SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-62-6
Chemical Name	Propionic anhydride
Structural Formula	CH_3-CH_2-C(=O)-O-C(=O)-CH_2-CH_3

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

Data for propionic acid and calcium propionate have been used to fulfill the SIDS endpoints for propionic anhydride. Propionic anhydride undergoes exothermic hydrolysis upon contact with water to form 2 moles of propionic acid for each mole of anhydride present. This reaction has been shown to occur with a measured half life of less than 10 minutes at pH 4 to 9. Calcium propionate is a suitable surrogate since it will dissociate in solution to the propionate anion, and propionic anhydride, after hydrolysis in water, will exist predominantly as the propionate anion at neutral pH.

Data for propionic acid (CAS No. 79-09-4) have been used to address or augment all human health endpoints except developmental toxicity. Because propionic anhydride readily hydrolyzes in water to form propionic acid, data for propionic acid are also used to address all environmental endpoints for propionic anhydride. Data for calcium propionate are used to address the developmental toxicity endpoint, and to augment environmental toxicity endpoints (acute toxicity to fish, invertebrates, and algae).

Human Health

No data on metabolism or toxicokinetics are available for propionic anhydride. However, some relevant information is available for propionic acid. 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 of propionic acid.

No adequate data for propionic anhydride are available for the acute inhalation and dermal endpoints; therefore only data on propionic acid are presented. Limited details were available for an oral study using propionic anhydride, therefore data on propionic acid are also included. There was no mortality among rats exposed for 8 hours to 36 ppm (0.14 mg/L) propionic acid vapor; exposed rats exhibited signs of nasal, ocular and skin irritation. Mortality was 1/20 among 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 LD_{50} for propionic acid in male rabbits was 490 mg/kg bw; necrosis of the skin was observed at the site of application. Animals that died displayed hemorrhage of the lungs and intestines, and congested livers and kidneys. An oral acute toxicity study using propionic anhydride in which only limited details were reported resulted in an LD_{50} > 1,600 mg/kg (none of the rats died). Clinical signs related to treatment included moderate to severe weakness, gasping, cyanosis, and rough hair coat. The acute oral LD_{50} value for propionic acid was 426 and 351 mg/kg bw for male and female rats, respectively; hemorrhage of the lungs and gastrointestinal tract, and "burned" surfaces of organs in contact with the gastrointestinal tract were observed in animals that died.

No adequate irritation data for propionic anhydride are available. The supporting chemical, propionic acid causes severe skin and eye irritation and is corrosive. Signs of nasal, ocular, respiratory, and skin irritation were noted in animals exposed to saturated propionic acid in the acute inhalation studies described above. There are no animal sensitization test data for propionic acid. There was no sensitization response in human subjects topically exposed to

the sodium propionate, the sodium salt of propionic acid. 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.

No repeated-dose data are available for propionic anhydride. However, repeated-dose data are available for propionic acid from 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 the definitive study for the investigation of repeated dose toxicity of propionic acid. Male and female Beagle dogs were exposed to 0, 0.3, 1.0, or 3.0% (0, 196, 660, 1848 mg/kg in males; 0, 210, 696, and 1,832 mg/kg in females) propionic acid in the diet for approximately 100 days. There was no mortality and no clinical signs of toxicity. High-dose animals had point-of-contact effect (diffuse epithelial hyperplasia of the esophageal mucosa). No lesions of the esophagus were observed in the high-dose animals after a 6-week recovery interval, and no lesions were observed in lower-dose animals. The LOAEL for this study was 3% propionic acid in the diet (1,848 mg/kg bw in male dogs and 1,832 mg/kg bw 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 exhibited decrease body weight gain, no other clinical signs of toxicity were observed. Examination of tissues revealed no lesions except point-of-contact changes of the mucosa of the forestomach in the high-dose treatment group, the changes observed in the forestomach were not observed in the post-exposure recovery group. The NOAEL for this study in rats was 2.5% propionic acid (approximately 1600 mg/kg-bw/day) in the diet.

Several repeated-dose dietary studies with different forms of diet (pelleted, powdered, or ground) administered to male rats have 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 shorter study (9, 15, 21 or 27 days) 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

No genotoxicity data are available for propionic anhydride. Propionic acid has been tested *in vitro* in bacterial reverse mutation assays using standard plate incorporation and pre-incubation protocols. The compound 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 *Saccharomyces cerevisiae* (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. There appears to be no potential for induction of gene mutations or chromosomal aberrations by propionic acid.

