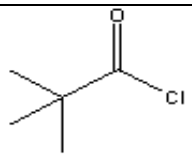
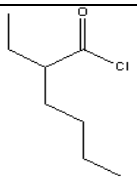
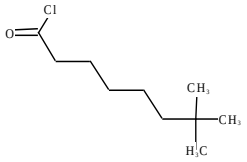
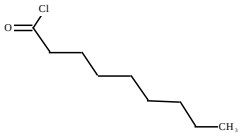
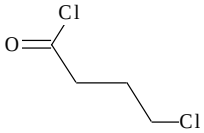
SIDS INITIAL ASSESSMENT PROFILE

Category Name	Acid Chloride Category
CAS Nos and Chemical Names	**Sponsored substances:** 3282-30-2 Pivaloyl chloride (PCl) 760-67-8 2-Ethylhexanoyl chloride (EhCl) 40292-82-8 Neodecanoyl chloride (NdCl) 764-85-2 Nonanoyl chloride (NnCl) **Analogue substance: similar structure** 4635-59-0 Chlorobutyryl chloride (CCl2) **Analogue substances: hydrolysis products** 75-98-9 Pivalic acid 149-57-5 2-Ethylhexanoic acid 26896-20-8 Neodecanoic acid 112-05-0 Nonanoic acid
Structural Formulae	*3282-30-2*  *760-67-8*  *40292-82-8*  *764-85-2*  *4635-59-0* 

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The members of the Acid Chloride Category are listed above. The category consists of 4 sponsored acid chlorides (pivaloyl chloride; PCl, CAS No. 3282-30-2), 2-ethylhexanoyl chloride (EhCl; CAS No. 760-67-8), neodecanoyl chloride (NdCl; CAS No. 40292-82-8) and nonanoyl chloride (NnCl; CAS No. 764-85-2). These chemicals are grouped into a category based on similar molecular structure and functionality, high reactivity, physicochemical and toxicological properties.

Similar molecular structure and functionality **: R (C=O)Cl [where R = alkyl]**

Similar high reactivity: The acid chloride group (i.e., -(C=O)Cl) is the most active functional group on these molecules and determines many aspects of the behaviour of the category members. Acid chlorides undergo various chemical reactions depending on the environment to which they are exposed. Hydrolysis is the primary reaction in aqueous systems and has been shown to occur very quickly for all compounds at pH 4 and 0 ^{o}C and/or pH 1.2 and 37 ^{o}C. Reactions with nucleophiles (such as - NH2, -SH and –OH) on biological macromolecules will also occur in mammalian tissues.

Similar chemical/physical properties: All category members are liquids with low melting points. Volatility and boiling points are largely dependent on molecular weight.

Similar toxicological properties: These category members are severely irritating and harmful at the site of contact (i.e., respiratory tract, skin, and eyes); systemic absorption at already severe local toxic effect concentrations (i.e. lethality via inhalation) is not expected.

The approach to address SIDS endpoints for the acid chloride category is to utilize data from the sponsored chemicals and the primary hydrolysis products. Chlorobutyryl chloride (CCl2; CAS No. 4635-59-0), which is also an acid chloride with similar size and structure, has been used with respect to acute and repeated dose toxicity, and mutagenicity. The primary hydrolysis products for the sponsored acid chlorides are hydrochloric acid (HCl; CAS No. 7647-01-0) and an organic acid (pivalic acid (CAS No. 75-98-9), 2-ethylhexanoic acid (CAS No. 149-57-5), neodecanoic acid (CAS No. 26896-20-8), and nonanoic acid (CAS No. 112-05-0), respectively). These hydrolysis products can be used as analogues because of the rapid hydrolysis of acid chlorides to HCl and the organic acids. Repeated-dose, mutagenicity and reproductive toxicity endpoints for the acid chlorides category are fulfilled through the use of data from the primary hydrolysis products. Acute aquatic toxicity data are also fulfilled through the use of data from the primary hydrolysis products, HCl, pivalic acid, 2-ethylhexanoic acid, neodecanoic acid and/or nonanoic acid.

