TOXICITY PROFILE

The British Industrial Biological Research Association

LACTIC ACID

SUMMARY

Lactic acid is a normal constituent of the body and certain foods. Its toxicity is largely related to its acidity, concentrated solutions having a pH of <1.0.

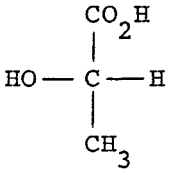
Lactic acid has caused eye damage in a number of species and skin irritation in rabbits. Ingestion of lactic acid (or its calcium salt) by man has resulted in gastro-intestinal damage and kidney injury has also been seen in infants. No evidence of mutagenicity was seen in an Ames bacterial test although other genotoxicity screening assays were inconclusive.

IDENTIFICATION

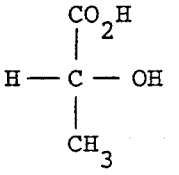
Unless otherwise specified by the investigators, we have assumed that the studies they report involved the testing of the DL-form of lactic acid. Information on D- and L-lactic acid and the sodium salts, where available, is included. The letters D- and L- relate to the spatial arrangement of the atoms when compared to L-glyceraldehyde and other sugars. The four different groups of atoms surrounding the central carbon atom mean lactic acid is an optically active substance in that it can rotate the plane of polarized light. D(-)-lactic acid is laevorotatory (rotates polarised light to the left) and L(+)-lactic acid is dextrorotatory (rotates polarised light to the right). L(+)-Lactic acid is found in muscle tissue. The metallic salts of each enantiomer (non-superimposable mirror image of lactic acid) rotate polarised light in the opposite direction to that of the acid (Merck, 1983).

STRUCTURAL FORMULAE:

$CH_3CHOHCO_2H$



L(+)-Lactic acid



D(-)-Lactic acid

EEC NO: E270 (DL-Lactic acid)

Further information may be obtained from the BIBRA Information Section
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COMMON SYNONYM: 2-Hydroxypropanoic acid

CHEMICAL ABSTRACTS REGISTRY NUMBERS:

50-21-5	Lactic acid
598-82-3 (DL)	Lactic acid
79-33-4 L(+)	Lactic acid
10326-41-7 D(-)	Lactic acid
72-17-3	Sodium lactate
814-80-2	Calcium lactate

RELEVANT PHYSICAL PROPERTIES: DL-lactic acid is soluble in water and alcohol and practically insoluble in chloroform, petroleum ether and carbon disulphide (Merck, 1983). The concentrated acid has a pH of less than 1.0 (Trainer et al. 1945).

LOCAL EFFECTS

SKIN IRRITANCY

Human. Wiping the face with a 5% aqueous solution of lactic acid produced a 'stinging sensation' in five of thirty volunteers in whom sweating had been induced. Stinging was felt by all of nine volunteers when 5% aqueous lactic acid was applied to areas of the cheek and back where the outer layer of skin had been removed (Frosch & Kligman, 1977).

Marked skin dehydration was produced in 19 volunteers following 24-hr covered contact with a 1% solution of a soap containing 1.85% lactic acid. The same soap solution was applied five times for 24 hr over 10 days to the skin of two volunteers. After three applications, the skin reddened and became scaly with fine cracks (Hassing et al. 1982).

No adverse effects were reported by any of 12 patients with ichthyosiform dermatoses [a condition where the skin is dry and scaly due to proliferation of the outer layer] treated twice daily with 5% lactic acid in an ointment. The duration of the treatment was not specified (Van Scott & Yu, 1974).

Non-human. In rabbits, patch tests (24-hr covered contact) with a 10% aqueous lactic acid solution were not irritating. A 20% aqueous solution was mildly irritating and the neat material moderately irritating (Guillot et al. 1982).

Severe irritation was seen on repeated application of neat lactic acid for one week to rabbits, but only mild reactions occurred following repeated exposure to 10% and 20% aqueous solutions (Guillot et al. 1982).

