

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-09-4
Chemical Name	Propionic Acid
Structural Formula	CH ₃ -CH ₂ -COOH

SUMMARY CONCLUSIONS OF THE SIAR**Analogue Justification**

Data for calcium propionate (CAS No. 4075-81-4) are used to satisfy the developmental toxicity endpoint for propionic acid and to augment some environmental endpoints (acute toxicity to fish, invertebrates and algae). Calcium propionate dissociates in water to yield propionate ions.

Human Health

Radiolabeled propionic acid administered to rats has appeared in glycogen, glucose, lipids, amino acids, and proteins. The route of metabolism involves interaction with co-enzyme A, carboxylation to form methylmalonyl-coenzyme A, and conversion to succinic acid which then enters the citric acid cycle. No data are available on the toxicokinetics of propionic acid.

There was no mortality among rats exposed for 8 hours to approximately 0.14 mg/L (a nominal value of 36 ppm) propionic acid vapor; exposed rats exhibited signs of nasal, ocular and skin irritation. There was one death among 20 rats exposed for 1 hour to 19.7 mg/L propionic acid as a vapor/aerosol atmosphere; exposed rats exhibited signs of nasal, ocular and respiratory irritation. The dermal LD₅₀ in male rabbits was 490 mg/kg-bw. Animals that died displayed hemorrhage of the lungs and intestines, and congested livers and kidneys. The range of acute oral LD₅₀ values reported for propionic acid in rats was between 351 and 3470 mg/kg bw. The reason for the variation in these values may be due to the age, body weights, or prandial state of the test animals. Clinical signs included squatting posture, agitation or apathy, dyspnea, cyanosis, and ruffled fur. Ascites, hemorrhage of the lungs and gastrointestinal tract, and "burned" surfaces of organs in contact with the gastrointestinal tract were observed in animals that died.

Propionic acid causes severe skin and eye irritation and is irritating to the respiratory tract. Signs of nasal, ocular, respiratory, and skin irritation were seen in animals exposed to propionic acid in the acute inhalation studies described above. There are no animal sensitization data for propionic acid. In humans topically exposed to sodium propionate, there was no sensitization response. Three of 91 human subjects with chronic urticaria (presumed to have had prior exposure to propionic acid as a food preservative) displayed a reproducible positive skin prick response to a 5% solution of propionic acid; none of the 247 control (non-urticarial) subjects displayed a positive response.

Repeated-dose oral toxicity in studies similar to OECD guidelines was evaluated in a 100-day study in dogs and in a 91-day study in rats. In both studies, no systemic toxicity was seen, and only point-of-contact effects were observed, including chronic irritation with associated inflammation and proliferative repair responses. Additional feeding studies in rats range from 28 days to lifetime exposure. However, these studies focused only on point-of-contact effects in the forestomach and the outcome of the studies varied with the consistency of the diet (pelleted vs.

powdered).

The dog feeding study is considered to be the definitive study for the investigation of the repeated dose toxicity of propionic acid. Male and female Beagle dogs were exposed to 0, 0.3, 1.0, or 3.0% propionic acid (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 approximately 100 days. There was no mortality and no clinical signs of toxicity. Three high-dose animals had point-of-contact effects that included diffuse epithelial hyperplasia of the esophageal mucosa. The incidence of lesions of the esophagus in the high-dose animals after a 6-week recovery interval was similar to controls. The LOAEL for this study was 3% propionic acid in the diet (1,848 mg/kg-bw/day in male dogs, and 1,832 mg/kg-bw/day in female dogs). The NOAEL was 1% propionic acid in the diet (660 and 696 mg/kg bw-day for male and female dogs, respectively).

Male and female Sprague-Dawley rats were exposed to 0, 0.62%, 1.25%, 2.5%, or 5% propionic acid in a pulverized diet for 91 days. There was no mortality. Males in the high dose group (5%) exhibited decrease body weight gain. No other clinical signs of toxicity were observed. Point-of-contact effects were observed in the epithelium of the rat forestomach mucosa in rats in the high dose group; these changes were not observed after a 6-week recovery interval. The NOAEL for male and female rats in this study was 2.5% propionic acid in the diet (approx. 1600 mg/kg-bw/day).

