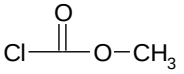
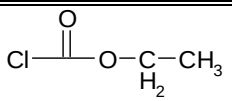
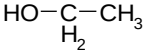
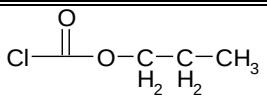
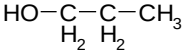
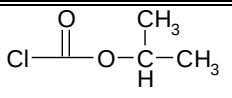
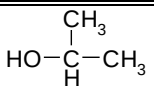
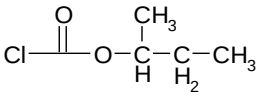
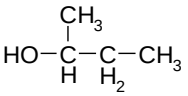
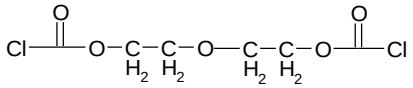
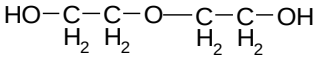
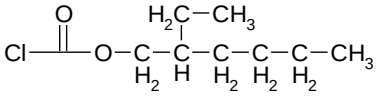
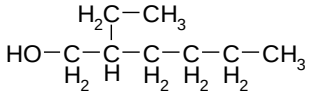
SIDS INITIAL ASSESSMENT PROFILE

Chemical category	CHLOROFORMATES
Category Members: **CAS Registry Numbers, Chemical Names and their Abbreviations**	**Sponsored substances**: 79-22-1 Methyl chloroformate (MeCF) 541-41-3 Ethyl chloroformate (EtCF) 109-61-5 Propyl chloroformate (PrCF) 108-23-6 Isopropyl chloroformate (IpCF) 17462-58-7 Sec-Butyl chloroformate (SbCF) 106-75-2 Oxydiethylene bis(chloroformate) (ObCF) 24468-13-1 2-Ethylhexyl chloroformate (EhCF) **Hydrolysis products:** 67-56-1 Methanol (Me) 64-17-5 Ethanol (Et) 71-23-8 1-Propanol (Pr) 67-63-0 Isopropanol (Ip) 78-92-2 Sec-Butanol (Sb) 111-46-6 Diethylene glycol (DEG) 104-76-7 2-Ethyl hexanol (Eh) 7647-01-0 Hydrogen chloride (HCl)

Category Members:

Structural Formulae

Sponsored substances	Hydrolysis products
MeCF: 	Me: 
EtCF: 	Et: 
PrCF: 	Pr: 
IpCF: 	Ip: 
SbCF: 	Sb: 

	ObCF: 	DEG: 
	EhCF: 	Eh: 
		HCl: 

SUMMARY CONCLUSIONS OF THE SIAR

Category/analogue rationale

The category consists of seven chloroformates: MeCF, EtCF, PrCF, IpCF, SbCF, ObCF and EhCF which are grouped into a category based on similar structure (i.e., the chloroformate group), high reactivity of the chloroformate group and toxicological and environmental effects. The justification for the category is based not only on a similar structure (specifically the –O(C=O)-Cl portion of the molecule) but also a similar mechanism of action which results in similar human health effects (i.e., severe irritation at the point of contact) and environmental effects. The chloroformate group on the molecule drives the observed irritation rather than the alkyl side chain.

The chloroformate group (i.e., -O(C=O)Cl) is the most active functional group and determines many aspects of the behaviour of the category members. Hydrolysis is the primary reaction in aqueous systems and has been shown to occur very quickly (Half-life ≤ 30 min). All category members hydrolyze in the presence of water or moisture to form hydrochloric acid (HCl), carbon dioxide (CO_2) and the corresponding alcohol (see above) according to the following reaction:

$$R\text{-}O(C{=}O)Cl + H_2O \rightarrow R\text{-}OH + HCl + CO_2$$

For human health, the chloroformates react and/or hydrolyze at the portal of entry resulting in localized injury. Systemic absorption is expected to be low. However, data for HCl and the corresponding alcohols are available to address potential systemic toxicity. Available toxicological data for the sponsored substances, supplemented by data for the hydrolysis products, support the grouping of these chemicals into a category.