2-Ethylhexanoic acid and hydrogen chloride have previously been assessed in the OECD HPV Program. The SIDS Dossier for 2-Ethylhexanoic acid will be available for review on the UNEP website when published. The hydrogen chloride documents are available at http://www.chem.unep.ch/irptc/sids/oecdsids/7647010.pdf . Pivalic acid has been assessed as part of the NeoAcids C5-C28 category in the U.S. HPV Challenge Program (http://www.epa.gov/hpvis/hazchar/Category_C5-C28%20%20Neoacids_HC_August%202007.pdf).

Physical-chemical properties

The acid chlorides are very reactive and hydrolytically unstable; they are liquids at normal temperature and pressure. PCl, EhCl and NdCl degrade spontaneously on contact with aqueous media; at pH 4 and 0^{o}C, > 50% hydrolysis occurred prior to analysis of the initial sample. The half-life of NnCl was 17 minutes at pH 7 and 0^{o}C. The acid chlorides hydrolyze to form one mole of their respective organic acids (pivalic, 2-ethylhexanoic, neodecanoic and nonanoic acids) and one mole of HCl. The melting points of the acid chlorides range from <-60.5^{o}C (NnCl) to 11.6 ^{o}C (NdCl); boiling points range from 67.8 ^{o}C (EhCl) to 215.3^{o}C (NnCl). The melting point and boiling point of CCl2 are -49 and 173.5 ^{o} C, respectively. Vapor pressures of the acid chlorides range from 0.22 hPa at 20^{o}C (NdCl; estimated based on measured) to 50.1 hPa at 25^{o}C (35.9 at 20^{o}C)(PCl). The vapor pressure of CCl2 is 1.31 hPa at 20 ^{o}C. The water solubility and partition coefficient estimates are not reliable because the acid chlorides are hydrolytically unstable. The water solubility values of the organic acid hydrolysis products range from 69 mg/L (estimated; un-dissociated neodecanoic acid) to 21,700 mg/L (measured; pivalic acid). The water solubility of HCl is 673 g/L at 30°C. The partition coefficients of the organic acid hydrolysis products in their neutral form range from 1.32 [estimated (un-dissociated); 4-chlorobutyric acid] to 3.9 [estimated (un-dissociated); neodecanoic acid].

Human Health

There are no data for toxicokinetics of the acid chlorides. Acute toxicity data are available for the inhalation, dermal and oral routes of exposure for the acid chlorides. The 1 and 4 hr-LC_{50}s in the rat range from 1.26 to 2.69 mg/L and

>0.31 to <3.58 mg/L, respectively. NdCl was the most toxic category member following acute inhalation. In the inhalation studies, eye irritation and respiratory irritation/distress were observed, with subsequent signs of generalized poor condition including decreased activity, rough fur, piloerection, emaciation, polyuria and wet fur. Observations at necropsy included discolouration of the lungs (gray, pale, red or dark, mottled) which were often edematous. Tracheal irritation and tracheal mucus, air-filled stomach and/or intestines (resulting from mouth-breathing) were also observed. The range of inhalation LC_{50}s for the analogue CCl2 is 0.65-0.87 mg/L/4h. The organic acid six hr-LC_{50}s in the rat were all >2.36 mg/L. Observations in the acute inhalation studies with pivalic acid included piloerection, epitasis, and dyspnea . No signs of toxicity were observed following exposure to neodecanoic acid at >3 mg/L, the highest dose tested.

Dermal LD_{50}s in rabbits for the acid chlorides were greater than 2000 mg/kg bw. Toxicological effects included decreased activity, ataxia, constricted pupils, decreased defecation and urination, diarrhea, emaciation, hemorrhaging (at exposure area), nasal discharge, polyuria and small feces. At necropsy findings included extensive ulceration throughout the exposure area, liver mottled pale red and red-brown, stomach distended with gas and almost empty, coloured material in the stomach, small intestine and/or cecum. Reliable acute dermal toxicity data were not located for the organic acids.