EYE IRRITANCY

Non-human. Severe damage and persistent scarring was evident when concentrations of more than 50% were in contact with the rabbit eye for 1 min (Guillery, 1910; Harley, 1952; Lewin & Guillery, 1913). Irritation was also evident on instillation of 5-20% [aqueous] solutions into the rabbit eye (Carpenter & Smyth, 1946; Guillot et al. 1982).

In the guinea-pig, a 30% solution produced eye damage and a long-lasting accumulation of blood (hyperaemia) in the conjunctiva. Similar reactions were seen in eyes treated with 5% and 10%, but the reaction subsided after 24 hr (Wilhelm & Gdynia, 1968).

Aqueous solutions containing up to 70% sodium lactate were 'slightly irritant' in the rabbit eye (Guillot et al. 1982).

OTHER LOCAL EFFECTS

Human. 10% solutions in water or milk (pH 1.6-2.5) were corrosive to the oesophagus [gullet - a muscular tube that extends from the throat to the stomach] and stomach (Delph, 1937; Trainer et al. 1945). "Concentrated" lactic acid (pH <1.0) was corrosive to "mucous membranes" (Lewin & Guillery, 1913).

Non-human. Severe damage to the vaginal lining occurred when rabbits were given four 20 ml daily applications of a douche solution [of pH 3 or below] containing lactic acid and sodium bicarbonate. Irritation was also seen at pH 3-7.5. Groups of eight rats exposed similarly to 0.5 ml at pH 2.3-4.0 exhibited only minimal effects comparable with the control group (Kaminsky & Willigan, 1982).

SENSITIZATION AND INTOLERANCE

Human. A standard text lists lactic acid as a cause of allergic dermatitis [but offers no supporting evidence]. It recommends that a 3% aqueous solution be used in 24-48-hr closed patch tests to identify sensitized individuals (Fisher, 1986).

GENERAL SYSTEMIC EFFECTS

SINGLE EXPOSURE

Human. Oral. Three premature infants died within 16 hr (one during the first hour) after the administration by stomach tube of a mixture supposedly containing equal amounts of evaporated milk, water and a lactic acid corn syrup aqueous solution. The exact volume of the milk formula given to the infants is unknown, but was believed to be about one ounce. [The paper implies that there was a mistake in the preparation of this mixture with a more concentrated lactic acid component being administered than was intended. The final mixture probably had a pH of 2.1.] Extensive bleeding, inflammation and perforation of the stomach wall was seen. Inflammation of the intestines had occurred in the two larger infants, with damage to the oesophagus present in all three. Other organs affected included the kidneys, liver and spleen. The same lactic acid milk formula was given to a full-term infant by bottle. One mouthful caused choking and reddening of the face, an infected throat and bronchial irritation developed but recovery was complete after 2 days (Young & Smith, 1944). The accidental administration of 1 teaspoon [about 3 g] of 'concentrated' lactic acid (an 88% solution of pH <1.0) burnt the mouth, throat and oesophagus of a 2-wk-old baby. Severe scarring and stricture of the oesophagus prevented the feeding of solid foods up to the age of 5 months. Subsequent blockage of the oesophagus led to the child's death at 7 months (Trainer et al. 1945).

The maximum tolerated dose of lactic acid has been reported as 1530 mg/kg bw (Nazario, 1951). In adults, no overt toxic effects were reported after ingestion of up to 3000 mg [42 mg/kg bw] (Fürth & Engel, 1930).

A dose of 10 g [about 142 mg/kg bw], but not 5 g, of calcium lactate in three men produced violent abdominal distress, vomiting and diarrhoea (Federal Register, 1980).

Other. Death occurred within 12 hr after the infusion into the small intestine of 33 g of lactic acid. The patient exhibited difficulty in breathing, vomited and had a rapid feeble pulse. Haemoglobin was present in the urine (indicating damage to the red blood cells) and the mucous membranes. Finger nails and lips were blue

(cyanosis). The intestines were inflamed and bleeding, with corrosion of the duodenum [the section of the small intestines immediately below the stomach] (Fühner, 1932).

The dizziness, unsteady gait and degenerative brain disease seen in some patients who had undergone gastro-intestinal surgery has been ascribed to changes in the gut microorganisms leading to the production of D(-)-lactic acid (Thurn et al. 1985).