Where appropriate, read-across or data for the corresponding alcohol and HCl are used to address physico-chemical, environmental fate and aquatic toxicity endpoints, and the reproductive toxicity endpoint for human health. Except for propanol, all hydrolysis products have been previously assessed in the OECD HPV Programme (http://webnet.oecd.org/hpv/ui/Search.aspx). Diethylene glycol is a member of the Ethylene Glycol category. These documents are available via the OECD Existing Chemicals Database at http://webnet.oecd.org/hpv/UI/SIDS_Details.aspx?Key=ac0359d3-c5c1-402b-9c47-14f61efd98e0&idx=0. 1-Propanol was extensively evaluated under the EU 2nd priority list of existing substances. The Risk Assessment Report is available at http://ecb.jrc.ec.europa.eu/esis/.

Physical-chemical properties

Category members

The category members are colourless liquids with measured melting points of <-81 to <-20 °C, except for ObCF which has a measured melting point of 5-6 °C. The measured boiling points range from 71 °C (MeCF) to 264.5 °C (ObCF). SbCF, ObCF and EhCF decompose before boiling. A vapour pressure of < 1 hPa was determined for ObCF, whereas the measured vapour pressures of the other category members are between 21.7

hPa (EhCF, 25 °C) and 137.5 hPa (MeCF, 20 °C). Adequate data on the log K_{ow} were not available; read-across from the hydrolysis products is provided. Water solubility ranged from 3 mg/L (20 °C, measured) for ObCF to 49 mg/L for EhCF (25 °C, calculated), and to higher values for other members ($1.1 \times 10^4 - 9.3 \times 10^5$ mg/L, 25 °C).

Hydrolysis products

The measured log K_{ow}s of the hydrolysis products are Me -0.74, Et -0.31, Pr 0.34, Ip 0.05 (25^oC), Sb 0.61 (20^0C), DEG -1.98/-1.47 and Eh 2.97 (25^oC).

These compounds are fully miscible with water, and the water solubility of Eh was experimentally determined to be 400 – 1000 mg/L (20 °C).

Human Health

No toxicokinetics data were available for the chloroformates; however, hydrolysis of these substances is expected to produce hydrochloric acid (HCl), carbon dioxide (CO2) and the corresponding alcohols.

The acute toxic effects of the chloroformates are primarily local caustic/irritating effects at the site of contact. Acute inhalation studies are available for the chloroformates category. LC_{50}s in the rat range from 0.46 (MeCF) to > 2.5 (ObCF) mg/L after 1-hour exposures and from 0.06 (MeCF) to < 2.33 (SbCF) mg/L after 4-hour exposures. Clinical findings include bloody/nasal discharge, dyspnoea, gasping, and irregular respiration. Hyperaemic, oedematous, red/haemorrhagic lungs were found at necropsy for multiple chloroformates. Lesser clinical symptoms included hydrothorax and emphysema. By the dermal route, the LD_{50}s >2000 mg/kg bw in rabbits; however, the chloroformates are very irritating and corrosive to the skin. With the exception of EhCF, there were no other gross pathologic findings. For EhCF, focal haemorrhages were observed in the lung and red lungs. The acute oral toxicity for category members in the rat ranges from 40 mg/kg bw (MeCF) up to 3038 mg/kg bw (EhCF) when given undiluted or as an aqueous solution. The acute oral toxicity of the sponsored substances is lower when applied in olive oil and ranges from 313 mg/kg bw (MeCF) up to 5420 mg/kg bw (EhCF) in rats. Clinical signs of toxicity included gastrointestinal irritation, necrosis and haemorrhage.

With the exception of EhCF, all of the sponsored chloroformates caused irreversible damage to the eye in animal tests. Experimental data suggest that chloroformates are moderately to extremely irritating/corrosive to the skin. Corrosive effects have been observed for MeCF, EtCf and PrCF. IpCF, SbCF and ObCF are moderately to severely irritating to the skin of rabbits. EhCF was moderately irritating in one study and corrosive in a second study. The upper respiratory tract irritation observed in rats and mice for these materials is also believed to be due to liberation of HCl. Chloroformates in the vapour phase may hydrolyze due to the water vapour present in the ambient air, water vapour present in the humid inhaled air in the respiratory tract, or upon contact with the mucous layer of the airways. Sensitisation data were not available for the chloroformates category.

