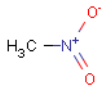
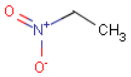
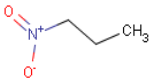
SIDS INITIAL ASSESSMENT PROFILE

Category	Short Chain Nitroparaffins
CAS No's.	75-52-5 79-24-3 108-03-2
Chemical Name	Nitromethane Nitroethane 1-Nitropropane
Structural Formulae	 Nitromethane  Nitroethane  1-Nitropropane

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The short chain nitroparaffins category consists of three structurally related nitroalkanes; nitromethane, nitroethane and 1-nitropropane. These chemicals are considered a category because of the similarities in structure, and in chemical and toxicological behaviour. The category members are expected to be absorbed, metabolized, and excreted in a similar fashion, resulting in the release of their respective aldehydes and nitrite.

Physical-Chemical Properties

The category members are liquids at room temperature. The melting points for nitromethane, nitroethane, and 1-nitropropane are -28.4, -89.5 and -104 ^{o}C, respectively: the corresponding boiling points are 101.2, 114 and 131.1 ^{o}C. The vapour pressures are 37.1, 27.7, and 13 hPa at 25^{o}C for nitromethane, nitroethane, and 1-nitropropane, respectively. The water solubility for nitromethane is 111,000 mg/L at 20 ˚C. The water solubility for nitroethane is 45,000 mg/L at 20 ˚C. The water solubility for 1-nitropropane is 15,000 mg/L at 25 ˚C. Water solubility values are based on a density of 0.9934-1.1322 g/cm^3. The measured log K_{ow}s are -0.33, 0.18, and 0.79 for nitromethane, nitroethane, and 1-nitropropane, respectively.

Human Health

The skin absorption of ^{14}C –labelled category members has been studied in female rhesus monkeys and indicates that none of the chemicals are readily absorbed by the skin but are more likely to evaporate before significant amounts of absorption take place. In rats administered a single oral dose of ^{14}C-nitromethane, -nitroethane or -nitropropane approximately 9% was retained in the body five days after dosing with excretion occurring via urine and faeces. The absorption following a single oral dose was high at approximately 92-96%. For nitromethane, nitroethane and 1-nitropropane, 19%, 5%, and 14% was excreted in the urine, respectively and 8.5%, 4% and 7% was excreted in the faeces, respectively. The majority (approximately 64%, 82% and 73%, respectively) of the radioactivity was not accounted for, and was presumed to have been exhaled. The short chain nitroparaffins are metabolized into nitrites and the respective aldehydes. In rats inhaling 100 ppm 1-nitropropane for 7 hours, a steady state concentration of approximately 9 µg/ml of the parent compound was obtained after 4 hours of exposure. The elimination $T_{1/2}$ (half-life) was 98 minutes.

Acute toxicity data are available for the inhalation, dermal and oral routes. The inhalation LC_{50} for nitromethane vapour in rats was >12.75 mg/L for 1 hour (within a 48-hour post-exposure observation period). Clinical signs from this study included

mild sedation and eye irritation. The oral LD_{50}s for nitromethane, nitroethane and 1-nitropropane in rats were 1478 mg/kg-bw, 1256 mg/kg-bw and 506 mg/kg-bw, respectively. Clinical signs of oral toxicity included ataxia and convulsions. At necropsy, severe intestinal haemorrhaging was seen. The 24-hr dermal LD_{50}s of all three category members were greater than 2000 mg/kg-bw in rabbits under occlusion. No clinical signs of toxicity were observed. The category members are not irritating to slightly irritating (nitroethane) to the skin. Nitromethane, nitroethane and 1-nitropropane are slightly to moderately irritating to the eyes.

