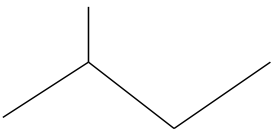
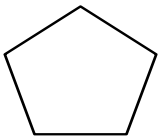
SIDS INITIAL ASSESSMENT PROFILE

Chemical Category:	C_5 Aliphatic Hydrocarbon Solvents Category
CAS Numbers and Chemical Names	**Substance Name** — **CAS Number** n-Pentane — 109-66-0 2-Methylbutane (Isopentane) — 78-78-4 Cyclopentane — 287-92-3
CAS Numbers with Structural Formula	**Structural Formula** — **CAS Number**  CH_3-CH_2-CH_2-CH_2-CH_3 — 109-66-0  CH_3-CH(CH_3)-CH_2-CH_3 — 78-78-4  CH_2 CH_2 CH_2 CH_2-CH_2 — 287-92-3

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analog Justification

The C_5 Aliphatic Hydrocarbon Solvents Category used n-pentane data which was adopted at SIAM 13. n-Pentane data are used as read across to other category members as needed.

The C_5 Aliphatic Hydrocarbon Solvents Category is composed of a straight chain (n-paraffins or n-alkanes), branched chain (isoparaffins), or cyclic (naphthenes) saturated hydrocarbons. For ecological effects, the category approach is reasonable because the substances in this category have similar physicochemical properties and are considered to be neutral organics. Log K_{ow} and ECOSAR estimated values indicate similar toxicity among the category members which has been supported by measured data. Additionally, the three category members act by a similar mode of action, e.g., nonpolar narcosis.

For mammalian toxicity, toxicokinetics studies support assessment of these substances as a category. Gas uptake studies have been conducted in rats for all three substances. n-Pentane and 2-methylbutane (isopentane) were evaluated in the same inhalation study showing 20% and 8.6% uptake at 2.95 – 14.75 mg/L (1000 - 5000 ppm), respectively. Cyclopentane uptake has also been evaluated in an inhalation study showing a 12% uptake at 2.95 mg/L (1000 ppm). Any unchanged n-, iso, or cyclo-pentane is rapidly eliminated via the exhaled air.

n-Pentane and isopentane are well absorbed, and widely distributed. Absorbed n-pentane and isopentane are similarly oxidized to the corresponding alcohol with subsequent conjugation primarily as a glucuronide. Excretion of the glucuronides is expected to be via the urine. There is no information on the toxicokinetics of cyclopentane; however, information from the structural analog, cyclohexane, indicates that it is oxidized to cyclohexanol. Conjugation and excretion of cyclohexanol is identical to n-pentane and isopentane. There is no evidence that cyclohexane is ring-opened and it is expected that the toxicokinetics of cyclopentane and cyclohexane are similar. Therefore, the information on the reproductive toxicity of cyclohexane is used in this assessment to fill the data gap for cyclopentane reproductive toxicity.

Commercial grade cyclopentane, consists of 80 – 85% cyclopentane; the remaining components are n-pentane (3 – 5%) and 2,2-dimethylbutane (10 – 15%). Data from pure and commercial grade cyclopentane

have been generated and reported in this dossier.

Human Health

Acute oral toxicity studies for n-pentane and cyclopentane show LD_{50} values greater than 2000 mg/kg-bw and 5000 mg/kg-bw, respectively. However, based on the values of kinematic viscosity of n-pentane (3.58 x 10^{-7} m^2/s), n-pentane is considered an aspiration hazard as it may cause lung damage if swallowed. Acute inhalation toxicity data in male and female rats for n-pentane, 2-methylbutane (isopentane) and cyclopentane show LC_{50} values of greater than approximately 18 mg/L (6,106 ppm), 12.5 mg/L (4,094 ppm) and greater than 5.6 mg/L (1,960 ppm), respectively. At high air concentrations, all of these substances have the potential to cause anesthetic effects. Acute dermal toxicity data for n-pentane in rabbits show an LD_{50} value of 3000 mg/kg bw. These chemicals are highly volatile and inhalation is the primary route of exposure.

The results of irritation studies indicate that the category members are slightly irritating to the skin and are minimally irritating to the eyes. n-Pentane, isopentane, and commercial grade cyclopentane (80 - 85%) are not respiratory irritants in mice. If these substances are in the compressed liquefied form and come into contact with the skin, they can cause freeze burns. Neither n-Pentane nor isopentane were found to be sensitizing to the skin of guinea pigs.