Repeated-dose inhalation toxicity studies are available for MeCF (28- and 90-days), EtCF (28-day), and IpCF (28-day). In these repeated-dose studies, the inflammatory response in the respiratory tract was severe and mortality occurred at the highest exposure concentrations. Toxicity to tissues other than the respiratory tract was not noted at concentrations up to approximately 35 ppm (0.0120 mg/L/day) of MeCF, EtCF, and IpCF. In a repeated dose inhalation toxicity study following OECD TG 412, MeCF was administered via inhalation by whole body exposure to rats (5/sex/concentration) at 0 (air), 0.00052, 0.0015, 0.0039, 0.0012, or 0.035 mg/L/day, for 6 hours/day, 5 days/weeks for 28 days. Based on no treatment-related effects to the respiratory tract, the local 28-day NOAEC for MeCF was 0.0039 mg/L/day; based on mortality, decreased body weight and food consumption and changes in haematological/clinical chemistry parameters at 0.035 mg/L/day, the systemic 28-day NOAEC for MeCF was 0.012 mg/L/day. In a repeated-dose inhalation toxicity study following OECD TG 413 (but without haematology or clinical chemistry evaluation and focusing on respiratory tract irritation), MeCF was administered via inhalation by whole body exposure to rats (10/sex/concentration) at 0 (air), 0.0016, 0.0078, 0.0157, or 0.0307 mg/L/day, for 6 hours/day, 5 days/weeks for 3, 10, 20 and 65 exposures (90-day study with interim necropsies after 3, 14 and 28 study days). Based on substance-related pathological alterations and changes in DNA replication in the respiratory tract at 0.0078 mg/L/day and above, the local 90-day NOAEC for MeCF was 0.0016 mg/L/day; based on significant weight loss at 0.0157 mg/L/day, the systemic 90-day NOAEC for MeCF was 0.0078 mg/L/day. In a repeated-dose

inhalation toxicity study comparable to OECD TG 412, IpCF was administered via inhalation by whole body exposure to rats (10/sex/concentration) at 0 (air), 0.021, 0.062 or 0.181 mg/L/day (analytical concentrations), for 6 hours/day, 5 days/weeks for 28 days. Based on effects to the respiratory tract at 0.062 mg/L/day and above, the 28-day local NOAEC for IpCF is 0.021 mg/L/day; based on treatment-related effects to the lungs and thyroid and decreased body weight gain and food consumption at 0.181 mg/L/day, the 28-day systemic NOAEC for IpCF is 0.062 mg/L/day.

The chloroformates category members are not mutagenic *in vitro*, with the exception of MeCF, which was positive for chromosomal aberrations in the presence of metabolic activation. The alcohol moiety hydrolysis products did not induce chromosomal aberrations *in vitro*. Positive results have been obtained in the *in vitro* chromosome aberration test with HCl; however, the positive results were considered to be the effect of low pH or cytotoxicity. The hydrolysis products, Et and Pr, did not induce chromosomal aberrations *in vivo*. The hydrolysis products, Me, Ip, and Eh, did not induce mouse micronuclei *in vivo*. The chloroformates are not expected to be genotoxic. Carcinogenicity data were not available for the chloroformates category.

No reproductive toxicity studies were available for the chloroformates category members. Data are available for all of the hydrolysis products. No effects on fertility were observed in inhalation studies with rats exposed to Me or Et . The inhalation NOAEC for reproductive toxicity ranges from 1000 ppm (1.3 mg/L) for Me to 16000 ppm (30 mg/L) for Et. In an inhalation study with Pr in rats, male fertility was impaired. The NOAEC for reproductive toxicity (males) was 3500 ppm (8.9 mg/L) and females 7000 ppm (17.9 mg/L) (highest dose tested). No effects on the gonads were observed after repeated inhalation exposures to HCl in rats up to 50 ppm. Similarly, there were no effects on the reproductive organs in rats after repeated inhalation exposures to Eh at 0.64 mg/L/day. No significant adverse effects on fertility were observed in drinking water studies with rats exposed to DEG, Sb and Ip. The NOAELs range from 625 mg/kg bw/day (male rat; Ip) to 1500 mg/kg bw/day for Sb and 6125 mg/kg bw/day for DEG. For Et, reproductive effects in rats exposed by the oral route, other than an increase in the number of small pups, were observed at very high concentrations; the NOAEL for reproductive toxicity is >2000 mg/kg/day. For Ip, in an oral 2-generation study in rats, there was a decrease in the male mating index at 1000 mg/kg bw/day. The NOAEL for reproductive toxicity is 500 mg/kg bw/day. No developmental effects were observed in the absence of maternal toxicity for Et, Ip, Sb, DEG, and Eh. Malformations and foetal weight changes were observed following the inhalation exposure of rats to Me. The NOAEC is 6.65 mg/L/day (5000 ppm). Inhalation exposure of rats exposed to Pr showed skeletal malformations at 17.9 mg/L/day. At 25.5 mg/L/day, there was a significant increase in the incidence of skeletal, visceral and external malformations and significant implantation loss. The NOAEC for developmental toxicity is 8.9 mg/L. For HCl, no reliable studies were available. As reproductive and developmental effects are seen only at high doses for the alcohol hydrolysis products, the chloroformates category members are not expected to be reproductive toxicants and are unlikely to show developmental toxicity.