There are no reproductive or developmental toxicity studies available for propionic anhydride. In a repeated-dose oral toxicity study using *propionic acid*, there were no changes in the reproductive organs of male and female dogs fed up to 3% propionic acid in the diet for approximately 100 days. No changes in reproductive organs were observed in 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 ranging from 3 to 300 mg/kg-bw/day, and to pregnant rabbits during gestation days 6-18 at doses from 4 to 400 mg/kg-bw/day. Pregnant female hamsters were fed calcium propionate during gestation days 6-10 at doses from 4 to 400 mg/kg-bw/day. In all species, there was no effect on maternal or fetal survival, and no effect of fetal or litter size. No increases in fetal or skeletal abnormalities were observed in any species when compared to controls.

Environment

The available physicochemical data are adequate to describe the properties of propionic anhydride. Propionic anhydride has a melting point of -45ºC, a boiling point of 167ºC, and a vapor pressure of 1.81 hPa at 25ºC. It has density of 1.01 g/cm^3 at 20 ºC. Water solubility and log K_{ow} are not applicable because of its rapid hydrolysis. Propionic anhydride hydrolyzes readily in water to propionic acid, with a hydrolysis half-life of 9, 4, and 2 minutes at pH 4, 7, and 9, respectively.

Because of its rapid hydrolysis to propionic acid, data are also presented for propionic acid. Propionic acid has a vapor pressure of 4.7 hPa at 25 ºC and a calculated log K_{ow} value of 0.33 at 25 ºC. Propionic acid is miscible with water and the propionate ion will predominate at neutral pH. Therefore, it is not anticipated to volatilize readily from surface waters. The unionized form of the acid will increase as the pH decreases.

In dry environments, vapor phase propionic anhydride is susceptible to photodegradation. The photochemical removal of propionic anhydride in the atmosphere, as mediated by hydroxy radicals, occurs with a calculated half-life between 11.7 and 28.7 days. If hydrolysis of propionic anhydride in contact with water vapor behaves in a manner similar to its hydrolysis in water, it will rapidly hydrolyse to propionic acid. 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.

Hydrolysis of propionic acid is not expected to occur due to the lack of hydrolyzable functional groups. Propionic acid is not likely to bioaccumulate in aquatic organisms based on its log K_{ow}. Based on Level III distribution modeling 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 soil (56.6%), water (37.4%), and air (5.5%) 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 in at neutral pH, the amount of substance partitioning to water may be underestimated in these calculations. Propionic acid is readily biodegradable under aerobic and anaerobic conditions.

Because of the rapid hydrolysis of the anhydride to the acid, aquatic toxicity data (fish, daphnia, and algae) are presented for propionic acid. Propionic acid was tested in 96-hour static test with *Promephales promelas* (fathead minnow), the 96-hour LC_{50} was 51.8 mg/L. In a static test with *Daphnia magna*, the 48-hour EC_{50} for propionic acid was 22.7 mg/L. In an OECD guideline test *Scenedesmus subspicatus* (green algae), the 72-hour E_rC_{50} for propionic acid based on growth rate was calculated to be 48.7 mg/L and the 72-hour E_bC_{50} for biomass is 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*) for calcium propionate is >10,000 mg/L, the 48-hr EC_{50} in *D. magna* is >500, and the 72-hr EC_{50} in algae (*S. subspicatus*) (biomass and growth rate) is >500 mg/L. These results suggest that the toxicity observed with propionic acid may be related to changes in pH.

Exposure

In the United States, propionic anhydride is manufactured by one company in a continuous process in enclosed synthesis equipment using engineering controls. Fixed, in-place piping or hoses connected directly to the container are used during production, transfer, and loading operations to minimize exposure, combustibility hazards, and odor complaints. Scrubbers are used to minimize emissions in the stack. Scrubber condensates are redistilled and the recycled organics are used as fuel or sold as solvents. Annual consumption of propionic anhydride is less than 10

thousand metric tons in the United States.

Propionic anhydride is used as a chemical intermediate in the production of alkyd resins, dyestuffs, agricultural chemicals and drugs. Propionic anhydride is not used directly as a component in consumer products.

Because of propionic anhydride's tendency to hydrolyze in an aqueous environment, exposure to propionic acid may result from the hydrolysis of this chemical.

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 effects. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is a low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic species between 1 and 100 mg/l) due to pH effects. However, the chemical is of low priority for further work because of its rapid biodegradation and limited potential for bioaccumulation.