Intravenous infusion of 560 mg/kg bw sodium lactate over 20 min has been found to provoke the onset of "panic attacks" in patients with anxiety disorders (Knott et al. 1981).

Non-human. Oral. LD_{50} rat: 3.73 g lactic acid/kg bw (Smyth et al. 1941)

mouse: 4.88 g lactic acid/kg bw (Fitzhugh, 1945)

guinea-pig: 1.81 g lactic acid/kg bw (Smyth et al. 1941)

Two of five male rats given 3.25 g L(+)-lactic acid/kg bw by stomach tube died within 24 hr. Toxic signs were breathing difficulties and abdominal swelling (Morotomi et al. 1981).

The majority of a group of rabbits [numbers unspecified] died within 3 days after receiving 600-1600 mg DL-lactic acid/kg bw (Fürth & Engel, 1930). Three rabbits fed a milk formula containing approximately 34% lactic acid (pH 2.1) [about 1.7 g/kg bw] by stomach tube died within 6 hr. There was extensive damage to the stomach, kidney and to a lesser extent the lungs (Young & Smith, 1944).

Intraperitoneal. LD_{50} rat: 2000 mg sodium lactate/kg bw (Rhône-Poulenc, 1965).

Intravenous. Administration of doses above 154 mg lactic acid/kg bw to cats caused severe convulsions and death. Doses of 44 mg/kg bw produced dilation of the pupils and excitement (Pike et al. 1931).

REPEATED EXPOSURE

Human. Oral. A large number of studies have investigated the effect of feeding lactic acid-acidified milk formulas to infants. In general, intakes in premature infants in excess of 600 mg/kg bw produced metabolic acidosis (an accumulation of acid in the body) and a reduced growth rate (Federal Register, 1980).

Adverse effects were not seen in 40 full-term newborn infants fed a commercial milk formula containing 0.4% [about 800 mg/kg bw/day] DL-lactic acid from the second to the fourth week of life (Jacobs & Christian, 1957). Conversely, a group of healthy babies given 0.35-0.5% [about 500-800 mg/kg bw/day] DL-lactic (pH 4.5) acid for 10 days during the first three months of their lives developed diarrhoea and acidosis. The urine became more acidic and there was a decrease in body weight and food consumption (Droese & Stolley, 1962 & 1964). Cellular material and debris [indicative of kidney damage] were occasionally seen in the urine of two 4- and 5-yr-old children who had consumed milk containing 'concentrated' lactic acid (8 ml acid/litre milk) [about 200 mg/kg bw/day] for 21 days. Red blood cells and cellular debris were present in the urine of a 3.5-month baby following the administration of 8 g calcium lactate [about 1.2 g/kg bw/day] and 240 ml 0.1 M hydrochloric acid daily for three days. When only calcium lactate was given, the cellular debris persisted. The urine returned to normal when calcium lactate was removed from the diet (Greene, 1928). No adverse effects on height or weight were seen in a group of malnourished children whose diet was supplemented with 1 g calcium lactate [about 40 mg/kg bw/day] for 49 days during an 11-wk period (Aykroyd & Krishnan, 1939).

Non-human. Oral. No overt toxic effects were noted in two pigs fed 100 ml of a lactic acid solution [3.6 g/kg bw/day] increasing gradually

to 500 ml [18 g/kg bw/day] over 150 days (Lamb & Evvard, 1919). An increased weight gain was observed in 24 pigs receiving 1% in their drinking water [approximately 5 g/kg bw/day] for 3 wk, even though they were eating less food (Kershaw et al. 1966). (This finding was attributed to the elimination of Escherichia coli bacteria from the gastro-intestinal tract.)

Groups of six young cows fed diets supplemented with 454 g of an equimolar mixture of sodium and calcium DL-lactate [2.6 g/kg bw/day] for 112 days exhibited no significant changes in their growth but blood and urine lactate levels were increased. No effect on milk production was seen in 12 lactating cows at the same dosage (Emery et al. 1966). There were no overt toxic effects in groups of two dogs receiving 600-1600 mg lactic acid/kg bw by stomach tube on 42 occasions during a 10-wk period (Faust, 1910).