The chloroformates possess properties indicating a hazard for human health (acute inhalation and oral toxicity, irritating/corrosive properties). Methanol (hydrolysis product) exhibits potential hazardous properties for human health (neurological effects, CNS depression, ocular effects, reproductive and developmental effects, and other organ toxicity). HCl (hydrolysis product) exhibits potential hazardous properties for human health (corrosiveness to the skin and the eyes). Adequate screening-level data are available to characterize the hazard to human health for the purposes of the OECD HPV Chemicals Programme.

Environment

Hydrolysis is the primary and major fate process of the chloroformates category members. The category members were shown to have very short half-lives in aqueous solutions (pH 4, 7, 9) ranging from a few minutes (ObCF, IpCF) to about 30 minutes for (EhCF). In the OECD TG 111 studies one of the expected hydrolysis products (corresponding alcohol) were confirmed by gas chromatography. Although stoppered flasks were used, hydrolysis rates could be an overestimation as evaporation during the tests could not be excluded. In the case of PrCF, for which no guideline study was available, results from an older hydrolysis study as well as read-across to an analogue category member (IpCF) were used to confirm its hydrolytic reaction profile. Read across to IpCF is also suitable for SbCF, for which no experimental results on hydrolytic activity were available. The alcoholic hydrolysis products do not have hydrolysable groups and are therefore hydrolytically stable.

In the atmosphere, indirect photo-oxidation of the category members by reaction with hydroxyl radicals is predicted to occur with half-lives ranging from less than 1 day (EhCF and ObCF) to ca. 49 days (MeCF). The estimations refer to a 12-h day with an assumed OH radical concentration of 1.5×10^6 OH/cm³.

Ready biodegradability testing was conducted on EtCF, as well as for all hydrolysis products. EtCF was readily biodegradable in a MITI (I) test following OECD TG 301C. All hydrolysis products, with one exception (DEG), are readily biodegradable (biodegradation > 70% at test end, 10-days window met). The weight of evidence suggests that the category members, with the exception of ObCF, are readily biodegradable, based on their rapid hydrolysis and ready biodegradability of their hydrolysis products.

A level III fugacity model calculation with equal distributions to air, water and soil compartments suggests that the main target compartments of the category members and their hydrolysis products are soil and water. The calculated BCF values for the sponsored substances (2.3 to 95) indicate a low bioaccumulation potential. The (predominantly calculated) BCF values for the hydrolysis products (1 to 42) indicate a low potential for bioaccumulation.

The following acute fish toxicity test results using nominal concentrations have been determined for the parent chloroformate category members, with the exception of IpCF for which mean measured concentrations were extrapolated via chemical analysis of the hydrolysis product isopropanol:

Leuciscus idus, MeCF: 96-h LC_{50} = 4.5 mg/L (static)

Danio rerio, PrCF: 96-h LC_{50} = 3.16 mg/L (static)

Danio rerio, IpCF: 96-h LC_{50} = 8.2 mg/L (semi-static)

Danio rerio, SbCF: 96-h LC_{50} = 46.4 mg/L (static)

Leuciscus idus, ObCF: 96-h LC_{50} = 1.78 mg/L (static)

Leuciscus idus, EhCF: 96-h LC_{50} = 3.16 mg/L (static)

Danio rerio, EhCF: 96-h LC_{50} = 4.18 mg/L (static)

(pH remained within acceptable limits during all testing)

Due to the short hydrolysis half-lives (≤ 30 min) of the chloroformates category members, results from the hydrolysis products are also used to fulfil the endpoint requirements with respect to ecotoxicology.

