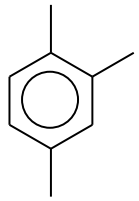
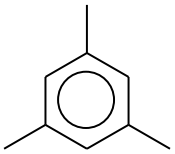
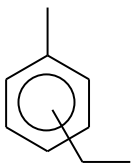
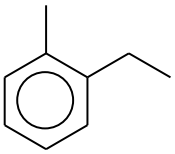
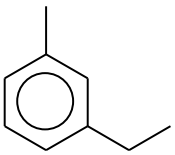
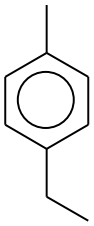
SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	C_9 Aromatic Hydrocarbon Solvents Category
CAS Numbers and Chemical Names	95-63-6 Benzene, 1,2,4-trimethyl 108-67-8 Benzene, 1,3,5-trimethyl 25550-14-5 Benzene, ethylmethyl (ethyltoluene mixed isomers) 64742-95-6 Solvent naphtha, (petroleum), light aromatic
CAS Numbers with Structural Formula	**Structural Formula** **CAS RN** C_9H_{12}  95-63-6 C_9H_{12}  108-67-8 Generalized structure; non-isomer specific: C_9H_{12} (average)  25550-14-5 Specific isomeric structures shown below:  1,2-Ethyltoluene  1,3-Ethyltoluene



1,4-Ethyltoluene

C_9H_{12} (average)

Solvent naphtha, (petroleum), light aromatic 64742-95-6

[Can contain all structures pictured above;
a UVCB substance containing aromatic molecules (one-ring) composed of carbon and hydrogen and consisting of C_9 aromatic hydrocarbons (approximately 90%). The category only includes substances with boiling ranges between ~160°C to ~175°C. The chemical substance definition is a CAS RN definition and reflects a broader boiling range (135°C to 210°C) than the hydrocarbon solvent category member with CAS RN 64742-95-6, which ranges from ~160°C to ~175°C.]

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The **C_9** Aromatic Hydrocarbons Solvents Category is comprised of a petroleum naphtha refinery stream, "Solvent naphtha, (petroleum), light aromatic," (CAS RN 64742-95-6; hereafter referred to as **C_9** aromatic naphtha), from which the other, more chemically pure members of this category are isolated. These other members include several C_9 aromatic isomers (1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, and mixed ethyltoluenes) that have relatively limited production and are used primarily as chemical intermediates. The justification for including these isolated C_9 aromatic isomers in the category includes:

1) Trimethylbenzene (TMB) and ethyltoluene (ET) isomers are major constituents in the C_9 aromatic naphtha. The C_9 aromatic naphtha, which was tested under a 1985 U.S. TSCA Section 4 test rule, was required to have a minimum total ET-TMB content of 75%. Commercial C_9 aromatic naphtha typically contains 1,2,4-trimethylbenzene at 20-45%, 1,3,5-trimethylbenzene at 8-15%, and mixed ethyltoluenes at 25-35%.

2) For category members that have data, physicochemical properties are very similar. In addition, existing data indicate that the mammalian and acute aquatic toxicity of the isolated **C_9** aromatic isomer substances are similar to the **C_9** aromatic mixture.

The four substances in this category contain >99% hydrocarbons. The composition of the C_9 aromatic naphtha substance (CAS RN 64742-95-6) will vary somewhat, but generally contains <1% aliphatics and >90% C_9 aromatic hydrocarbons. This substance may contain C_8 and C_{10} aromatic hydrocarbons, typically in the range 5-10%, though these are not considered impurities, they are constituents of the substance. This substance may contain traces of benzene (<10 ppmv), sulfur (<10 ppmv), and nitrogen (<10 ppmv); however, these chemicals are considered impurities that are intentionally removed during production. The three remaining category members typically have purities of >98%.