Oral (gavage) LD_{50}'s for the acid chlorides ranged from 683 to 1410 mg/kg bw when applied neat (without vehicle) or from 1470-2500 mg/kg bw when applied in olive oil. PCl was the most toxic category member following acute oral gavage. The acute toxicity of NnCl has not been investigated; however, a similar order of toxicity is expected as found with other category members. Toxicological effects of the acid chlorides observed during acute oral (gavage) studies in rats included decreased activity, muscle weakness, ataxia, agitation, slow, short, gasping, or noisy, breathing patterns, clear or coloured discharge from the eyes and/or nose, constricted and/or dilated pupils, reduced corneal reflexes, exophthalmos, red or black discoloured urine, polyuria, and general signs of poor condition including rough coat, piloerection, ptosis, diarrhea, emaciation, salivation and/or swollen tongue. Necropsy findings included extensive ulceration, hemorrhage or necrosis in the stomach and intestine, and edema in the lung. The oral LD_{50} of the analogue CCl2 is 1510 mg/kg (without vehicle).

The oral LD_{50}s for the organic acids range from >1600 to < 3200 mg/kg bw. Clinical signs included muscle weakness, CNS depression, dyspnea, and ataxia. Necropsy findings in high dose animals indicated congestion of lungs, liver, kidneys, and adrenals. The oral LD_{50} value of HCl is reported to be 238-277 mg/kg bw for female rats.

PCl, EhCl and NdCL are corrosive to skin. PCl and EhCl are moderate to severely irritating to the eye. NdCl was not irritating to the eyes. Data are not available for NnCl, however it is assumed this substance may be corrosive to the skin and severely irritating to the eyes. The acid chlorides are expected to be sensory irritants. NnCl was a sensitiser in a murine local lymph node assay. Sensitization data were not located for PCl, EhCl or NdCl.

Repeated-dose toxicity studies are not available for the sponsored acid chlorides; data are available for the hydrolysis products, the analogue substance, CCl2 and HCl. Rats exposed to the analogue substance CCl2 by inhalation at 0, 0.002, 0.012, and 0.059 mg/L for 4 weeks (6h/day; 5 days/week) showed clinical symptoms linked to respiratory tract inflammation and irritation. Growth retardation, changes in blood parameters clinical chemistry, and organ weights were secondary to effects on the respiratory tract. The LOAEL for respiratory tract effects was 0.002 mg/L. Based on histology findings, there was no other target organ than the respiratory tract in concentrations up to 0.059 mg/L. Irritation was observed in all the treatment groups in a 90-day inhalation study using HCl. The NOAEL (except for the effects of irritation) was 20 ppm (0.03 mg/L) for rats and mice. Repeated-dose dermal toxicity studies (14 days) with rabbits with pivalic, neodecanoic, and nonanoic acid indicate a low order of systemic toxicity in the presence of moderate to severe skin irritation at the site of contact. The NOAELs for systemic toxicity were 300 mg/kg bw/day (pivalic acid), 2280 mg/kg bw/d (neodecanoic acid) and 500 mg/kg bw/d (nonanoic acid) [highest doses in each study]. Observations of toxicity were limited to local irritation effects in rats in a 28-day oral gavage study with pivalic acid; the NOAEL was 300 mg/kg bw/day. A diet containing 0.5 % 2-ethylhexanoic acid caused no adverse effect in rats in a 13 week feeding study (calculated NOAEL ca. 300 mg/kg bw/day). No adverse effect was observed in mice receiving a diet containing 0.5 % 2-ethylhexanoic acid in a 13 week feeding study. The NOAEL was calculated to be 200 mg/kg bw/day. In both studies, all toxicity observed at higher concentrations (changes in clinical chemistry, absolute and relative organ weights, microscopic changes in kidney liver and fore stomach) was reversible within 28 days after exposure ceased.

