SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-05-7
Chemical Name	2-Ethylhexaldehyde
Structural Formula	O=CH-CH(CH2-CH3)-CH2-CH2-CH2-CH3

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Several of the health endpoints for 2-ethylhexaldehyde make use of data from 2-ethylhexanol and 2-ethylhexanoic acid experiments. The logic for this "metabolic series" approach includes the metabolism of alcohols (2-ethylhexanol) proceeding via a readily reversible reaction with alcohol dehydrogenase(s) to rapidly form the respective aldehydes (2-ethylhexaldehyde). The aldehydes are short-lived due to the enzymatic activity of aldehyde dehydrogenase that forms the respective organic acids (2-ethylhexanoic acid). Assuming 2-ethylhexaldehyde behaves as other aldehydes, direct exposure to 2-ethylhexaldehyde will result in the rapid formation of both 2-ethylhexanol and 2-ethylhexanoic acid. The metabolic processes of these two chemicals are well characterized. Toxicity data from studies conducted with 2-ethylhexanol and 2-ethylhexanoic acid have been used to identify the hazards associated with systemic exposure to 2-ethylhexaldehyde and therefore are useful in identifying hazards associated with 2-ethylhexaldehyde systemic exposures. Structural analogues are used to address several Environmental Hazard endpoints: 2-methyl propionaldehyde (CAS No.78-84-2), 2-ethyl butyraldehyde (CAS No.97-96-1), 2-methyl valeraldehyde (CAS No. 123-15-9), valeraldehyde (CAS No. 110-62-3), hexaldehyde (CAS No.66-25-1), and octylaldehyde (CAS No. 124-13-0).

Physical-Chemical Properties

2-Ethylhexaldehyde is a liquid at standard temperature and pressure, with a boiling point of 163 ºC and a melting (freezing) point of <–100 ºC. It is less dense than water with a specific gravity of 0.854 g/cm^3 at 20ºC. The solubility limit in water is approximately 400 mg/L at 25 ºC. 2-Ethylhexaldehyde is combustible with a flash point of 44 ºC. It has a vapour pressure of 2.61 hPa at 25 ºC. Given its solubility limits of 400 mg/L at 25 ºC and its molecular weight of 128.22 g/mole, the preferred Henry's law constant at 25 ºC has been calculated to be 7.59X10^{-4} atm-cu m/mole. The estimated log Kow is 2.71.

Human Health

2-Ethylhexaldehyde is formed from the metabolism of 2-ethylhexanol and is presumed to undergo subsequent oxidation to 2-ethylhexanoic acid. Although 2-ethylhexaldehyde formed from 2-ethylhexanol has not been demonstrated in vivo, metabolism and toxicokinetics studies with 2-ethylhexanol have demonstrated the presence of 2-ethylhexanoic acid in the plasma as well as glucuronide conjugates and oxidation products of 2-ethylhexanoic acid metabolism in the urine following intravenous, dermal and oral exposures. Elimination of 2-ethylhexanol metabolites following oral exposure was complete within 24 hours. Comparison of 2-ethylhexanol and 2-ethylhexanoic acid metabolic/toxicokinetics information and toxicity databases suggests that the metabolic processes necessary to convert 2-ethylhexanol to 2-ethylhexanoic acid explain the difference in toxicity of these chemicals. When other aldehydes are administered in vivo, both the parent alcohol and the acid metabolite are formed initially. Assuming that 2-ethylhexaldehyde undergoes similar metabolic processes, 2-ethylhexanol and 2-ethylhexanoic acid are expected to be formed following exposure to the aldehyde. Therefore, toxicity information from these two

chemicals are relevant for 2-ethylhexaldehyde hazard identification. The rapid, irreversible formation of 2-ethylhexanoic acid from 2-ethylhexaldehyde suggests that this chemical is most relevant for identification of toxicity properties for 2-ethylhexaldehyde. The site of contact toxicity noted in the 28-day repeated dose toxicity study of 2-ethylhexaldehyde limits the exposure concentrations that could be used in a repeated dose toxicity study and therefore the data from 2-ethylhexanol and 2-ethylhexanoic acid are considered adequate to assess the systemic toxicity of 2-ethylhexaldehyde.