Analogue Justification

Human health data for 1,2,3-trimethylbenzene (1,2,3-TMB; CAS RN 526-73-8) are used to support this category. 1,2,3-TMB data can be used because the chemical is present in solvent naphtha (CAS RN 64742-95-6) at approximately 6% by weight and because 1,2,3-TMB is an isomer of two other category members (1,2,4-TMB and 1,3,5-TMB).

Physical-chemical properties

The physical properties of the C_9 Aromatic Hydrocarbon Solvents Category members are given in ranges as the substances do not differ significantly in these properties: Melting point (°C) ranges from -95.5 to -43.8; boiling

point (°C) ranges from 161.2 to 173.2; relative density (g/cm^3 at 25°C) ranges from 0.861 to 0.881; vapour pressure (hPa at 25°C) ranges from 2.80 to 4.05; water solubility (mg/L at 25°C) ranges from 40 to 75; and the log Kow (at 25°C) ranges from 3.42 to 3.90. These substances are colorless liquids at 25°C.

Human Health

Acute Toxicity

Acute toxicity studies (oral, dermal and inhalation routes of exposure) have been conducted in rats using various solvent products containing predominantly mixed C_9 aromatic hydrocarbons (CAS RN 64742-95-6). Inhalation LC50's range from 6,000 to 10,000 mg/m^3 for C_9 aromatic naphtha and 18,000 to 24,000 mg/m^3 for 1,2,4 and 1,3,5-TMB, respectively. A rat oral LD50 reported for 1,2,4-TMB is 5 grams/kg bw and a rat dermal LD50 for the C_9 aromatic naphtha is >4 ml/kg bw. These data indicate that C_9 aromatic solvents show that LD50/LC50 values are greater than limit doses for acute toxicity studies established under OECD test guidelines.

Irritation and Sensitization

Several irritation studies, including skin, eye, and lung/respiratory system, have been conducted on members of the category. The results indicate that C_9 aromatic hydrocarbon solvents are mildly to moderately irritating to the skin, minimally irritating to the eye, and have the potential to irritate the respiratory tract and cause depression of respiratory rates in mice. Respiratory irritation is a key endpoint in the current occupational exposure limits established for C_9 aromatic hydrocarbon solvents and trimethylbenzenes. No evidence of skin sensitization was identified.

Repeated Dose Toxicity

Inhalation: The results from a subchronic (3 month) neurotoxicity study and a one-year chronic study (6 hr/day, 5 days/week) indicate that effects from inhalation exposure to C_9 Aromatic Hydrocarbon Solvents on systemic toxicity are slight. A battery of neurotoxicity and neurobehavioral endpoints were evaluated in the 3-month inhalation study on C_9 aromatic naphtha tested at concentrations of 0, 101, 452, or 1320 ppm (0, 500, 2,220, or 6,500 mg/m^3). In this study, other than a transient weight reduction in the high exposure group (not statistically significant at termination of exposures), no effects were reported on neuropathology or neuro/behavioral parameters. The NOAEL for systemic and/or neurotoxicity was 6,500 mg/m^3, the highest concentration tested.

In an inhalation study of a commercial blend, rats were exposed to C_9 aromatic naphtha concentrations of 0, 96, 198, or 373 ppm (0, 470, 970, 1830 mg/m^3) for 6 hr/day, 5 days/week, for 12 months. Liver and kidney weights were increased in the high exposure group but no accompanying histopathology was observed in these organs. The NOAEL was considered to be the high exposure level of 373 ppm, or 1830 mg/m^3. In two subchronic rat inhalation studies, both of three months duration, rats were exposed to the individual TMB isomers (1,2,4- and 1,3,5-) to nominal concentrations of 0, 25, 100, or 250 ppm (0, 123, 492, or 1230 mg/m^3). Respiratory irritation was observed at 492 (100 ppm) and 1230 mg/m^3 (250 ppm) and no systemic toxicity was observed in either study. For both pure isomers, the NOELs are 25 ppm or 123 mg/m^3 for respiratory irritation and 250 ppm or 1230 mg/m^3 for systemic effects.

