test (inoculated) 8.5-9.9
DMEA	*Desmodesmus subspicatus*	ErC_{50} = 24.2; EbC_{50} = 17	nominal; not neutralized; pH at test start: 8.6-9.4; pH at test end (uninoculated) 8.1-8.2; pH at test (inoculated) 8.3-9.0
TEA	No data located		read-across
DMCHA	*Desmodesmus subspicatus*	ErC_{50} >2; EbC_{50} = 0.79	nominal; not specified

The following chronic toxicity test results have been determined:

Fish

Substance	Species	Result (mg/L)	Remark
TEA	*Oncorhynchus mykiss*	60d, $LOEC_{(body\ weight)}$ = 3.2 m, $LOEC_{(body\ length)}$ = 100, $LOEC_{(mortality)}$ >100, $LOEC_{(total\ embryotoxicity)}$ >100	nominal; semi-static; not specified

The tertiary amines category members possess properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). The category members are readily biodegradable and are not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

In the sponsor country (United States), several companies reported manufacturing or importing the tertiary amines:

Substance	Production Volume (metric tons)
TMA	45,400 < 227,000
DMEA	454 < 4,540
TEA	4,540 < 22,700
DMCHA	454 < 4,540

Tertiary amines can be synthesized in various ways but the reaction between ammonia and alcohols forms the basis for most of the present commercial processes for making tertiary amines.

Major uses for the category members are as follows:

TMA. as a proton scavenger, an intermediate in the synthesis of a variety of organic chemicals, surfactant, as a solvent, as a warning agent in natural gas (due to its odor), and other applications include bacteriocides, disinfectants, insect attractant. The hydrochloride salt of **TMA** is used to make specialty chemicals in the electronics industry.

DMEA. mainly in the foundry industry, as a catalyst for the production of sand cores (cold box process). It is also used in the manufacturing of pharmaceutical active ingredients, intermediates in making other compounds, casting resins, and laboratory uses.

TEA. in the production of chemicals (principally as an organic base in the preparation of quaternary ammonium products but also in the synthesis of pesticides, pharmaceuticals, paints and coatings, and corrosion inhibitors, catalyst in polymerization reactions), in gas treatment, use in foundry and mining chemicals. an extraction

solvent in pharmaceutical applications.

DMCHA. as a catalyst used primarily to promote the urethane (polyol - isocyanate) reaction in a wide range of rigid foam (insulation) applications. Other potential uses are in flexible foams, coatings, adhesives, sealants and elastomers, and a gel catalyst.

According to a survey of the American Chemistry Council Amines Panel producers, all of the members of the Tertiary Amines category are produced in closed systems. Inhalation and dermal exposure may be possible during occupational use. Primary uses of the tertiary amines are within industrial settings. However, some category members may be present in some consumer products. Some environmental releases are possible.