PCl and NnCl were weakly positive for mutagenicity in *S. typhimurium* strain TA 100 in OECD TG 471 studies; EhCl, NdCl and analogue substance, CCl2 were negative in these studies. The organic acids (pivalic, 2-ethylhexanoic and neodecanoic acid) were negative for mutagenicity in standard bacterial reverse mutation assays. The hydrolysis product, HCl, was also negative in the Ames test. The analogue CCl2 was negative for the induction of chromosome aberrations in human lymphocytes (*in vitro*). Pivalic acid (rat liver cells), neodecanoic acid (human lymphocytes), and HCl (CHO cells) were negative in *in vitro* chromosome aberration assays. Positive results have been obtained in the *in vitro* chromosome aberration test with HCl; however, the positive result was considered to be

the effect of low pH. 2-Ethylhexanoic acid was negative in an *in vivo* mouse micronucleus assay. Therefore, based on the current available data, the acid chlorides are not expected to be genotoxic.

Reproductive toxicity data are not available for the acid chlorides. Data are available for the hydrolysis products (2-ethylhexanoic acid, neodecanoic acid, nonanoic acid, and HCl). The reproductive toxicity of 2-ethylhexanoic acid has been investigated in a one generation study in rats [OECD TG 415] and the NOAEL for reproductive effects in parental animals was 300 mg/kg-bw/day; this effect occurred in the presence of maternal toxicity. The NOAEL for F1 offspring was 100 mg/kg-bw/day. The developmental toxicity of 2-ethylhexanoic acid has been investigated in a standard study in rabbits [USEPA TSCA Health Effects Testing Guidelines CFR 798.4900 (similar to OECD TG 414)] and the NOAEL for maternal animals was 25 mg/kg–bw/day and the NOAEL for offspring was 250 mg/kg-bw/day (the highest dose tested). In a guideline study [OECD TG 414] 2-ethylhexanoic acid was administered via drinking water to an unspecified number of Wistar rats at 0, 100, 300, or 600 mg/kg-bw/day, for days 6-19 of gestation. Clubfoot was the only skeletal malformation; changes in skeletal variations were also noted (wavy ribs, reduced cranial ossification, and twisted hind legs). However, wavy ribs and delayed ossification were not dose dependent. There is a high background incidence of wavy ribs in Wistar rats and the incidence observed was within the background range. Therefore, the NOAEL for offspring was 100 mg/kg-bw/day and the NOAEL for maternal animals was 300 mg/kg-bw/day. The developmental toxicity of 2-ethylhexanoic acid has also been investigated in another study in Fischer rats [USEPA TSCA Health Effects Testing Guidelines CFR 798.4900 (similar to OECD TG 414)]. The NOAEL for maternal animals was 250 mg/kg–bw/day and the NOAEL for offspring was 100 mg/kg-bw/day as well. Based on these results, 2-ethylhexanoic acid is not likely to cause effects on fertility but is likely to be a developmental toxicant.

The reproductive toxicity of neodecanoic acid has been investigated in a three generation study in rats. In this study, neodecanoic acid was administered via the diet to 10 males/20 females/dose (P1) at 0, and approx. 5, 25 and 75 mg/kg-bw/day for 9 weeks prior to mating to produce F1A and F1B (P2) generations. No adverse effects on reproductive or developmental parameters were observed up to the highest dose tested. There were no treatment related effects on parental animals observed at any dose. The NOAEL for parental, F1 offspring, and F2 offspring was 1500 ppm (75 mg/kg-bw/day). Based on these results, neodecanoic acid is considered not to be a reproductive/developmental toxicant.

The reproductive toxicity of nonanoic acid has been investigated in two standard developmental toxicity studies in rats. In both studies, nonanoic acid was administered via gavage to an 11 pregnant animals/dose at 0 or 1500 mg/kg-bw, for gestational days 6 through 15. No adverse effects on development were observed. There were no treatment related effects on parental animals. The NOAEL for developmental toxicity from these studies is 1500 mg/kg-bw/day. Based on these results, nonanoic acid is considered not to be a developmental toxicant. As stated in the Hazard Characterization for Neoacids C5 to C28 (http://www.epa.gov/hpvis/hazchar/Category_C5-C28%20%20Neoacids_HC_August%202007.pdf): "The potential health hazard of the neoacids C5 to C28 category is moderate based on the limited data available for repeated-dose and reproductive toxicity and the findings in the developmental studies." As such, a potential hazard for reproductive toxicity cannot be excluded for pivalic acid. As stated in the SIAR for HCl, no reliable studies were identified regarding reproductive toxicity in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. However, based on a weight of evidence analysis, conclusions from two studies suggest HCl is not a reproductive toxicant.

