SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Mixture of two isomers: 109-52-4 and 116-53-0
Chemical Name	Commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid commercial mixture of approximately 64% n-pentanoic acid, CAS No.109-52-4 and 36% 2-methyl-1-butyric acid, CAS No. 116-53-0
Structural Formula	CH_3-CH_2-CH_2-CH_2-COOH n-pentanoic acid CH_3-CH_2-CH(CH_3)-COOH 2-methyl-1-butyric acid

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid contains two aliphatic acid isomers: n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%). 2-Methyl-1-butyric acid is not isolated and is not produced except as the minor component of the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid.

Data from chemicals with structures and carbon chain lengths similar to the components of the commercial mixture have been used to satisfy endpoints or augment available data for the mixture. Propionic acid's use as an analogue for n-pentanoic acid is based on the fact that propionic acid is a metabolite of n-pentanoic acid and 2-methyl-1-butyric acid and has similar irritative potential *in vivo* as n-pentanoic acid. Butyric acid data was also used as an analogue based on similar physical chemical properties and *in vivo* irritative potential.

For the environment, Henry's Law constant, Log Kow, dissociation constant, photodegradation potential, and distribution in environmental compartments endpoints are addressed individually for each component, n-pentanoic acid and 2-methyl-1-butyric acid. For human health toxicity endpoints, data for propionic acid (CAS No. 79-09-4) are used as support for repeated-dose and reproductive toxicity endpoints. Propionic acid (a 3-carbon carboxylic acid) can be used as an analogue of n-pentanoic acid based on similarities in structure along with a common functional group. Both chemicals are corrosive, which is thought to contribute to the similar toxicities in repeated-dose studies. Finally, propionic acid is also a metabolic product of n-pentanoic acid and 2-methyl-1-butyric acid through intracellular oxidation pathways. Calcium propionate (CAS No. 4075-81-4), the calcium salt of propionic acid, is used as support for the developmental toxicity endpoint. Calcium propionate dissociates to propionate ions in water. In the stomach, both calcium propionate and propionic acid exist as the non-ionized acid. 2-Methyl-1-propionic acid (CAS No. 79-31-2), similar in structure to 2-methyl-1-butyric acid, is used to supplement the genetic toxicity endpoint. Due to similarities in metabolism (via beta-oxidation) and lower acute toxicity for the mixture compared with n-pentanoic acid, the straight chain (n-pentanoic acid) is an appropriate analogue for the mixture.

n-Pentanoic acid is being presented at SIAM 29 as a separate case by the United States. Propionic acid has previously been assessed in the OECD HPV Chemicals Programme at SIAM 25.

Physical-Chemical Properties

The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is a colourless liquid with a melting point of -44°C*, a boiling point of 183.1°C* and a vapour pressure of 0.1h Pa* at 20 °C. The calculated range for partition coefficients (log K_{ow}) for the commercial mixture is 1.18 to 1.39 at 25°C, and the water solubility is 32,000 mg/L* at 20°C. As the dissociation constant (pKa) for n-pentanoic acid is 4.83; the pKa for 2-methyl-1-butyric acid is 4.80. The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid has a pKa between 4.80 and 4.83, and is anticipated to exist in its dissociated forms at environmentally relevant pH values.

* Reliability = 4, data provided by manufacturer; however, supported by the analogue data

Human Health

n-Pentanoic acid and 2-methyl-1-butyric acid are metabolized by intracellular β–oxidation pathways in fatty acid metabolism at concentrations up to 67 mM and 1 M, respectively, with products being acetic acid and propionic acid. Both acetic and propionic acids are normal constituents of cells and are formed during oxidative degradation of isoleucine.

The oral LD_{50} value for the commercial mixture n-pentanoic and 2-methyl-1-butyric acid, administered as a 40% solution in corn oil, is 4920 mg/kg bw for female rats and >4000 mg/kg bw for male rats. Signs of toxicity included hypoactivity, abnormal or uncoordinated gait, lacrimation, slow breathing, and prostration. Necropsy of animals dying on study revealed haemorrhages in the glandular portion of the stomach with multiple areas of ulceration. The dermal LD_{50} in female rabbits is 1070 mg/kg bw; the commercial mixture was applied undiluted and produced oedema, necrosis, ulceration and desquamation at the application site. There was no mortality or signs of toxicity among male and female rats exposed for 6 hours to a substantially saturated vapour of the commercial mixture of n-pentanoic and 2-methyl-1-butyric acid. The commercial mixture of n-pentanoic and 2-methyl-1-butyric acid is corrosive and causes irreversible injury to the skin and eye. Severe irritation and ulceration, followed by necrosis, scabbing, alopecia, and desquamation were observed in a skin irritation assay performed in rabbits. The commercial mixture is a severe eye irritant. Severe corneal injury, iritis, and severe conjunctival irritation; haemorrhage, necrosis of the nictitating membrane, and corneal vascularization were observed in an eye irritation assay performed in rabbit. It is anticipated that high concentrations of the commercial mixture, produced as an aerosol or a vapour/aerosol mixture, will result in nasal and/or respiratory irritation. No experimental data are available for skin sensitisation in animals or humans for the commercial mixture or its components.