The following acute aquatic toxicity test results have been determined with the alcohol hydrolysis products:

Fish [*Leuciscus idus*], 2-ethylhexanol (Eh): 96-h LC_{50} = 17.1 mg/L (nominal, flow-through)

Fish [several *spp*.], all other alcohols: 96-h $LC_{50} \geq 3200$ mg/L (nominal)

Invertebrate [*Daphnia magna*], 2-ethylhexanol (Eh): 48-h EC_{50} = 35.2 mg/L (nominal, static)

Invertebrate [*Daphnia magna*], all other alcohols: 24/48-h $EC_{50} \geq 1000$ mg/L (nominal, static)

Algae [*Scenedesmus subspicatus*], 2-ethylhexanol (Eh): 72 h EC_{50} = 11.5 mg/L (nominal)

Algae and aquatic plants [div.], all other alcohols: EC_{50} > 100 mg/L (nominal)

The following chronic toxicity test results have been determined:

Invertebrate [*Ceriodaphnia dubia*], Ethanol (Et): 9-d NOEC = 9.6 mg/L (nominal)

Invertebrate [*Daphnia magna*], Isopropanol (Ip): 21-d NOEC = 30 mg/L (nominal)

Although the members of the chloroformates category hydrolyze quickly, it is possible that the observed toxicity to fish is partly related to high reactivity of unhydrolyzed chloroformates at the very beginning of the test. The toxicity may be explained by reactions with nucleophiles (such as -NH2, -SH and -OH) on biological macromolecules.

The hydrolysis product, HCl, is acutely toxic to fish due to the acidification of the test medium. The latter effect, however, is unlikely to be responsible for the toxicity of the chloroformates. The following acute toxicity test results have been determined with the HCl hydrolysis product:

Fish [*Cyprinus carpio*] 96-h LC_{50} = 4.92 mg/L (pH 4.3)

Invertebrate [*Daphnia magna*] 48-h EC_{50} = 0.492 mg/L (pH5.3)

Algae [*Selenastrum capriornutum*] 72-h EC_{50} = 0.780 (pH 5.1) and 0.492 (pH5.3) mg/L for biomass and growth rate, respectively.

The available results from acute toxicity studies on fish show that the chloroformate category members produce toxic effects in aquatic systems. Similar toxic effects would also be expected for other environmental organisms such as daphnia and algae.

The chloroformates possess properties indicating a hazard for the environment (acute aquatic toxicity values between < 1 and 100 mg/L). The substances are readily biodegradable with the exception of ObCF, and all have a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

The worldwide quantity of chloroformate production in 2008 was estimated at 10,000 - 12,000 metric tons for Europe and 3,000 – 5,000 metric tons for Asia. In the United States (sponsor country), chloroformate production ranged from 500,000 to 50 million pounds (225 – 22,500 metric tons) in 2006. Most alkyl chloroformates are discontinuously or continuously prepared by the reaction of the corresponding liquid anhydrous alcohol with molar excess of dry, chloride-free phosgene. Evolving HCl is absorbed in a tower after recovering excess phosgene. Unreacted phosgene is removed from the crude chloroformates by vacuum stripping or gas purging.

Chloroformates are highly reactive and can be used as intermediates in the synthesis of numerous compounds. Derivatization of chloroformates with alcohols and amines leads to carbamates and carbonates which are further processed to solvents, polycarbonates (high temperature resistant), polyurethanes [especially from bis(chloroformic) esters] and plastics of high optical quality. Chloroformates are also valued as general purpose derivatizing agents for gas and liquid chromatographic analysis of molecules containing active functionality such as amines and carboxylic acids. Chloroformates are also used as amino acid blocking agents during the synthesis of complex organic compounds.

Chloroformates are manufactured within enclosed reactors and drums are filled using closed systems. Reactors are housed in enclosed buildings. Occupational exposure is expected to be low because engineering controls (such as room air exchange, local exhaust, automatic phosgene monitoring) and personal protective equipment (respirators, protective rubber suits) are used as standard industry practice to limit occupational exposures during maintenance, cleaning, etc. Additionally, employees are trained on safe use and handling, as well as emergency procedures in the event of an accident.

Chloroformates may be used in chromatographic analyses in laboratory settings, with some potential for occupational exposure. However, once they react during the analysis, exposure is expected to be limited.

Chloroformates are manufactured within enclosed reactors and are filled into tanks, drums or other suitable containers through closed systems, which limits environmental exposure. Available data indicate that in 2008 in the sponsor country, more than 9,500 kg of MeCF and approximately 120,000 kg of EtCF were incinerated (as a waste disposal method). Other releases totalled less than 100 kg of each of these chemicals in 2008.

Chloroformates are not used in consumer products and therefore, exposure is not expected. Any residual content is expected to be low.