Groups of two rats received daily doses of 1000 or 2000 mg lactic acid/kg bw/day for 16 days without showing overt toxic effects (Fürth & Engel, 1930). Apparently, enlarged ovaries and parathyroid glands were seen in rabbits fed 100 or 200 mg/kg bw/day every other day for five months. Acetic acid gave similar results at the same dosage (Fazekas, 1953). Doses of 180 mg [120 mg/kg bw/day] for 38 days increased the secretion of hormones from the adrenal cortex in female rabbits. Greater effects were seen at equivalent levels of glutamic and citric acids (Jonek, 1961). [Hormones excreted from the adrenal cortex control carbohydrate metabolism.]

Hens fed 0.25% calcium lactate in the diet [about 50 mg/kg bw/day] for 15 months evidently suffered no obvious adverse effects (Roberson, 1971).

Dermal. No marked toxic effects were induced in groups of eight rabbits (four of each sex) treated with up to 1 g lactic acid/kg bw/day, 5 days/wk for 3 months (Scatina et al. 1984).

REPRODUCTIVE TOXICITY

Non-human. On the basis of a brief report, no overt adverse effects were apparently observed in the offspring of male and female rats maintained on diets containing 2.5 or 5.0% lactic acid [equivalent to about 1.25 or 2.5 g/kg bw/day] (D'Amour, 1934). [No further details are available.]

An increased death rate was seen in chick embryos [numbers unspecified] exposed to 10-30 ul of a 0.01% solution [1-3 ug/egg]. Direct application to the yolk sac produced abnormalities of the head, eye and beak in 12% of the survivors (Grabowski, 1961). [The validity of this type of assay as a screen for mammalian effects is uncertain.]

CARCINOGENICITY

No relevant information identified.

OTHER GENOTOXICITY

A limited report states that in mammalian cells in culture, lactic acid induced chromosomal damage in the absence of a liver metabolising fraction (Ishidate, 1981). A later report from the same investigators noted that lactic acid did not produce chromosome damage under these same conditions, but did not offer any explanation of these apparently contradictory findings (Ishidate et al. 1984).

No mutagenic activity was displayed in the yeast Saccharomyces cerevisiae (Federal Register, 1980) or the bacterium Salmonella typhimurium (Ames test) in the presence or absence of a liver metabolic activation system (Federal Register, 1980; Ishidate et al. 1984). In a limited mutagenicity test (without adequate positive or negative controls and with a low survival rate of the test organism), lactic acid appeared slightly mutagenic in the bacterium Escherichia coli, whereas the sodium salt was inactive (Demerec et al. 1951).

OTHER TOXICITY CONSIDERATIONS

L(+)-Lactic acid is a normal metabolic intermediate produced by most mammalian cells and by other organisms such as bacteria. During vigorous muscular activity in man, its formation under anaerobic (oxygen free) conditions may lead to the acidification of the muscle fibre resulting in fatigue. In man, about 2 g/kg bw is generated daily through various metabolic processes (Kreisberg, 1972).

Lactic acid occurs naturally in several foods such as sour milk, yoghurt, beer, wine, and fruits, and the estimated maximum daily intake is 15 mg per person in the USA (Federal Register, 1980). L(+)-Lactic acid is metabolised in preference to D(-)-lactic acid in man, dog and the rat (Federal Register, 1980).

The Joint FAO/WHO Expert Committee on Food Additives has concluded that a limit need not be assigned to the Acceptable Daily Intake (ADI) for L(+)-lactic acid and its ammonium, calcium, potassium and sodium salts in man. An ADI without an explicit indication of the upper limit of intake is given to substances of very low toxicity. An ADI of 0-100 mg/kg bw has been assigned to D(-)-lactic acid. The Committee recommended that neither D- nor DL-lactic acid should be used in infant foods (JECFA, 1974).

ENVIRONMENTAL ASPECTS

No relevant information identified.

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