SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-62-3
Chemical Name	n-valeraldehyde
Structural Formula	CH_3-CH_2-CH_2-CH_2-CH=O

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

As a group, aliphatic aldehydes have similar structures, reactivities, and effects (e.g., respiratory irritation). As a result, their data can be used to assess the potential toxicity of valeraldehyde. *In vitro* and *in vivo* studies have demonstrated that aliphatic aldehydes are oxidized to their respective acids. Valeraldehyde is metabolized to valeric acid. Following the metabolic series approach, studies investigating the toxicity of valeric acid are considered useful in evaluating the potential systemic toxicity of valeraldehyde. Data from the supporting chemicals propionaldehyde (CAS# 123-38-6), butyraldehyde (CAS# 123-72-8), isobutyraldehyde (CAS# 78-84-2) and isovaleraldehyde (CAS# 590-86-3) are used to support and address the data gaps for the mammalian endpoints.

Human Health

Data for valeraldehyde are available for acute toxicity, skin and eye irritation, as well as skin sensitization. The acute oral LD_{50} value for male rats was 4590 mg/kg. The dermal LD_{50} in male rabbits was 4865 mg/kg; necrosis was observed at the application site. There was 50 percent mortality among rats exposed to 4000 ppm (11600 mg/m^3) valeraldehyde vapor for 4 hours. Valeraldehyde is a corrosive liquid. Valeraldehyde causes severe skin and eye irritation and necrosis. Animal studies show it to be an upper respiratory tract irritant but not a skin sensitizer.

There are no repeated-dose toxicity studies for n-valeraldehyde. Repeated-dose toxicity studies with other aldehydes (n-buteraldehyde, isobutyraldehyde and propionaldehyde) have demonstrated mortality and localized lesions in response to irritation as well as some effects on hematology and clinical chemistry; however, systemic effects have not been observed. A similar toxicity profile is expected for n-valeraldehyde. Thirteen-week rat and 14-week dog inhalation studies at **n-butyraldehyde** concentrations of 125, 500, and 2000 ppm (363, 1450, and 5800 mg/m^3) resulted in nasal lesions at all doses with LOAECs of 125 ppm for both species. A subsequent 12-week rat study determined a NOAEC for **n-butyraldehyde** vapor in rats of 50 ppm (145 mg/m^3, the highest dose tested). A 13-week gavage study with **n-butyraldehyde** in rats and mice at doses of 75, 150, 300, 600, and 1200 mg/kg bw/day resulted in nasal lesions at all doses and lesions of the stomach at 600 and 1200 mg/kg bw/day in rats. A dose-related increase in mortality was also observed in rats**.** In mice, treatment-related nasal lesions were noted at 300 mg/kg and above and mortality, stomach lesions, and decreased body weight gain were observed at 1200 mg/kg bw/day, resulting in a NOAEL of 150 mg/kg bw/day.

In a 103-week inhalation study with **isobutyraldehyde** vapor, rats and mice were exposed to 0, 500, 1000, or 2000 ppm (0, 1450, 2900, 5800 mg/m^3). There was no treatment-related dose-dependent increase in the incidence of tumors in rats or mice. Non-neoplastic nasal lesions were significantly increased at all doses (females only at 500 ppm), resulting in a LOAEC of 500 ppm for rats. Survival of mice was reduced at 2000 ppm and mean body weights of females were reduced at 1000 and 2000 ppm. Degeneration of the olfactory epithelium was observed at the two highest doses in mice, for a NOAEC of 500 ppm in mice. A shorter (13-week) inhalation study in rats and mice using **isobutyraldehyde** vapor concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (0, 1450, 2900, 5800, 11600, and 23200 mg/m^3) resulted in mortality at 4000 and 8000 ppm in both species. Non-neoplastic lesions of the nasal

cavity occurred at concentrations of 2000 ppm and greater in rats and 1000 ppm and greater in mice resulting in NOAECs of 1000 ppm and 500 ppm, respectively. Nasal lesions observed included necrosis, hyperplasia, squamous metaplasia, and olfactory epithelial degeneration.

In a combined repeated-dose toxicity study with reproduction and developmental toxicity screening test, rats were exposed to **propionaldehyde** vapor concentrations of 150, 750, and 1500 ppm (345, 1725, and 3450 mg/m^3) via inhalation. Effects on the nasal epithelium were seen at all doses, including vacuolization in the low and intermediate dose groups and squamous metaplasia (in a few animals) and atrophy in the intermediate and high dose groups. Some effects on hematology (increased erythrocytes, hemoglobin and hematocrit values) and increased monocytes were observed at 1500 ppm. Increased kidney weights were also observed at the highest dose. The LOAEC is 150 ppm.