There are no repeated-dose toxicity studies for the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid. Data are available for n-pentanoic acid and structural analogue propionic acid.
There are short-term repeated-dose data available for n-pentanoic acid for rabbits via the dermal route of exposure, and for rats via the oral route. In a repeated-dose dermal toxicity study in male and female rabbits, n-pentanoic acid in a mineral oil solution was applied to the skin at a dose of 500 mg/kg bw for a total of 10 applications over fourteen days. Death was observed in one female rabbit; all test animals displayed vocalization upon handling, decreased food consumption, decreased body weight, and severe signs of dermal irritation. In a repeated-dose oral toxicity study in female rats, n-pentanoic acid in corn oil was administered by gavage at doses of 0, 125, 250, 500, 750, and 1000 mg/kg bw/day for 10 consecutive days. Dyspnea or rales were observed in all treated groups. Decreased activity, lethargy, and immobilization were observed at 750 and 1000 mg/kg bw/day. Mortality occurred at doses of 250 mg/kg bw/day and greater and all animals died at 1000 mg/kg bw/day. In a third study, n-pentanoic acid was administered to 10 rats in a rice diet at doses up to 10% (w/w) of the diet; half were sacrificed at 115 days and the other half at 150 days. Stomachs were examined microscopically if gross lesions were observed. n-Pentanoic acid induced benign hyperplasia, hyperkeratosis, acanthosis and papillomas in the forestomach. No malignant changes were detected and there were no changes in the glandular portion of the stomach.

Repeated-dose oral toxicity data in dogs and rats are available for the analogue propionic acid. Dogs (4 to 8/sex/dose) were exposed to 0, 0.3, 1.0, or 3.0% propionic acid (approximately 0, 196, 660, and 1,848 mg/kg-bw/day for males and 0, 210, 696, and 1,832 mg/kg-bw/day for females) in the diet for 100 days. There was no mortality, no clinical signs of toxicity, and no haematological or clinical biochemistry changes. Microscopic examination of tissues revealed no lesions except point-of-contact diffuse epithelial hyperplasia of the mucosa of the esophagus in three dogs in the high-dose group. The incidence of lesions in the esophagus was similar in lower dose animals and controls. The incidence of lesions of the esophagus in the high-dose animals after a 6-week recovery interval was similar to controls. Based on the point-of-contact effect observed in the esophagus, the LOAEL for this study in dogs is 3% propionic acid (1,848 mg/kg-bw/day in male dogs, and 1,832 mg/kg-bw/day in female dogs) in the diet, and the NOAEL is 1% propionic acid or 660 mg/kg bw/day for males and 696 mg/kg bw/day for females. In a repeated dose oral toxicity study, rats (20/sex/dose) received 0, 0.62%, 1.25%, 2.5%, or 5% propionic acid in the diet for 91 days. There was no mortality. Males in the high dose group (5% in diet) exhibited decreased food consumption and decreased body weight gain, no other clinical signs of toxicity were observed. Point-of-contact effects observed were acanthosis, hyperkeratosis, and proliferation of the epithelium of the forestomach mucosa in rats in the high dose group; these changes were not observed after a 6-week recovery interval. Based on point-of-contact effects observed in the forestomach, the NOAEL for male and female rats in this study is 2.5% propionic acid in the diet, or approximately 1600 mg/kg bw/day.

Additional studies focused on the site-of-contact effect of the analogue propionic acid on the stomach; other tissues were not examined. Male rats (6 males/dose) were fed a control diet or a ***pellet*** diet containing 4%

propionic acid (approximately 2,700 mg/kg bw/day) for 24 weeks. Macroscopic and histopathological examination of the stomach revealed no adverse effects. Male rats (6/dose) were also given a control *powdered* diet, or a *powdered* diet containing 4% propionic acid for 12 weeks. Rats displayed severe hyperplastic changes and ulcerations in the forestomach but not in the glandular stomach.

In another study, groups of 30 male rats were fed 0, 0.4 or 4% propionic acid in ground rat feed for 20 weeks or lifetime. Of the rats fed 0.4% propionic acid (approximately 270 mg/kg bw/day), hyperplasia and hyperkeratosis were observed histologically in the forestomach. Among rats fed 4% propionic acid, forestomach epithelial changes such as hyperplasia and hyperkeratosis were noted at 20 weeks, and hyperplasia with ulceration, dyskeratosis and papillomatous elevations (one with unspecified "carcinomatous" changes) were noted after lifetime exposure. No histopathological changes were observed in the glandular stomach in these studies. The consistency of the diet appeared to influence the incidence of lesions observed. The point-of-contact effects observed in the rat forestomach in response to feeding high doses of short-chain fatty acids are likely to be the result of severe irritation and inflammation and the associated hyperplastic proliferative repair response.