In summary, there is no indication of reproductive effects for the acid chlorides based on the available data. 2-Ethylhexanoyl chloride is likely the only category member with a potential for developmental toxicity; however, there is a potential concern for developmental effects associated with pivaloyl chloride.

The chemicals possess properties indicating a hazard for human health (lethality from acute inhalation, localized irritation of skin, eye and respiratory tract, potential for sensitization, toxicity at the site of contact or entry, liver and kidney toxicity, developmental toxicity for EhCl). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The overall OH rate constant for the acid chlorides and resulting half-life and rate constant due to indirect photolysis are estimated to range from 1.6 x 10^{-12} cm^3/molecule-sec (PCl) to 11.5 x 10^{-12} cm^3/molecule-sec (NnCl) and 0.9 d (EhCl and NnCl) to 6.7 d (PCl). Photodegradation as a mode of removal is unlikely as the AC are hydrolytically unstable. It is assumed that reaction with water vapor is the predominant degradation process for acid chlorides in air. The products resulting from acid chloride hydrolysis (organic acids) in the atmosphere are expected to further react with hydroxyl radicals. The half-lives due to the atmospheric oxidation from indirect photolysis of the organic acids were determined to range from 1.1 d (nonanoic acid) to 10.5 d (pivalic acid); the overall OH rate constants ranged from 1.02 x 10^{-12} cm^3/molecule-sec (pivalic acid) to 9.8 x 10^{-12} cm^3/molecule-sec (nonanoic acid). HCl can react with hydroxyl radicals to form chloride free radical and water and its half-life time is calculated as 11 d. Level

III Fugacity modeling, using loading rates of 1000 kg/h each for air, soil, and water, shows the following percent distribution range for the acid chlorides: Air = 7.5 (NdCl) to 35 (PCl); Soil = 11.3 (PCl) to 62.3 (NdCl); Water = 29.2 (NdCl) to 53.6 (PCl); Sediment = 0.11 (PCl) to 1.0 (NdCl). However, because the acid chlorides are very reactive and hydrolytically unstable, the substances are unlikely to be found in the environment. Therefore, Level III Fugacity modeling for the hydrolysis products (organic acids) was conducted using loading rates of 1000 kg/h each for air, soil, and water. The model estimated the following percent distribution ranges, when the organic acids are released simultaneously to all three compartments: Air = 2.2 (neodecanoic acid) to 6.1 (pivalic acid); Soil = 57.5 (pivalic acid) to 72.1 (neodecanoic acid), Water = 23.3 (neodecanoic acid) to 36.4 (pivalic acid); and Sediment = 0.09 (pivalic acid) to 2.4 (neodecanoic acid). These hydrolysis products will also exist as ionised substances (anion) under environmental conditions based upon calculated pKa values ranging from 4.69 to 4.75 for the category member hydrolysis products, and fugacity modelling may not be appropriate. The Fugacity model cannot be applied for ionized substances such as HCl. The biodegradation of the acid chlorides has not been determined due to their rapid hydrolysis; any expected biodegradation is likely reflective of the corresponding organic acid hydrolysis product. Studies with pivalic and neodecanoic acid indicate these organic acids are not readily biodegradable. 2-Ethylhexanoic acid and nonanoic acid are readily biodegradable. Bioaccumulation is not anticipated since these materials are very reactive and hydrolytically unstable. BCFwin modelling indicates the organic acids are not likely to bioaccumulate.