In vitro data on genetic toxicity are available for valeraldehyde and *in vivo* data are available for valeric acid. Valeraldehyde tested negative both in the presence and absence of a metabolic activation systems in several bacterial reverse mutation assays with several strains of *Salmonella typhimurium*. When tested in assays conducted in the absence of metabolic activation, valeraldehyde was positive in a mouse lymphoma assay and gene mutation assays in Chinese hamster V79 cells; it was negative in sister chromatid exchange assay in human lymphocytes. When tested in the presence of inherent or added metabolic activation, valeraldehyde was negative in a UDS (DNA repair) assay in human and rat hepatocytes and a mouse lymphoma gene mutation assay. Valeric acid, the "downstream" metabolite of valeraldehyde, did not result in increased micronuclei in an *in vivo* mouse micronucleus assay. These results show that valeraldehyde is genotoxic in some *in vitro* test systems in the absence of metabolic activation. However, negative results were obtained in those assays with inherent or added metabolic activation systems. Similar genotoxicity results were obtained for the structural analog, isobutyraldehyde. Isobutyraldehyde was negative in a two-year chronic inhalation bioassay in mice and rats; the only effects related to treatment were non-neoplastic degenerative lesions of the nasal olfactory epithelium. There is insufficient evidence to suggest that the chemical is mutagenic in humans.

Several studies with structurally similar aldehydes evaluated reproductive organs and one evaluated fertility. In a combined repeated-dose study with a reproduction/developmental toxicity screening test, no reproductive effects were observed in male and female rats exposed to 150, 750, or 1500 ppm (345, 1725, or 3450 mg/m^3) **propionaldehyde** vapor resulting in a reproductive NOAEC of 1500 ppm. Male and female rats exposed to **isobutyraldehyde** concentrations up to 2000 ppm (5800 mg/m^3) for 103 weeks had normal reproductive organs and tissues. Male and female rats exposed 0, 500, 1000, 2000, or 4000 ppm (1450, 2900, 5800, or 11600 mg/m^3) **isobutyraldehyde** for 13 weeks had normal reproductive organs and tissues; no effect on sperm motility, density or morphology was observed in male rats exposed to 4000 and 2000 ppm, however motility was decreased at 500 and 1000 ppm. Significant mortality was observed in female rats at 4000 ppm, at which some differences in the relative time in different stages of estrous were observed in the surviving females. No effects were observed on vaginal cytology or average estrous cycle length. In the same study, male and female mice showed no reproductive effects.

Developmental toxicity data are available for propionaldehyde, isobutyraldehyde, and valeric acid. No external physical abnormalities were observed in neonates in the combined repeated-dose toxicity study with reproduction/ developmental toxicity screening test using **propionaldehyde** vapor described above. However, pup body weight gain between lactation day 0 and 4 in the high dose group was slightly decreased resulting in a NOAEC of 750 ppm. The parental LOAEC was 150 ppm. Groups of pregnant female rats were exposed by inhalation to 0, 1000, 2500, or 4000 ppm (2900, 7250, or 11600 mg/m^3) **isobutyraldehyde** vapor for 6 hr/day for ten consecutive days during gestational days (GD) 6 through 15. Maternal toxicity, as evidenced by a significant decrease in body weight gain, was observed in dams exposed to 2500 and 4000 ppm resulting in a maternal NOAEC of 1000 ppm. There was no effect on gestational or litter parameters; no embryofetal toxicity or fetal malformations were observed at any exposure level, resulting in a developmental NOAEC of 4000 ppm. A developmental toxicity study using **valeric acid** on groups of timed pregnant female rats by oral gavage during GD 6 through GD 15 at doses of 0, 50, 100, and 200 mg/kg bw/day resulted in severe maternal toxicity. Vocalization, rales, and dyspnea were noted in dams immediately after dosing of the material, and mortality occurred in all treatment groups (4% at 50 mg/kg, 13% at 100 mg/kg, and 42% at 200 mg/kg). Fetal body weights were reduced at all dose levels. Although maternal toxicity makes it difficult to interpret the significance of the results, the percent incidence of fetuses with small sternebrae or reduced ossification was statistically increased at all dose levels. No fetal malformations or other variations were observed.

Due to severe maternal toxicity a NOAEL couldn't be established for developmental toxicity.