The oral LD_{50} values for 2-ethylhexaldehyde are 3,078 mg/kg bw and 3,536 mg/kg bw for male and female rats, respectively. Clinical signs from all acute oral studies include central nervous system signs (weakness, narcosis or prostration) and/or gastrointestinal tract irritation with >2500 mg/kg bw and slight weakness noted in animals treated with 1250 mg/kg bw. Inhalation exposure of rats (5/group) for 4 hours caused no deaths at 6.83 mg/L (1279 ppm) with gradual reduction in respiratory rate, response to external (noise) stimuli and irritation of mucosal surfaces noted at this concentration. The dermal LD_{50} in male and female rats is >20 ml/kg bw (17,080 mg/kg bw); the substance was applied undiluted under an occlusive wrap for 24 hours and produced erythema at the application site. 2-Ethylhexaldehyde is a moderate to severe skin irritant in rabbits and guinea pigs and a severe eye irritant in rabbits. Respiratory tract irritation has been reported in the acute inhalation toxicity studies at 6.83 mg/L (1,279 ppm and higher). An RD_{50} sensory irritation value of 1.2 mg/L (225 ppm) was reported in mice. 2-Ethylhexaldehyde was negative for skin sensitization in a Kligman human patch test with 2% in petrolatum.

A 28-day repeated exposure inhalation study with limited histopathology is available for 2-ethylhexaldehyde. Effects observed at the highest concentration (1.34 mg/L; 250 ppm) included porphyrin tears, reduced body weights and feed efficiency, decreased lymphocytes and increased neutrophils, decreased serum glucose and cholesterol, increased serum triglycerides, increased alkaline phosphatase activity, decreased thymus weights, increased testes, heart (males only), liver, adrenal, kidney and lung weights. No histopathological effects were noted in the testes or liver (the only tissues examined). Increased alkaline phosphatase activity was also noted at the 0.134 mg/L (25 ppm) and 0.536 mg/L (100 ppm) concentrations. Biochemical measures of peroxisome proliferation were found at the 0.536 and 1.34 mg/L exposure concentrations. Several metabolism studies with 2-ethylhexanol have demonstrated the primary metabolite to be 2-ethylhexanoic acid; presumably via the 2-ethylhexaldehyde metabolite. Therefore, information on both 2-ethylhexanol and 2-ethylhexanoic acid have been included to supplement the toxicity data for 2-ethylhexaldehyde. The NOEC from the thirteen week inhalation rat study with 2-ethylhexanol was 0.639 mg/L (120 ppm; the highest vapour concentration achievable). A thirteen week gavage study with 2-ethylhexanol in rats caused stomach irritation, increased reticulocytes and liver effects (increased liver weight, decreased serum cholesterol, albumin and total protein, liver histopathology and peroxisome proliferation) in the 500 mg/kg bw/day male and female rats. Milder liver effects indicative of peroxisome proliferation was noted in male and female rats at 250 mg/kg bw/day. The NOAEL in male and female rats was 125 mg/kg bw/day. A similar study in mice produced a NOAEL of 125 mg/kg bw/day based on increases in relative liver weights in male mice at the 250 mg/kg bw/day dose level. The ability of 2-ethylhexanol to induce hepatic peroxisome proliferation in male and female rats and mice following 14 days of oral exposure has been demonstrated. Two-week and 13-week dietary studies in rats and mice with 2-ethylhexanoic acid demonstrated effects on the liver (increased absolute and relative liver weights, hepatocytes hypertrophy, increased cholesterol and decreased triglyceride serum levels, and peroxisome proliferation). The lowest NOEL from these studies was 180 mg/kg bw/day in male mice from the subchronic study.

In vitro studies demonstrate that 2-ethylhexaldehyde was not mutagenic to *Salmonella typhimurium* at concentrations up to 666 µg/plate, with and without metabolic activation. *In vivo*, 2-ethylhexaldehyde did not induce micronuclei in bone marrow of male and female mice following an oral limit dose of 2000 mg/kg bw/day. In addition, 2-ethylhexanol (via intraperitoneal injection) and 2-ethylhexanoic acid (by oral gavage) did not induce an increase in micronuclei in erythrocytes in mice.