In a 90-day inhalation study in rats with n-pentane at exposure concentrations ranging from 5 - 20 mg/L (1694 - 6777 ppm), no effects were seen resulting in the determination of a NOAEC of 20 mg/L (6660 ppm). In a four week oral screening study designed to evaluate the nephrotoxicity of n-pentane, no histopathological changes were noted in the kidneys in rats exposed up to 2000 mg/kg bw/day. However, mortality was reported at 500 mg/kg bw/day (2/10) and at 2000 mg/kg bw/day (4/10). In a 16 week study in rats evaluating the neurobehavioral effects of n-pentane, none were observed after exposure to 8.85 mg/L (3000 ppm). In a 28-day inhalation study with cyclopentane, slight hematological changes (decreased erythrocyte count, decreased mean corpuscular hemoglobin and increased mean corpuscular volume) were observed only in male rats and were the only effect observed at the highest dose of 5.3 mg/L (1793 ppm). These effects were not present after the 2-week post-exposure recovery period. The NOAEC and LOAEC values for males were 1.12 mg/L (380 ppm) and 5.3 mg/L (1793 ppm), respectively and the NOAEC for females was 5.3 mg/L (1793 ppm), the highest dose tested. A subsequent 13-week repeat-dose inhalation study in rats at cyclopentane concentrations up to 30 mg/L (10,200 ppm), showed no effects on hematology or other clinical parameters including neurofunctional observations, clinical chemistry, and ophthalmology. Since the hematological changes were reversible in the first study and absent in the second study of 13-week duration, they were not considered relevant.

The studies that reported CNS effects were conducted prior to OECD guidelines and GLPs and were conducted at levels that exceed the minimum fire hazard concentrations (14,000 ppm and above). Studies conducted below these levels did not show CNS effects.

Cyclopentane and isopentane showed negative results in the standard Ames assays. In a mouse lymphoma gene mutation assay (OECD TG 476), cyclopentane showed an increase in mutation frequency in the absence of metabolic activation. Cyclopentane also showed a statistically significant increase in chromosome aberrations without activation in an *in vitro* test using human lymphocytes. However, via the inhalation route, cyclopentane did not induce chromosomal aberrations *in vivo* up to 10,000 ppm. Mixed results were seen for n-pentane in a chromosomal aberration assay in Chinese Hamster Ovary cells. However, an *in vivo* bone marrow micronucleus test for inhaled n-pentane, did not show any clastogenicity when tested up to 20 mg/L (6777 ppm). Weight-of evidence evaluation indicates that there is a minimal concern for genotoxicity.

No reproductive (one- or two-generation) toxicity studies were available for category members. In a 13-week subchronic inhalation toxicity study of n-pentane up to 20 mg/L (6777 ppm), the toxic effects on the reproductive organs in male and female rats were evaluated. At termination of the study, no statistical differences in the mean absolute weights for epididymis, seminal vesicles, prostate, testes or ovaries and uterus were noted between control and exposed animals of either sex. Furthermore, no microscopic changes were observed that were considered related to the exposure to n-pentane. In the two-generation reproductive toxicity study in rats, no effects were seen on reproductive parameters when cyclohexane (analog) was administered via inhalation up to 7000 ppm (24,080 mg/m^3). Based on these results,, the category substances are not considered to be reproductive toxicants.

In a developmental toxicity study, orally administered n-pentane did not result in maternal and developmental toxicity at the highest dose tested, 1,000 mg/kg-bw/day, which was determined as the NOAEL. There were no statistically-significant differences in mean body weight, body weight change, uterine weight, corrected body weight, or uterine implantation data between treated and control dams. Additionally, there was no mortality observed, and no adverse clinical/post-mortem signs which were considered treatment-related. There was no evidence of growth retardation or increased fetal death in the treated group compared to controls. No statistically significant differences in total or individual fetal variations or malformations (external, visceral, or skeletal) were noted in the treated group compared to

controls. Based on these results,, the category substances are not considered to be developmental toxicants.

Studies that evaluate carcinogenicity were not available.

Environment

The members of the C_5 Aliphatic Hydrocarbon Solvents Category are liquids at room temperature. The melting point values range from -159.9 to -94.4ºC (isopentane to cyclopentane). The boiling points range from 27.9 to 49.3ºC. The vapor pressure values are 685, 918, and 424 hPa at 25ºC for n-pentane, isopentane, and cyclopentane, respectively. Water solubility values range from 38.5 to 156 mg/L with a relative density range of 0.620 to 0.746 g/cm^3. The log K_{ow} values for the category members are 3.39, 2.72, and 3.00 for n-pentane, isopentane, and cyclopentane, respectively.

Members of the C_5 Aliphatic Hydrocarbon Solvents Category have the potential to rapidly volatilize from surface waters, based on Henry's Law constants (HLC) that range from 19,064 to 138,564 Pa-m^3/mole. In the air, category members have the potential to degrade through indirect photolytic processes mediated primarily by hydroxyl radicals ($^{\bullet}$OH) with calculated degradation half-lives ranging from 28 to 32 hours or 2.4 to 2.7 days, based on a 12-hr day and a $^{\bullet}$OH concentration of 1.5 x 10^6 $^{\bullet}$OH/cm^3.

Category members have no functional groups that are subject to hydrolysis or degrade in water at room temperature and neutral pH. These saturated hydrocarbons are stable in water under these conditions.

Two category members, n-pentane and isopentane, are readily biodegradable. In comparison, cyclopentane is not readily biodegradable, but was found to be inherently biodegradable.