In an NTP study, rats were exposed to nitromethane vapour at 94, 188, 375, 750, or 1500 ppm (0.23, 0.46, 0.94, 1.87, or 3.74 mg/L) via inhalation for 6 hours/day, 5 days/week for 13 weeks. Animals exhibited changes in haematology indicative of slight anaemia at all concentrations resulting in a systemic LOAEC of 94 ppm (0.23 mg/L). Other effects in this study included increased methaemoglobin and thyroid effects at $\geq$ 188 ppm (0.46 mg/L), sciatic nerve and spinal cord degeneration and bone marrow hyperplasia at $\geq$ 375 ppm (0.94 mg/L), hind limb paralysis and decreased strength at 750 ppm (1.87 mg/L) and higher. Changes in various organ weights were also observed at $\geq$ 188 ppm (0.46 mg/L). Degeneration of the nasal epithelium resulted in a local NOAEC of 188 ppm (0.46 mg/L). All lesions in this study were characterized as minimal to mild. In another study, rats exposed to nitromethane vapour at 98 and 745 ppm (0.26 and 1.86 mg/L) for 7 hours/day, 5 days/week up to 24 weeks exhibited reduced body weight gains, decreased haemoglobin and haematocrit and increased thyroid weights at 745 ppm (1.86 mg/L), resulting in a systemic NOAEC of 98 ppm (0.26 mg/L). Rabbits exposed in this study had thyroid effects at both doses resulting in a LOAEC of 98 ppm (0.26 mg/L). In another NTP study, mice exposed to nitromethane vapour for 6 hours/day, 5 days/week for 13 weeks at the same doses used in the rat 13-week study exhibited minimal increases in kidney weights at all concentrations. Sperm motility was decreased and oestrous cycle length and spleen toxicity were increased at 375 ppm (0.94 mg/L) and higher. Lesions were characterized as mild/minimal. Based on differences in multiple organ weights and effects on sperm motility and oestrous cycle length, the systemic NOAEC is 188 ppm (0.47 mg/L). Based on nasal degeneration, which increased in severity with test concentrations, the local NOAEC is 94 ppm (0.23 mg/L).

Rats were exposed to nitroethane vapour at 100, 350 or 1000 ppm (0.31, 1.0 or 3.0 mg/L) for 6 hrs/day, 5 days/week for 13 weeks. Animals exhibited changes in haematology at all concentrations. Minimal changes in the histopathology of the spleen and salivary glands and time-dependent increase in methaemoglobinemia occurred at all concentrations. Fatty livers were also noted at higher concentrations. The systemic LOAEC was 100 ppm (0.31 mg/L); the NOAEC was not established. Increased nasal degeneration versus controls occurred at $\geq$ 350 ppm (1.0 mg/L) resulting in a local NOAEC of 100 ppm (0.31 mg/L). In mice exposed to nitroethane vapour for 6 hrs/day, 5 days/week for 13 weeks, organ weight changes and effects on kidney (changes in relative weight and blood urea nitrogen) were seen at all concentration ($\geq$ 100 ppm). At $\geq$ 350 ppm (1.0 mg/L), methaemoglobin was increased and haematology and liver effects were observed. At the highest concentration, multinucleated spermatids were observed in testes. Based on kidney effects, the systemic LOAEC is 100 ppm (0.31 mg/L); no systemic NOAEC was established. Changes in nasal turbinates resulted in a local NOAEC of 100 ppm (0.31 mg/L).

In a combined inhalation repeated-dose/reproductive developmental screening test (OECD TG 422) rats were exposed to 1-nitropropane vapour at 24, 48, or 96 ppm (0.088, 0.18, or 0.35 mg/L), 6 hr/day, 7 days/week for at least 28 days. At 96 ppm (0.35 mg/L), there was decreased food consumption in both sexes, and slightly decreased body weights of males (by 6.9%) prior to mating. The systemic NOAEC is 96 ppm (0.35 mg/L) the highest dose tested. Histopathologic changes in the nasal tissues were seen at increased incidences at $\geq$ 48 ppm. Based on these findings, the local NOAEC was 24 ppm (0.085 mg/L). In a 28-day oral gavage study, rats were exposed to 10, 30, or 100 mg/kg bw/day. At 100 mg/kg bw/day, rats showed clinical signs that included ataxia, salivation, hunched posture. Other effects included significant increases in absolute and relative brain weights without corresponding morphologic changes, multiple changes in clinical chemistry and haematology parameters, and increased methaemoglobin. Although certain effects occurred at lower doses, they were minimal, transient and/or not dose-dependent. Based on effects at 100 mg/kg bw/day, the NOAEL was established as 30 mg/kg bw/day.