In a bacterial reverse mutation assay with multiple strains of *Salmonella typhimurium*, and in an *in vitro* HGPRT forward mutation assay using Chinese hamster ovary (CHO) cells, n-pentanoic acid was negative with and without metabolic activation. An *in vitro* chromosomal aberration test using CHO cells with n-pentanoic acidwas positive with and without metabolic activation. An *in vitro* sister chromatid exchange assay in CHO cells, n-pentanoic acid was negative without metabolic activation and positive with metabolic activation. The effect of pH in these studies is uncertain because it was not measured. An *in vivo* micronucleus assay in mice, n-pentanoic acid was negative at doses of 25%, 50% and 80% of the LD50 via intraperitoneal injection, as determined in range-finding studies. Cytotoxicity (PCE/NCE ratios) was seen in females (but not males) in the rangefinding test at 200 mg/mL, but was not observed in the definitive test at concentrations up to 266 mg/mL. Based on these data, the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is not expected to induce gene mutations but may induce chromosomal aberrations *in vitro*; it is not expected to induce micronuclei *in vivo*.

There are no valid carcinogenicity studies for the commercial mixture or its components. In an invalid (reliability score of 3) 80-week dermal toxicity assay in mice with significant methodological deficiencies, repeated dermal application of undiluted n-pentanoic acid (25 mg/mouse or approximately 950 mg/kg bw applied two times per week) induced mortality (66%), severe skin ulcerations, chronic inflammation, and regenerative repair with disproportionate cell proliferation which resulted in scar tissue formation and subsequent dysplasia, hyperplasia, and skin tumours. The controls also showed high mortality (48%). There is some uncertainty regarding the skin tumors observed in the repeated exposure dermal toxicity study and the positive in vitro genotoxicity results. However, these effects were likely due to the low pH of the test solutions.

There are no fertility studies available for the commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid or its components. Data are available regarding effects on reproductive organs for the structural analogue, propionic acid. In repeated-dose oral toxicity studies, there were no effects on reproductive organ weights, and reproductive organs and tissues were normal in male and female rats exposed to propionic acid at doses up to 5% in the diet (approximately 3300 mg/kg bw/day) for 91 days, with a NOAEL of 3300 mg/kg bw/day for reproductive organ toxicity. Similarly, there were no effects on reproductive organs in dogs fed propionic acid at doses up to 3% in the diet (1848 mg/kg bw/day for male dogs; 1832 mg/kg bw for female dogs) for up to 106 days, with a NOAEL of 1832 mg/kg bw/day for reproductive organ toxicity.

There are three developmental toxicity studies for n-pentanoic acid. Fetal malformations were not observed. However, significant maternal mortality limits the ability to make firm conclusions from these studies. In the most robust study, n-pentanoic acid in corn oil was administered by oral gavage to Sprague-Dawley rats on gestation days 6 through 15 at doses of 0, 50, 100, and 200 mg/kg bw/day. Rales and vocalization were reported during dosing in dams at all doses. Mortality of the dams occurred in all treated groups and was greater than 10% at 100 and 200 mg/kg bw/day. Necropsy of dams dying on study revealed respiratory tract congestion, distension of the gastrointestinal tract, and gastric irritation. Decreased fetal body weights were observed at 100 and 200 mg/kg. Developmental toxicity, as evidenced by an increased incidence of reduced ossification of the sternebrae, was observed at 50 and 100 mg/kg bw/day. Developmental effects may have been confounded by maternal toxicity.

The analogue, calcium propionate is the non-corrosive salt of propionic acid, and does not induce significant point-of-contact toxicity typical of the parent acid. Calcium propionate was administered to pregnant mice and rats vial oral gavage during gestation days 6-15 at doses of 0, 3, 14, 65, and 300 mg/kg bw/day. Pregnant rabbits and hamsters were given calcium propionate via gavage at 0, 4, 19, 86, and 400 mg/kg bw/day during gestation days 6-18 (rabbits) or 6-10 (hamsters). In all species, there was no effect on maternal or fetal survival, or on fetal or litter size. No increases in fetal or skeletal abnormalities were observed. Both NOAELs for maternal toxicity

and developmental effects were the highest doses tested (300 mg/kg-bw/day mice and rats; 400 mg/kg-bw/day for rabbits and hamsters).