In oral (gavage) assays with 2-ethylhexanol in rats using dose levels of 0, 50, 150 or 500 mg/kg bw/day (24 months), reduced body weight gain was noted in rats in the 150 (males, 11%; females, 9%) and 500 (males, 23%; females, 21%) mg/kg bw/day dose groups. Laboured breathing and

poor condition was noted in the 500 mg/kg bw/day animals. Dose-related increases in relative liver, stomach, and kidney weights were noted at sacrifice in the 150 and 500 mg/kg bw/day groups. Mortality in female rats (52%) was markedly increased at 500 mg/kg bw/day. The sum of the hepatocellular adenomas and carcinomas was less in the male treated groups (7) than in the two male control groups (8). The incidence of hepatocellular carcinomas in the female water control group was 1, in the 500 mg/kg bw/day was 0, and were a total of three in the 50 and 150 mg/kg bw/day groups combined. The test material was not oncogenic in rats.

In oral (gavage) assays with 2-ethylhexanol in mice using dose levels of 0, 50, 200 or 750 mg/kg bw/day (18 months), no dose-related changes were noted in mice receiving 50 or 200 mg/kg/day. At 750 mg/kg/day, reduced body weight gain (12% in males and 14% in females), decreased feed consumption (9% in males and 12% in females) and increased mortality were noted (30% in males and females by weeks 79-81). Increases in relative kidney (females only), liver (females only) and stomach weights (males and females) were noted at sacrifice in the 750 mg/kg bw/day group. The test material was not considered oncogenic in male mice. An increase in hepatocellular carcinomas in the female 750 mg/kg bw/day group was statistically significant when compared to the vehicle control group but not when compared to the concurrent water control group. This lead to the conclusion that 2-ethylhexanol was considered a weak or equivocal liver carcinogen in female mice at this dose level. Interpretation of this data is complicated by the severe toxicity (increased mortality) noted in mice at the 750 mg/kg bw/day dose level, the known ability of 2-ethylhexanol to induce peroxisome proliferation in rodent liver (as a potential mechanism of action for tumour formation) and the background incidence of liver tumours in this strain of mice.

2-Ethylhexaldehyde is a developmental toxicant. A rat oral gavage study conducted with 2-ethylhexaldehyde reported maternal toxicity (piloerection, reduced activity, 23% reduction in body weight gain, 8% reduction in body weight, reduced feed consumption) and developmental toxicity (overt malformations and a 34% reduction in foetal body weights) at the 798 mg/kg bw/day dose level. At the 300 mg/kg bw/day dose level, no maternal toxicity was reported while evidence of foetal developmental delay (increased incidence of fetuses with incomplete ossification of the 5th/6th sternebrae and of the sacrocaudal vertebral arches) was present. No foetal abnormalities were noted at 100 mg/kg bw/day. 2-Ethylhexanol causes developmental toxicity (reduced foetal body weights (-9.5%), a single type of skeletal vertebral malformation, reduced skeletal ossification) in rats only at oral dose levels of 650 mg/kg bw/day, a dose level causing significant maternal toxicity. The highest dose level (1300 mg/kg bw) caused maternal deaths, reduced feed consumption and body weight gain in the dams, increased resorptions, foetal death and decreased foetal weights and malformations in the surviving foetuses. 2-Ethylhexanol is not a developmental toxicant via the dermal (up to 2,520 mg/kg/day) or inhalation routes of exposure (up to 0.85 mg/L) in rats. 2-Ethylhexanoic acid is a developmental toxicant in rats with a NOAEL of 100 mg/kg bw/day and maternal and foetal findings similar to those for 2-ethylhexaldehyde.

No reproductive toxicity studies were available for 2-ethylhexaldehyde. The 28-day inhalation study in rats with 2-ethylhexaldehyde did not find any histopathological effects on the testes. 2-Ethylhexanol is not considered a reproductive toxicant based on data from repeated exposure studies as well as *in vitro* investigations. There were no treatment-related histological changes in either the testes or ovaries (in mice and rats) after 13 weeks of treatment with 2-ethylhexanol at dosages up to 500 mg/kg bw/day. 2-Ethylhexanoic acid is not a reproductive toxicant. 2-Ethylhexaldehyde is not considered a reproductive toxicant.

2-Ethylhexaldehyde possesses properties indicating a hazard for human health (severe skin and eye irritation, respiratory tract irritation and developmental toxicity). Adequate screening-level data are available to characterize the hazard for the human health purposes of the OECD HPV Programme.