In vitro bacterial mutagenicity studies are available for nitromethane, nitroethane, and 1-nitropropane. Nitromethane and 1-nitropropane have been tested for chromosomal aberrations *in vitro*. *In vivo* genotoxicity was evaluated in all three category members. High concentrations of nitromethane and nitroethane in air did not induce gene mutations in bacteria. 1-Nitropropane also did not induce gene mutations in bacteria. 1-Nitropropane did not induce micronuclei in mouse or rat bone marrow *in vivo* but was positive for micronuclei in rat liver cells *in vivo*. The members of the short chain nitroparaffins category did not result in genotoxicity *in vitro*, but may result in genotoxicity *in vivo*.

Nitromethane was carcinogenic in mice (B6C3F1) and female rats (F344) via the inhalation route at concentrations $\geq$ 188 ppm. However, nitroethane and 1-nitropropane were not carcinogenic in Long-Evans rats via the inhalation route at concentrations of 200 and 100 ppm respectively. Based on differences in doses, animal species and use of only one species in nitroethane and 1-nitropropane carcinogenicity studies, firm conclusions regarding carcinogenicity were not possible.

Reproductive organs and performance were evaluated in repeated-dose toxicity studies, and. data for 1-nitropropane are available from the OECD TG 422 study. No histopathological effects were observed in the reproductive organs of rats or mice exposed via inhalation to nitromethane or nitroethane. However, a significant decrease in sperm motility was noted in male rats exposed to 750 ppm (1.87 mg/L)and 1500 ppm (3.74 mg/L) nitromethane. Male rats also had decreased cauda, epididymis and testes weights. Also, a decrease in sperm motility and an increase in oestrous cycle length were noted in mice exposed to $\geq$ 375 ppm ($\geq$ 0.94 mg/L) nitromethane. At 1000 ppm (3.0 mg/L) nitroethane, multinucleated spermatids were observed in testes of male mice. In the combined repeated-dose/reproductive/developmental toxicity screening test with 1-nitropropane, rats were exposed via inhalation for 6 hours/day, 7 days/week beginning 14 days prior to mating, during mating and for females, through gestation day 19. In parents, body weights of males were slightly decreased at 96 ppm (0.35 mg/L) and changes in nasal tissues were seen at $\geq$ 48 ppm (0.18 mg/L), resulting in a local NOAEC of 24 ppm (0.088 mg/L). At 96 ppm (0.35 mg/L), litter sizes and mean numbers of pups born live were decreased, resulting in a NOAEC for reproductive/developmental toxicity of 48 ppm (0.18 mg/L). The category members showed potential for reproductive/developmental toxicity; data on developmental effects were limited to gross observations in the OECD 422 study.

The category members possess properties indicating a hazard for human health (acute oral toxicity, repeated-dose toxicity, reproductive/developmental toxicity, genotoxicity and carcinogenicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

Experimental photolysis data are available for nitromethane, nitroethane, and 1-nitropropane using radiolabeled test material irradiated by a mercury vapour lamp. Results after 17 hours indicate 35.2% degradation of nitromethane, 23.9% degradation of nitroethane, and 54.8% degradation of 1-nitropropane. Indirect photolysis half-lives for the three nitroparaffins range from (approximately) 25-82.3 days. Abiotic hydrolysis of these materials is unlikely. These nitroparaffins have no functional groups that are subject to hydrolysis or degradation in water at room temperature with neutral pHs. The organo-nitro group is stable in water under these conditions.

Distribution (fugacity) modelling using Mackay Level III indicates that the category members released into the air compartment (most likely emission scenario based on use pattern and physical/chemical properties) will partition predominantly to air (69.1%, 91.2%, 88.7% for nitromethane, nitroethane, and 1-nitropropane, respectively), water (19.1%, 12.0%, 7.3%, respectively), soil (11.8%, 6.8%, 4.1%, respectively), and sediment (<0.1% for all three).

The short-chain nitroparaffins are not readily biodegradable.

Acute toxicity test results are available with two fish species for each of the three category members. Laboratory acute aquatic toxicity data are also available for freshwater invertebrates and algae for the nitroparaffins. The weight of evidence clearly suggests that acute exposure EC/LC_{50} values for the nitroparaffins with standard laboratory species are greater than 100 mg/l except for algae, where the 72-hr inhibition of growth ranges from 6 to >456 mg/L. Modelling toxicity data using Topkat and AIES were used to support nominal test data for nitromethane. The predicted Daphnia 48-hr EC50 was 399 mg/L and the fish 96-hr LC_{50} was 127 mg/L using the Topkat and AIES models, respectively.

