

toxic effects caused by propanoic acid and its calcium and sodium salts are discussed in this unit.

Propanoic acid is a three carbon acid with a molecular formula of  $\text{CH}_3\text{CH}_2\text{COOH}$ . It is considered to be a medium strong acid. It occurs naturally in animal and dairy products such as butter and cheese. Propanoic acid and the salts of propanoic acid are direct food additives. (discussed in unit III.7.) The toxicological database for propanoic acid was determined to be adequate for reregistration eligibility at the time that the Reregistration Eligibility Document (RED) was completed in September 1991. A comprehensive search of the open literature from 1991 forward and a search for in-house toxicological data failed to reveal any new information on propanoic acid which would change the toxicological findings in the RED. Therefore, the toxicological findings/data from the Propionic Acid RED (which also addresses the calcium and sodium salts) are applicable to this current evaluation.

1. *Acute toxicity.* Technical propanoic acid is of moderate to low acute toxicity via the oral, dermal, and inhalation routes of exposure (toxicity category of III), and is not a skin sensitizer. However, propanoic acid is acutely toxic in eye and dermal irritation tests (toxicity category I).

2. *Subchronic toxicity.* No subchronic toxicity data are available on propanoic acid itself; however, data on calcium and sodium propionate are used to assess subchronic toxicity. Rats fed calcium or sodium propionate at one percent of the diet (equivalent to 750 milligrams/kilogram/day (mg/kg/day) of propanoic acid) for four weeks followed by 3% (equivalent to 1,200 mg/kg/day of propanoic acid) for three weeks showed no changes in weight gain compared to the controls. Rats fed 5% propanoic acid in the diet (approximately 5,000 mg/kg body weight) for 110 days developed lesions of the forestomach.

Propanoic acid was given in the feed to dogs at 220, 735, or 2,066 mg/kg/day for 90 days. The high dose dogs showed reduced food consumption, increased incidence of epithelial hyperplasia in the esophagus, and increased nitrite in the urine. These effects were no longer present in dogs held for a six week recovery period. In a limited 90-day dog study with calcium propionate (2,523 mg/kg/day) the dogs showed vomiting and diarrhea.

3. *Chronic toxicity.* Twenty male rats per group were fed four percent propanoic acid in the diet for 2 years. The highest dose animals had hyperplasia and hyperplastic ulcers in

the forestomach. Rats fed bread containing sodium propionate (4,000 mg/kg/day) for a year showed no adverse effects, nor did rats fed a similar diet for 32 weeks, other than an initial depression of growth.

4. *Developmental toxicity.* No maternal or fetal effects were seen upon feeding calcium propionate to pregnant animals at rates up to 300 mg/kg/day for hamsters and rabbits.

#### 5. *Mutagenicity*

Propanoic acid gave negative results in mutagenicity assays in five strains of *S. Typhimurium*, and one strain of *S. Cerevisiae*, with and without activation.

Additional data on calcium and sodium propionate indicated that both tested negative for mutagenicity in *S. Typhimurium*, and *S. Cerevisiae*.

6. *Metabolism* Propanoic acid is produced in large quantities in ruminants (dairy cows), thus accounting for its presence in butter and dairy products. In humans, propanoic acid is one of the metabolic products from the breakdown of several amino acids. Propanoic acid is formed as the body oxidizes longer chain odd-numbered fatty acids or the side chain of cholesterol. It is a normal intermediary metabolite in the body that is utilized by most organs and tissues, and can be metabolized to glucose, carbohydrates, amino acids, and lipids.

If directly ingested, propanoic acid is rapidly absorbed from the mammalian gastrointestinal tract, and thus enters a known metabolic pathway.

7. *FDA uses.* The Food and Drug Administration (FDA) has approved various uses of propanoic acid, and its calcium and sodium salts. Under 21 CFR 178.1010, propanoic acid can be used in food contact surface sanitizing solutions when the ready-for-use end-use concentration does not exceed 297 ppm. The calcium salt of propanoic acid is affirmed Generally Recognized As Safe (GRAS) under 21 CFR 184.1221. It is used as a mold inhibitor in bread. The sodium salt of propanoic acid is affirmed GRAS under 21 CFR 184.1784. It is used as a mold inhibitor in cakes and unleavened goods and as a chemical preservative in animal drugs and feeds. Propanoic acid is affirmed GRAS under 21 CFR 184.1081. It is an antimicrobial agent and a flavoring agent.

8. *Findings of the United Nations Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives.* Propanoic acid has been examined at several meetings of the FAO/WHO Joint Expert Committee on Food Additives (JECFA). The Seventeenth Report contained the following information:

“In human plasma propionic acid represents 0% to 4% of the total fatty acid and is a by-product of normal intermediary metabolism. Absorbed propionate is removed by the liver, kidneys, heart, muscle and adipose tissue. The liver can deal with 4.5 g free acid or 5.8 g sodium propionate per hour.”

In 1973, the Committee determined that “propionate is a normal intermediary metabolite, and a normal constituent of foods.” Based on an understanding of this metabolic information, the Committee also determined that it was not necessary to specify an estimate of acceptable daily intake (ADI) in man. It was specified as “unlimited.” This finding was reviewed in 1997: The 1973 ADI was maintained.

9. *Conclusions on the Toxicity of Propanoic Acid and its Calcium and Sodium Salts.* Propanoic acid demonstrates an acute toxicity profile that is consistent with that of an acid: it is highly acutely toxic for eye and dermal irritation, i.e., it is corrosive to the eyes and skin. These effects are most appropriately addressed through the use of protective equipment and labeling, not through establishment of tolerance exemptions.

The JECFA monograph deemed propanoic to be of such low concern that the acceptable daily intake is “not specified.” A consideration in this decision was the understanding that “propionate is a normal intermediary metabolite, and a normal constituent of foods.” Propanoic acid and its calcium and sodium salts are FDA affirmed GRAS direct food additives.

When considering the oral exposure pathway, the most relevant in establishing a tolerance exemption, propanoic acid and its calcium and sodium salts have low toxic potential. There are no concerns for mutagenicity, carcinogenicity, or developmental or reproductive concerns. Propanoic acid is a normal component of metabolism in the human body. The human body has a known pathway to metabolize propanoic acid. No additional data are necessary to assess the toxicity of these chemicals.

#### IV. Aggregate Assessment

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).