Oral: The C_9 aromatic naphtha has not been tested via the oral route of exposure. Individual TMB isomers have been evaluated in a series of repeated-dose oral studies ranging from 14 days to 3 months over a wide range of doses. The effects observed in these studies included increased liver and kidney weights, changes in blood chemistry, increased salivation, and decreased weight gain at higher doses. Organ weight changes appeared to be adaptive as they were not accompanied by histopathological effects. Blood changes appeared sporadic and without pattern. One study reported hyaline droplet nephropathy in male rats at the highest dose (1000 mg/kg bw-day), an effect that is often associated with alpha-2µ-globulin-induced nephropathy and not considered relevant to humans. The doses at which effects were detected were 100 mg/kg-bw day or above (an exception was the pilot 14 day oral study – LOAEL 150 mg/kg bw-day - but the follow-up three month study that had a LOAEL of 600 mg/kg bw-day with a NOAEL of 200 mg/kg bw-day). Since effects generally were not severe and could be considered adaptive or spurious, oral exposure does not appear to pose a high toxicity hazard for pure trimethylbenzene isomers.

Mutagenicity

In vitro genotoxicity testing of a variety of C_9 aromatics has been conducted in both bacterial and mammalian cells. In vitro point mutation tests were conducted with *Salmonella typhimurium* and *Escherichia coli* bacterial strains, as well as with cultured mammalian cells such as the Chinese hamster cell ovary cells (HGPRT assay) with and without metabolic activation. In addition, several types of *in vitro* chromosomal aberration tests have

been performed (chromosome aberration frequency in Chinese hamster ovary and lung cells, sister chromatid exchange in CHO cells). Results were negative both with and without metabolic activation for all category members. For the supporting chemical 1,2,3-TMB, a single *in vitro* chromosome aberration test was weakly positive. In an i*n vivo* bone marrow cytogenetics test, rats were exposed to C_9 aromatic naphtha at concentrations of 0, 153, 471, or 1540 ppm (0, 750, 2,310, or 7,560 mg/m^3) 6 hr/day, for 5 days. No evidence of *in vivo* somatic cell genotoxicity was detected. Based on the cumulative results of these assays, genetic toxicity is unlikely for substances in the C_9 Aromatic Hydrocarbon Solvents Category.

Reproductive and Developmental Toxicity

Results from the three-generation reproduction inhalation study in rats indicate limited effects from C_9 aromatic naphtha. In each of three generations (F0, F1 and F2), rats were exposed to High Flash Aromatic Naphtha (CAS RN 64742-95-6) via whole body inhalation at target concentrations of 0, 100, 500, or 1500 ppm (actual mean concentrations throughout the full study period were 0, 103, 495, or 1480 ppm, equivalent to 0, 505, 2430, or 7265 mg/m^3, respectively). In each generation, both sexes were exposed for 10 weeks prior to and two weeks during mating for 6 hrs/day, 5 days/wks. Female rats in the F0, F1, and F2 generation were then exposed during gestation days 0-20 and lactation days 5-21 for 6 hrs/day, 7 days/wk. The age at exposure initiation differed among generations; F0 rats were exposed starting at 9 weeks of age, F1 exposure began at 5-7 weeks, and F2 exposure began at postnatal day (PND) 22. In the F0 and F1 parental generations, 30 rats/sex/group were exposed and mated. However, in the F2 generation, 40/sex/group were initially exposed due to concerns for toxicity, and 30/sex/group were randomly selected for mating, except that all survivors were used at 1480 ppm. F3 litters were not exposed directly and were sacrificed on lactation day 21.