A potential to bioaccumulate for category members is not likely, based on calculated BCF values that range from 25 to 81 (log BCF = 1.4 to 1.9). Results of Mackay Level I distribution modeling at steady state show that category members will partition to the air compartment (99.95 to 100%). Mackay Level III modeling indicates that category members partition primarily to the air (20.3 to 39.1%) and water (57.9 to 73.6%) compartments and slightly to soil (1.6 to 3.9%) and sediment (0.2 to 2.2%) compartments when an equal emission rate (1,000 kg/hr) to the air, water, and soil compartments is assumed.

A category member, n-pentane, demonstrated a measured fish 96-hour LC_{50} of 4.26 mg/L. The three category members exhibited measured 48-hour EC_{50} values for aquatic invertebrates between approximately 2 to 11 mg/L. The algal 72-hour EC_{50} value was 7.5 mg/L for growth rate, which was measured for n-pentane. This study also provided a 72-hour EC_{50} value of 10.7 mg/L for biomass. Calculated toxicity values for these endpoints for all category members range from approximately 2 to 13 mg/L, which is consistent with the measured data range of approximately 2 to 11 mg/L.

Use/Exposure

C_5 aliphatic hydrocarbon solvents are derived from petrochemical process streams refined out of natural gas and crude oil. In the U.S. in 2002, domestic production and importation totals for n-pentane and isopentane were reported at > billion pounds each and >1 to 10 million pounds (>454 to 4,535.92 metric tons) for cyclopentane, though it's unclear how much of that production was as a constituent or by-product in streams. There are several manufacturing facilities in the U.S. that produce neat n-pentane, isopentane, and cyclopentane with total production of approximately 50 to 100 million pounds (22,680 to 45,359 metric tons) for all three chemicals.

n-Pentane is used in consumer products such as spot lifters/cleaners (at concentrations <20.0%) and foaming shave gels (at concentrations of 1.0 to 5.0%) and in commercial products such as a blowing agent (at concentrations of 5.0%) for expanded polystyrene (foam) insulation. It may also be used as a solvent (in pure form) in laboratory, chemical analysis, and other settings where a highly volatile non-polar solvent is needed.

Isopentane is used in consumer products such as foaming shave gels (at concentrations of 1.0 to 5.0%) and in commercial products such as a blowing agent (at concentrations of 2.5%) for expanded polystyrene (foam) insulation. It may also be used as a solvent (in pure form) in laboratory and chemical analysis. It is also used as a chemical intermediate in the manufacture of chlorinated derivatives and the production of amyl-naphthalene and isoprene.

Cyclopentane is used as a solvent and a laboratory reagent. Commercially, cyclopentane has been used in the manufacture of insecticides and in the pharmaceutical industry for the manufacture of a variety of analgesics, sedatives, hypnotics, antitumor agents, central nervous system depressants, and prostaglandins.

Pentanes (n-, iso-, cyclo-) are also frequently constituents of gasoline streams. The sources for potential environmental exposure to C_5 aliphatics could include releases from chemical and petroleum manufacturing/processing facilities, releases from manufacturing facilities that use C_5 aliphatics, releases from consumer products that include C_5 aliphatics, and possibly biogenic and combustion sources (biomass, automobile emissions, fires, etc.). The International Hydrocarbon Solvent Consortium collected industrial

hygiene samples of n-pentane, isopentane, and cyclopentane at three manufacturing facilities from 1996 through 2001. The average concentration reported from this survey was approximately 5.3 mg/m^3 or about 2 ppm, with a range from 0 to 74 mg/m^3 (0 to 25 ppm). These results are well below the current ACGIH TLV of 600 ppm (8-hr TWA) and the U.S. Occupational Safety and Health Administration permissible exposure limit of 1,000 ppm. There is also a published review of occupational hydrocarbon solvent exposure studies over a period from the 1960s through 1997. Two papers with data on exposure to pentane in the solvent-use industries reported a total sample population of 203, with a mean 8-hr TWA exposure of 32 mg/m^3 (11 ppm) and a range of 0 to 567 mg/m^3 (0 to 200 ppm).

Non-occupational exposure to pentanes would most likely come from using consumer products such as foaming shave gels that contain n-pentane and isopentane. Non-occupational exposures have not been quantified but are likely to be low given the generally small amounts used in applications and the short duration of exposure.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in this category are of low priority for further work. These chemicals possess properties indicating a hazard for human health (eye and skin irritation (defatting effects), possible lung damage if swallowed). These hazards do not warrant further work as they are related to reversible acute toxicity which may become evident only at high exposure levels.

Environment: The chemicals possess properties indicating a potential hazard for the environment (acute toxicity for fish, invertebrates, and algae between 1 and 100 mg/L).

n-Pentane (CAS No. 109-66-0) and 2-methylbutane (isopentane, CAS No. 78-78-4) are currently of low priority for further work for the environment because of their ready biodegradability and limited potential for bioaccumulation.

Cyclopentane (CAS No. 287-92-3) is not readily biodegradable. Therefore, this chemical is a candidate for further work. Member countries are invited to perform an exposure assessment and if necessary a risk assessment.