Environment

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is a likely route of degradation, and is predicted to occur with an estimated half-life of 3.7 hours. A 28-day aerobic test, OECD TG 301F, using 2-ethylhexaldehyde, was conducted using activated sludge. Biodegradation was 70-80% after 28 days, indicating the material is readily biodegradable.

2-Ethylhexaldehyde is stable in water, as it has no hydrolysable groups. Fugacity modelling (Level III) was conducted for 2-ethylhexaldehyde. The resulting distributions are 2.02% to air, 24.9% to

water, 72.8% to soil and 0.246% to sediment. An octanol/water partitioning coefficient (Log K_{ow}) value of 2.71 has been estimated for 2-ethylhexaldehyde. This value suggests that 2-ethylhexaldehyde will not significantly bioconcentrate in aquatic organisms. Using the log K_{ow} of 2.71, a BCF of 24 was calculated, which further indicates a low bioaccumulation potential.

The vapour pressure of 2-ethylhexaldehyde is 2.61 hPa at 25°C, and the Henry's law constant is 7.59 X 10^{-4} atm-cu m/mole at 25°C. These values suggest that volatilization of 2-ethylhexaldehyde from the water phase is expected to be moderate, with estimated half-lives for a model river and model lake at 4.6 hours and 5 days, respectively. The K_{oc} of 2-ethylhexaldehyde is estimated at approximately 54, which suggests that 2-ethylhexaldehyde has medium mobility in soil.

There were no fish toxicity data available for 2-ethylhexaldehyde. The ECOSAR estimated 96-hr LC_{50} for 2-ethylhexaldehyde in fish is 6.43 mg/L. Several studies examining the toxicity of 2-methyl propionaldehyde, 2-ethyl butyraldehyde, valeraldehyde, 2-methyl valeraldehyde, n-hexaldehyde, and n-octylaldehyde in fish are available. A study with branched- and straight-chain aldehydes in fish used guppy (*Poecilia reticulata)* in a 14-day static renewal test system. The 14-day LC_{50} was 26.8, 7.8, 13.0, 9.8, and 7.9 mg/L for 2-methyl propionaldehyde, 2-ethyl butyraldehyde, valeraldehyde, n-hexaldehyde, and n-octylaldehyde, respectively. Acute flow-through tests were conducted with fathead minnows (*Pimephales promelas)* with hexaldehyde, valeraldehyde, and 2-methyl valeraldehyde. The 96-hr LC_{50} values were reported as 14.0, 12.4, and 18.8 mg/L, respectively. The test solutions in all studies were not buffered.

The critical study that evaluated the toxicity of 2-ethylhexaldehyde to aquatic invertebrates is a study conducted with *Daphnia magna*. The 48-hour EC_{50} for immobilization is 11.5 mg/L. The test solutions were not buffered.

An acute toxicity study in algae (*Scenedesmus subspicatus*) with 2-ethylhexaldehyde reported a 96-hour EC_{50} for growth inhibition of 52.1 mg/l.

The results of these studies indicate that aquatic vertebrates, invertebrates and algae are all similar in response to exposures of 2-ethylhexaldehyde and surrogate aldehydes.

2-Ethylhexaldehyde possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L in unbuffered systems). However, the chemical is readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

2-Ethylhexaldehyde had a production and/or import volume (aggregated across companies) in the United States between 22,680 and 45360 tonnes (50 million and 100 million pounds) during 2005. Virtually all of the reported production of 2-ethylhexaldehyde in the United States is for use as an industrial intermediate in the manufacture of 2-ethylhexanoic acid. There are some reports of minor uses of 2-ethylhexaldehyde as a component in fragrances. 2-Ethylhexaldehyde is a naturally-occurring volatile found in baked potatoes. It has also been detected in the emissions from particle board. No monitoring data within production and processing sites in the United States were available. 2-Ethylhexaldehyde is a combustible liquid with a pungent odour. This material may undergo hazardous polymerization on exposure to heat, accelerators/initiators, and other contaminants. 2-Ethylhexaldehyde can form organic peroxides of unknown stability. 2-Ethylhexaldehyde is manufactured in an enclosed, continuous process and engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to minimize workplace exposure and odour complaints. Emission controls are usually employed to minimize release of 2-ethylhexaldehyde during manufacture and use. However, 2-ethylhexaldehyde may be released to the environment as a fugitive emission during production and use.