Systemic Effects on Parental Generations: The F0 males showed statistically and biologically significantly decreased mean body weight by ~15% at 1480 ppm when compared with controls. Seven females died or were sacrificed *in extremis* at 1480 ppm. The F0 female rats in the 495 ppm exposed group had a 13% decrease in body weight gain when adjusted for initial body weight when compared to controls. The F1 parents at 1480 ppm had statistically significantly decreased mean body weights (by ~13% (females) and 22% (males)), and locomotor activity. F1 parents at 1480 ppm had increased ataxia and mortality (six females). Most F2 parents (70/80) exposed to 1480 ppm died within the first week. The remaining animals survived throughout the rest of the exposure period. At week 4 and continuing through the study, F2 parents at 1480 ppm had statistically significant mean body weights much lower than controls (~33% for males; ~28% for females); body weights at 495 ppm were also reduced significantly (by 13% in males and 15% in females). The male rats in the 495 ppm exposed group had a 12% decrease in body weight gain when adjusted for initial body weight when compared to controls. Based on reduced body weight observed, the overall systemic toxicity LOAEC is 495 ppm (2430 mg/m^3).

Reproductive Toxicity - Effects on Parental Generations: There were no pathological changes noted in the reproductive organs of any animal of the F0, F1, or F2 generation. No effects were reported on sperm morphology, gestational period, number of implantation sites, or post-implantation loss in any generation. Also, there were no statistically or biologically significant differences in any of the reproductive parameters, including: number of mated females, copulatory index, copulatory interval, number of females delivering a litter, number of females delivering a live litter, or male fertility in the F0 or in the F2 generation. Male fertility was statistically significantly reduced at 1480 ppm in the F1 rats. However, male fertility was not affected in the F0 or in the F2 generations; therefore, the biological significance of this change is unknown and may or may not be attributed to the test substance. No reproductive effects were observed in the F0 or F1 dams exposed to 1480 ppm (7265 mg/m^3). Due to excessive mortality at the highest concentration (1480 ppm, only six dams available) in the F2 generation,, a complete evaluation is precluded. However, no clear signs of reproductive toxicity were observed in the F2 generation. Therefore, the reproductive NOAEC is considered 495 ppm (2430 mg/m^3), which excludes analysis of the highest concentration due to excessive mortality.

Developmental Toxicity - Effects on Pups: Because of significant maternal toxicity (including mortality) in dams in all generations at the highest concentration (1480 ppm), effects in offspring at 1480 ppm are not reported here. No significant effects were observed in the F1 and F2 generation offspring at 103 or 495 ppm. However, in F3 offspring, body weights and body weight gain were reduced by ~ 10-11% compared with controls at 495 ppm for approximately a week (PND 14 through 21). Maternal body weight was also depressed by ~ 12% throughout the gestational period compared with controls. The overall developmental LOAEC from this study is 495 ppm (2430 mg/m^3) based on the body weights reductions observed in the F3 offspring.

Conclusion: No effects on reproductive parameters were observed at any exposure concentration, although a confident assessment of the group exposed at the highest concentration was not possible. A potential developmental effect (reduction in mean pup weight and weight gain) was observed at a concentration that was

also associated with maternal toxicity.

Chemicals in this category possess properties indicating a hazard for human health (respiratory, eye, and skin irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

In the air, category member constituents have the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with calculated degradation half-lives ranging from 0.54 to 2.81 days (based on a 12-hour day and a hydroxyl radical concentration of $5x10^5$). Aqueous photolysis and hydrolysis will not contribute to the transformation of category chemical constituents in aquatic environments because they are either poorly reactive or not susceptible to these reactions.

Results of the Mackay Level I environmental distribution model show that chemical constituents of C_9 Aromatic Hydrocarbon Solvents Category members have the potential to partition to air (96.8 to 98.9 %), with a negligible amount partitioning to water (0.2 to 0.6%) and soil (0.9 to 2.7%). In comparison, Level III modeling indicates that category members partition primarily to soil (66.3 to 79.6%) and water (17.8 to 25.0%) compartments rather than air (2.4 to 8.4%) when an equal emission rate (1000 kg/hr) is assumed to each of the air, water, and soil compartments. When release (1000 kg/hr) is modeled only to either the air, water, or soil compartment, constituents are indicated in the modeling to partition primarily (>94%) to the compartment to which they are emitted as advection and degradation influence constituent concentration in compartments to which constituents are not released.