Acute toxicity studies with fish have been conducted with acid chlorides (sponsored substances and the hydrolysis products). The 96-hr LC_{50}'s of the acid chlorides ranged from 66.3 mg/L (not neutralized, measured, EhCl) to 287 mg/L (not neutralized, measured, PCl) in *Brachydanio rerio*. The 96-hr LC_{50}'s of the hydrolysis products were 104 mg/L (neutralized measured nonanoic acid; *Pimephales promelas*), 91 mg/L (nonanoic acid, *Oncorhynchus mykiss*) and 4.92 mg/L at pH 4.3 (HCl, *Cyprinus carpio*). Acute aquatic invertebrate tests have not been conducted with acid chloride category members. The 48 hr EC_{50} values for the hydrolysis products in the water flea (*Daphnia magna*) were 203 mg/L (nominal, pivalic acid), 85.4 mg/L (neutralized, nominal, 2-ethylhexanoic acid), 47 mg/L (nominal, neodecanoic acid), 96 mg/L (nonanoic acid), and 0.492 mg/L (at pH 5.3; HCl). The 72-hr EC_{50}s for the hydrolysis product pivalic acid with *Pseudokirchneriella subcapitata* was E_bC_{50} = 878 mg/L (E_rC_{50} = 979 mg/L, measured), and 2-ethylhexanoic acid with *Scenedesmus subspicatus* were E_bC_{50} = 60.5 mg/L and E_rC_{50} = 49.3 mg/L (not neutralized, nominal). The 72-hr EC_{50} value for HCl with *P. subcapitata* was 0.492 mg/L (at pH 5.3). The hazard of HCl for the environment is caused by the proton (pH effect). For this reason the effect of HCl on the organisms depends on the buffer capacity of the aquatic ecosystem. HCl has been previously discussed and agreed upon in the OECD HPV Programme.

The chemicals have properties that result in moderate toxicity to aquatic organisms, mainly due to acidification of the test medium. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Acid chlorides are prepared through the reaction of carboxylic acids and phosgene in the presence of catalysts such as N,N-dialkylcarbamides or tertiary amines. Given the high reactivity and toxicity of reactants and reaction products, the synthesis is conducted in closed-systems under strictly controlled conditions. The following summarizes the 2005 production volumes in tonnes of the acid chlorides for the sponsor country, Europe and Japan; ranges are provided in order to protect confidential business information.

	Sponsor country	Europe	Asia
PCl	ca. 4536-22680	ca. 0-4536	ca. 0-4536
EhCl	ca. 4536-22680	ca. 0-4536	ca. 0-4536
NdCl	ca. 4536-22680	ca. 0-4536	ca. 0-4536
NnCl	0	0	0

NnCl is produced in batch such that it may not be produced every year: production volume for 2002 was > 1,000,000 pounds (ca 454 tonnes). All category members are used solely as industrial intermediates and are sold only to industrial customers.

Acid chlorides are manufactured within enclosed reactors and are filled into drums through closed systems. There are no intentional releases to the environment. The reactive nature of the acid chlorides destroys the parent material in water, thus limiting environmental exposure. Acid chlorides hydrolyze rapidly; resulting in the production of one mole of HCl and one mole of an organic acid.

In order to limit exposures due to the irritating nature of these substances and their high acute toxicity, these chemicals are manufactured within enclosed reactors and are filled into drums through closed systems. Engineering controls (such as room air exchange, local exhaust) and personal protective equipment (respirators) are also used as standard industry practice to further prevent exposure. Additionally, due to the highly irritating nature of these

materials and their high vapor pressure, employees are trained on the safe use and handling as well as emergency procedures in the event of an accident. Inhalation is the route of exposure with the greatest concern in the occupational setting due to the relatively high vapor pressures of these materials.

Customers of these materials use acid chlorides solely as chemical intermediates due to their high reactivity. As first step intermediates, these materials are reacted with nucleophiles containing various functional groups such as oxygen, sulfur, and nitrogen. Available analytical information indicates the residue concentration of acid chlorides in final products is expected to be extremely low due to their reactivity. As demonstrated for the nucleophile "water", hydrolysis is complete in less than 24 h with remaining residual acid chlorides in amounts below detection limit.