The odor threshold for valeraldehyde (0.028 to 0.060 ppm) is well below the 8-hour TWA occupational exposure limit of 50 ppm established by ACGIH to prevent irritation. There are no human studies that evaluated the relationship between odor threshold and irritation.

Environment

The melting point of n-valeraldehyde is -91.5ºC, the boiling point is 103ºC, and the vapor pressure is 35 hPa at 20ºC. The water solubility is 11,700 mg/L at 25ºC. The photochemical removal of valeraldehyde, as mediated by hydroxyl radicals, occurs with a calculated half-life of 9.0 hours. Valeraldehyde is not anticipated to hydrolyze in water. Based on Level III fugacity modelling, and assuming all releases are to air and none to water or soil, it is estimated that the majority of valeraldehyde released into the environment will partition into air (93.4%), with a smaller amount into water (5.65%), soil (0.961%) and sediment (<0.1%). Valeraldehyde will volatilise readily from moving rivers, but only moderately from quiescent lakes and other surface water bodies (calculated volatilisation half-lives of 8.3 hours from a river and 5.4 days from a lake). Valeraldehyde is readily biodegradable under aerobic conditions. The octanol:water partitioning coefficient (log K_{ow}) for valeraldehyde ranges from 1.31 to 1.39 at 25ºC (preferred value 1.38), and the estimated bioconcentration factors (BCF) range from 2.3 to 5.8 (preferred value 2.3). These data indicate that valeraldehyde has a low potential to bioaccumulate.

Data are available from valeraldehyde to address the acute aquatic toxicity endpoints. A GLP analytical study conducted according to OECD Guideline 203 with rainbow trout (*Oncorhynchus mykiss*) in a flow-through system demonstrated a 96-hr LC50 of 27.9 mg/L. Two additional flow-through studies with fathead minnows (*Pimephales promelas*) resulted in 96-hr LC50s of 12.4 mg/L and 13.4 mg/L. Two static studies that examined the toxicity of valeraldehyde to *Daphnia magna* resulted in 48-hr EC50s of 70.7 and > 100 mg/L for immobilization. A single 96-hr GLP study in algae conducted according to OECD Guideline 201 with *Pseudokirchnerilla subcapitata* (formerly know as *Selanastrum capricornutum*) resulted in 72-hr and 96-hr EC50 values for growth inhibition of 32.4 mg/L and 42.2 mg/L, respectively; the 72- and 96-hr EC50 values for biomass (area under the curve) were 31.4 mg/L and 37.1 mg/L, respectively.

Exposure

Valeraldehyde is used primarily as an industrial intermediate in the production of valeric acid and amyl alcohol. Reported minor uses include use in resin chemistry and to make rubber accelerators. Manufactured valeraldehyde does not appear intentionally in commercial or consumer products, although naturally-occurring valeraldehyde may be used as a flavoring agent in foods. Valeraldehyde has been identified as a naturally-occurring plant volatile and it has been detected in foods and beverages at low ppm concentrations. Consumption in 2006 is projected at 38,000 tonnes the US, 32,000 tonnes in Western Europe, and approximately 100 tonnes in Japan in 2006. Valeraldehyde is a flammable liquid with a flammable range of 2.1 – 7.8 volume % in air (21,000 – 78,000 ppm) and a flash point of 5ºC (41ºF). In the US, due to its physical/chemical properties, valeraldehyde is manufactured in an enclosed, continuous process and stored in vapor-tight equipment under an atmosphere of oxygen-free nitrogen. Engineering controls and vapor collection systems are utilized during production, transfer, and loading operations to minimize flammability hazards as well as worker exposure. Workplace exposure during manufacture and use as industrial intermediate is also limited in the US by an occupational exposure limit of 50 ppm; the odor threshold for n-valeraldehyde (28-60 ppb) is well below the exposure limit and is expected to decrease the potential for significant worker exposure. Valeraldehyde may be released to the environment as a fugitive emission during production and use, or as naturally occurring emissions from vegetation, food products, and wood fires.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently a low priority for further work. The chemical possesses properties indicating a hazard for human health (skin, eye, respiratory irritation and potential reproductive/developmental effects based on data for analogous compounds). Based on data presented by the Sponsor country (relating to production in one country which accounts for 50-60% of the consumption in OECD countries and relating to the use pattern in several OECD countries), adequate risk management measures are being applied (engineering controls, occupational standards, Material Safety Data Sheets (MSDSs), and regulation as a food additive). Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However, the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.