The commercial mixture of n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%) possesses properties indicating a hazard for human health (acute skin and eye irritation, repeated-dose toxicity associated with point of contact effects, and possible developmental toxicity in the presence of maternal toxicity). Adequate screening-level data are available to characterize the hazard for human health for the purposes of the OECD HPV Programme.

Environment

The commercial mixture of n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%) is not expected to undergo hydrolysis in the environment, due to the lack of hydrolyzable functional groups. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with an estimated half-life between 2.6 to 2.8 days (62.4-67.7 hours). For n-pentanoic acid, a half-life of 62.4 hours for atmospheric photo-oxidation was determined. For 2-methyl-1-butyric acid, a half-life of 67.7 hours for atmospheric photo-oxidation was determined. An OECD 301D Closed Bottle Test with the commercial mixture resulted in 72% biodegradation after 28 days. The commercial mixture is readily biodegradable under aerobic conditions.

Based on Level III fugacity modelling with equal and continuous distributions to air, water and soil compartments, it is estimated that the majority of n-pentanoic acid and 2-methyl-1-butyric acid will distribute mainly to the soil (61.8%, 57.2%) and water (33.8%, 36.8%) compartments with minor distribution to the air compartment (4.33, 5.84%) and negligible amount in the sediments compartment. When released to water, this commercial mixture will remain in the water compartment. The Henry's law constant for n-pentanoic acid is 4.48 x 10^{-7} atm-m^3/mol (0.045 Pa-m^3/mol) at 25 °C; the Henry's law constant for 2-methyl-1-butyric acid is 1.467 x 10^{-6} atm-m^3/ mol (0.149 Pa-m^3/mol) at 25ºC. These values suggest that volatilization of the components of the commercial mixture from the water phase is not expected to be high. The K_{oc} for n-pentanoic acid and 2-methyl-1-butyric acid were calculated to be 4.084 and 3.661 L/kg, respectively.

Bioaccumulation potential is low based on the preferred Log K_{ow} values of 1.39 and 1.18 for n-pentanoic acid and 2-methyl-1-butyric acid, respectively. The estimated BCF values with BCFWIN (v3.00) are 3.162 for both components of the commercial mixture.

The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is comprised of two fatty acid isomers: n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%). The following acute toxicity test results* on the commercial mixture have been determined for aquatic species:

Fish	*Oncorhyncchus mykiss*	OECD TG 203	96 h LC_{50} = 75.9 mg/L
Fish	*Pimephales promelas*	Static test system	96 h LC_{50} = 29 mg/L 96 h LC_{50} = 34 mg/L
Aquatic invertebrate	*Daphnia magna* Straus	OECD TG 202	48-hr EC_{50} = 88.1 mg/L
Algae	*Pseudokirchnerilla subcapitata*	OECD TG 201	96-hr E_bC_{50} = 51.8 mg/L (biomass) 96-hr E_rC_{50} = 66.2 mg/L (growth rate) 96-hr NOEC = 12.8 mg/L (biomass and rate)

*all results are based on measured test concentrations in unbuffered test solutions

The commercial mixture of n-pentanoic acid (64%) and 2-methyl-1-butyric acid (36%) possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L in unbuffered systems). However, the commercial mixture is readily biodegradable, has low bioaccumulation potential, and the observed aquatic toxicity is due to reductions in pH. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Global production of n-pentanoic acid and 2-methy-1-butric acid was estimated to be approximately 30,000 tonnes in 2004. Consumption in 2004 was estimated to be 17,000 tonnes in the US, and 10,000 tonnes in Western Europe. The commercial mixture of n-pentanoic acid and 2-methyl-1-butyric acid is produced in an

enclosed, continuous process by an air-oxidation reaction of a mixture of valeraldehyde and 2-methybutyraldehyde.

The commercial mixture is used as an industrial intermediate in the manufacture of neopolyol esters for the production of industrial lubricants used in refrigeration applications, fire-resistant hydraulic fluids, and jet engines. Some specialty applications include its use as a pharmaceutical intermediate, and in the manufacture of isoamyl valerate (an ester solvent), metallic salts, and plasticizers. The two components, n-pentanoic acid and 2-methyl-1-butyric acid, have been identified as naturally-occurring volatiles in foods and both are food additives permitted for direct application to food. Both components are products of mammalian and microbial intercellular metabolism.

No monitoring data within production and processing plants in the United States are available. The commercial mixture is manufactured in an enclosed, continuous process. Engineering controls and vapour collection systems are used during production, transfer, and loading operations. These measures are used to limit workplace exposures and odour complaints.

Because of its objectionable odour, additional scrubbers and other emission controls are usually employed to minimize release of the commercial mixture of during manufacture and use. However, the commercial mixture may be released to the environment as a fugitive emission during production and use; its individual components may be found in the environment as naturally-occurring emissions from food products, microorganisms, animal wastes, and diesel exhaust.