Solvent naphtha, (pet.), light aromatic (CAS RN 64742-95-6), 1,2,4-trimethylbenzene (CAS RN 95-63-6), and 1-ethyl-3-methylbenzene (CAS RN 620-14-4) were determined to be readily biodegradable based on the studies that used the TG OECD 301F (the latter substance is used to characterize the potential biodegradability of the category member, ethylmethylbenzene (CAS RN 25550-14-5)). These three substances exceed 60% biodegradation in 28 days and met the 10-day window criterion for ready biodegradation. In comparison 1,3,5-trimethylbenzene (CAS RN 108-67-8) was not readily biodegradable. It achieved 42% biodegradation after 28 days and 60% biodegradation after 39 days. The result for the multi-constituent substance (CAS RN 64742-95-6), a UVCB, characterizes the biodegradability of that substance as a whole, but it does not suggest that each constituent is equally biodegradable. As with all ready biodegradation test guidelines, the test system and study design used with these substances (OECD TG 301F) is not capable of distinguishing the relative contribution of the substances' constituents to the total biodegradation measured.

Based on Henry's Law constants (HLCs) representing a potential to volatilize from water that range from 590 to 1000 Pa-m^3/mole, the potential to volatilize from surface waters for chemicals in the C_9 Aromatic Hydrocarbon Solvents Category is expected to be high.

Based on the measured bioconcentration factors that range from 23 to 342 for 1,2,4-trimethylbenzene and 1,3,5-trimethylbenzene, the category members are not expected to be bioaccumulative.

Acute toxicity values used to characterize this category for fish (LL_{50}; LC_{50}) and invertebrates (EL_{50}; EC_{50}) range from 3.5 to 9.2 mg/L, based on measured data. For algae, one study for a category member (CAS RN 64742-95-6) resulted in a 72-hr EC_{50} of 2.4 mg/L (biomass) and 2.7 mg/L (growth rate) based on measured concentrations. The algal 72-hour NOEC (no observed effect concentration) for biomass and growth rate is 1.3 mg/L, based on mean measured concentrations. A 21-day *Daphnia magna* reproduction study with 1,3,5-trimethylbenzene (CAS RN 108-67-8) resulted in a NOEC value of 0.4 mg/L, based on a minimum measured value.

Chemicals in this category possess properties indicating a hazard for the environment (acute toxicity for fish, invertebrates, and algae from 1 to 10 mg/L). Category members are readily biodegradable, except 1,3,5-trimethylbenzene (CAS RN 108-67-8). Category members are not expected to be bioaccumulative. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Use/Exposure

Annual worldwide production of C_9 aromatic naphtha (CAS RN 64742-95-6) for solvent use is estimated at 500,00-250,000 metric tonnes. U.S. solvent applications are primarily industrial coatings/sealants, marine paint, wood deck sealer, and automotive applications such as fuel injection cleaner and fuel additive diluent. Production of the individual trimethylbenzene isomers in the U.S. is estimated at 50,000-100,000 tonnes for 1,2,4-trimethylbenzene and 500-5,000 tonnes for 1,3,5-trimethylbenzene. Ethyltoluene (mixed isomers)

production in the U.S. is estimated at 5,000-25,000 tonnes. The trimethylbenzene isomers and ethyltoluenes are used largely as chemical intermediates. Exposure to C_9 aromatic hydrocarbons has been reported in a number of environmental and indoor air exposure assessments. There are anthropogenic and biogenic environmental sources of C_9 aromatics, such as automobile emissions, tobacco smoke, forest fires and other combustion products, in addition to industrial and consumer exposure sources. Occupational exposures were reported in the range of <1 to 3 ppm (<1 to 15 mg/m^3) for solvent-use industries and 0 to 1.3 ppm (0 to 6 mg/m^3) for chemical manufacturing industries. The reported non-occupational exposures are generally in the range of <1 to 5 ppb (<1 to 25 µg/m^3), though these levels are often somewhat elevated in homes or offices that have recently been renovated or in homes of heavy smokers.