These chemicals are volatile substances and some tests were conducted in open systems, and therefore, were supported by modelling toxicity data. Caution should be exercised in interpreting these test results and the toxicity observed may be underestimated.

Key studies on the acute toxicity of the category members are:

Category Member	***Acute Fish Toxicity***	***Acute Invertebrate Toxicity***	***Algal Growth Inhibition***	
Nitromethane	96-hr LC_{50} = 127 mg/L (calculated) OECD 203 96-hr LC_{50} = >659.2 mg/L (open system, nominal) 48-hr LC_{50} = 460 mg/l (closed system, nominal)	48-hr EC_{50} = 399 mg/L (calculated) OECD 202 24-hr EC_{50} = 450 mg/L (open system, measured)	OECD 201 72-hour E_rC_{50} = 36 mg/L (closed system, measured)	72-hour E_yC_{50} = not reported
Nitroethane	OECD 203 96-h LC_{50} = 596 mg/L (nominal) 48-hr LC_{50} = 880 mg/l	OECD 202 24-hr EC_{50} = 1200 mg/l	OECD 201 72-hour E_rC_{50} = 6 mg/L (closed system,	72-hour E_yC_{50} = not reported

	(closed system, nominal)	(open system measured)	measured)	
1-Nitropropane	OECD 203 96-hr LC_{50} = 227 mg/L (measured) 48-hr LC_{50} = 205 mg/L (closed system, nominal)	OECD 202 48-hr EC_{50} = 380 mg/L (closed system, measured) OECD 202 24-hr EC_{50} = 258 mg/L (open system, measured)	OECD 201 72-hour ErC_{50} > 456 mg/L (closed system, measured)	72-hour EC_{50} = 263 mg/L (closed system, measured)

The category members possess properties indicating a hazard for to the environment (toxicity to aquatic plants) at concentrations between 1 and 100 mg/L. Category members are not considered readily biodegradable or bioaccumulative. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

The production volumes in the United States (sponsor country) for 2005 were each over 5 x 10^6 pounds (2268 tonnes).

The category members are primarily used as intermediates in the synthesis of other chemicals, as industrial solvents, and in fuels. In production, these materials are handled in closed systems. Engineering controls during production include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure from splashing, or exposure to the air. Transfer of these materials is in closed pipe systems rather than in open systems.

Environmental exposure is possible through low level losses in process waste waters, which are discharged to a waste water treatment system. Some limited potential exists for release of material to the Publicly Owned Treatment Works (POTWs) after primary biological treatment on site. Industrial customers may have on-site biological treatment facilities but general consumers may only have access to POTW's without pre-treatment. These chemicals are stored in closed tanks and transported in tank cars and tank trucks, and smaller amounts are transported in drums or Intermediate Bulk Containers (IBCs), with the exception of >96% pure nitromethane which is not transported in containers larger than 55-gallon drums.

The most likely route of human exposure to the category members is via inhalation or dermal contact. Occupational inhalation exposure may occur during manufacture or processing; however, these exposures are negligible due to the use of engineering controls such as closed process systems, closed piping systems and local ventilation, as well as the use of personal protective equipment. There are industrial occupational exposure guidelines set for these chemicals in the sponsor country; Occupational Safety and Health Administration (OSHA) permissible exposure limit Time Weighted Average (TWA)-8 hours is 100 ppm for nitromethane, or nitroethane and 25 ppm for 1-nitropropane. Exposure may occur during cleaning or drumming operations, but these exposures are limited by appropriate protective clothing and the existence of appropriate control measures. Bulk storage, handling and transport of product further limit exposure potential by handling in enclosed storage vessels and piping. Automated container filling equipment is used to fill drums and IBC's, thus making exposure during this process highly unlikely.

Products using these short chain nitroparaffin ingredients are not widely available to consumers. However, consumers could be exposed to nitromethane via inhalation during use of hobby or racing fuels, to limited amounts of nitroethane by inhalation through use in certain paints or coatings, and to very small amounts of 1-nitropropane by inhalation where it is present as a minor fuel additive or as a solvent. Dermal exposure may occur at low levels for consumers in these same end-use applications of industrial solvents, paints/coatings, or fuels/fuel additives.