Repeated-dose dietary studies with different forms of diet (pelleted, powdered, or ground) administered to male rats suggest that the form of the diet may influence the types of effects observed. In Wistar rats fed 4% test substance (approximately 2,700 mg/kg-bw/day) in a pelleted diet for 24 weeks, no effects on the forestomach or gastric mucosa were observed.

However, when Wistar rats were fed the same amount in powdered feed for 12 weeks, severe changes in the forestomach (including crater-like growths, marginal hyperplasia, and central ulceration) were seen. No changes, however, were observed in the glandular stomach. In a 4-week study using 4% in a powdered diet of Fischer 344 rats, histopathological changes were seen in the forestomach at 27 days, including thickened mucosa with acanthosis and hyperkeratosis and some infiltration of white blood cells.

Finally, a study in male rats in which propionic acid was given at 0.4% (approximately 270 mg/kg bw/day) in ground feed for 20 and 24 weeks resulted in a few effects in the forestomach (some hyperplasia and hyperkeratosis). In the same study, ground feed containing 4% (approximately 2,700 mg/kg bw/day) for 20-24 weeks produced papilloma elevations (one with unspecified "carcinomatous" changes), marked squamous hyperplasia of the epidermis, ulceration and hyperplasia of the mucosa of the forestomach. The changes observed upon feeding of high dose of propionic acid in these types of studies are the result of chronic irritation and inflammation and the associated hyperplastic proliferative repair response.

Propionic acid has been tested *in vitro* in bacterial reverse mutation assays using *Salmonella typhimurium* strains TA98, 100, 102, 104, 1535, 1537, 1538 with standard plate incorporation and pre-incubation protocols. The test substance did not result in gene mutations in either the presence or absence of metabolic activation; it was also negative in an *in vitro* gene mutations assay using *Schistosaccharomyces pombe* (yeast). Propionic acid was negative in a DNA repair assay using *E. coli* in the presence of metabolic activation, but displayed a non-dose-related positive response in the absence of metabolic activation. Propionic acid was also negative in an *in vivo* micronucleus test using male and female Chinese hamsters. Based on these results, propionic acid has shown no potential to induce gene mutations or chromosomal aberrations.

There are no reproductive, fertility, or developmental toxicity studies available for propionic acid. In a repeated-dose oral toxicity study, there were no changes in the reproductive organs of male and female dogs fed up to 3% propionic acid (up to 1,848 and 1,832 mg/kg-bw/day in males and females, respectively) in the diet for approximately 100 days. There were no changes in the reproductive organs (testes and ovaries) of male and female rats fed up to 5% propionic acid in the diet for 91 days.

In a developmental toxicity study, calcium propionate was fed to pregnant mice and rats during gestation days 6-15 at

dose levels from 3 to 300 mg/kg-bw/day. Pregnant rabbits and hamsters were fed calcium propionate at doses ranging from 4 to 400 mg/kg-bw/day during gestation days 6-18 (rabbits) or gestation days 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 in any species when compared with controls.

Environment

Propionic acid has a melting point of -21.5°C and a boiling point of 141°C . It has a vapor pressure of 4.7 hPa at 25°C , a log K_{ow} value of 0.33 at 25°C , and is miscible with water. With a pKa of 4.9, the propionate ion will predominate at neutral pH; the unionized form may be found in significant concentrations in acidic environments.

Hydrolysis is not expected to occur due to the lack of hydrolyzable functional groups. The photochemical removal of vapor-phase propionic acid in the atmosphere, as mediated by hydroxyl radicals, occurs with a calculated half-life between 7.7 and 9.2 days. Based on Level III distribution modelling for propionic acid (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of propionic acid released to the environment will partition into air (5.5%), water (37.4%) and soil (56.5%) with a smaller amount (<0.1%) into sediment. The Fugacity modelling for the acid used the log K_{ow} predicted for the acid in its unionized form. However, because propionic acid will exist primarily as the propionate anion at neutral pH, the amount of substance partitioning to water may be underestimated in these calculations. Propionic acid is not anticipated to volatilize readily from surface waters (calculated volatilization half-lives for propionic acid are 61 days from a model river and 1.83 years from a model lake). Propionic acid is readily biodegradable under aerobic and anaerobic conditions. Propionic acid is not likely to bioaccumulate in aquatic organisms based on its log K_{ow} value.

Acute aquatic toxicity data (fish, daphnia, and algae) are available for propionic acid. A 96-hour static test with the fathead minnow (*Pimephales promelas*) resulted in a 96-h LC_{50} of 51.8 mg/L. In a static test with *Daphnia magna*, the 48-h EC_{50} was 22.7 mg/L. In a test with green algae (*Scenedesmus subspicatus*), the 72-hr E_rC_{50} (growth rate) was calculated as 48.7 mg/L and the 72-hr E_bC_{50} (biomass) was calculated to be 43.3 mg/L. In these studies, the test solution was not buffered prior to addition of the test organisms, resulting in low pH in the test solution. Aqueous solutions of calcium propionate do not display significant changes in pH and are less toxic to aquatic organisms. The 96-hr LC_{50} in fish (*Leuciscus idus*) is >10,000 mg/L, the 48-hr EC_{50} in *D. magna* is >500, and the 72-hr EC_{50} (both growth rate and biomass) in algae (*S. subspicatus*) is >500 mg/L. These results suggest that the toxicity observed with propionic acid may be related to changes in pH.

Exposure

Approximately 115 thousand metric tons were produced in the United States and 124 thousand metric tons were produced in Western Europe; annual production in Japan is reported to be 3 thousand metric tons. In the United States, propionic acid is manufactured by three companies in a closed continuous synthesis and distillation process. At the manufacturing facility, fixed, in-place piping or hoses connected directly to the container are used during production, transfer, and loading operations to minimize exposure, flammability hazards, and odor complaints. Scrubbers are used to limit emissions from the stack. Scrubber condensates are redistilled and the recycled organics are used as fuel or sold as solvents. Annual consumption of propionic acid in the United States was about 91 thousand metric tons in 2003.

Propionic acid is used as a chemical intermediate for the production of propionate salts that are used as feed and corn preservatives and herbicides. When used as an intermediate, propionic acid is typically received and transported to reactors via hard-piped lines which decreases the potential for exposure. Propionic acid is also used directly as a grain preservative and as an additive to control bacteria and fungi in drinking water for livestock and poultry. Occupational exposure may occur during application of propionic acid as a feed preservative, especially when applied to growing crops or crops after harvest.

Propionic acid is also used as a chemical intermediate for the production of cellulose propionate plastics and other polymers, and in pharmaceuticals. Additional smaller uses include the manufacture of propionic anhydride, methyl

propionate, and chlorinated derivatives.

Propionic acid is also used in the manufacture of synthetic flavoring agents. It is also used as a preservative in food for human consumption.

The 8-hour occupational exposure limit for propionic acid in the Sponsor country is 10 ppm (30 mg/m³).

Propionic acid is found naturally in humans as a normal intermediary metabolite that represents up to 4% of the normal total plasma fatty acids. It is formed as a result of catabolism of amino acids, as a terminal 3-carbon fragment in the oxidation of longer-chained fatty acids, and from the oxidation of the side chain of cholesterol. Propionic acid occurs naturally in foods, and together with other short-chain fatty acids, is ubiquitous in the gastrointestinal tract of humans and other mammals as end-products of microbial digestion.

The general population may be exposed to propionic acid as a fugitive emission, or from ingestion of foods that contain propionic acid naturally or as a preservative, or as an endogenous chemical. Propionic acid may also be released from food, landfills, and sewage. Propionic acid is considered "generally regarded as safe" or GRAS material by the U.S. Food and Drug Administration for direct addition to human food when used as a preservative, and the allowable daily intake (ADI) is considered to be "unlimited" by the FAO/WHO Expert Committee on Food Additives.

Propionic acid has been detected in the air possibly as a result of photooxidation of anthropogenic compounds during long-range transport. In the 1970s and 1980s it was detected in ground water near a coal gasification site and as a contaminant with leachates from municipal and industrial landfills and hazardous waste sites.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently a low priority for further work. The chemical is corrosive and possesses properties indicating a hazard for human health (skin, eye and respiratory tract irritation). These hazards do not warrant further work as they are related to acute toxicity. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/L) due to pH effects. However the chemical is readily biodegradable and has limited potential for bioaccumulation.