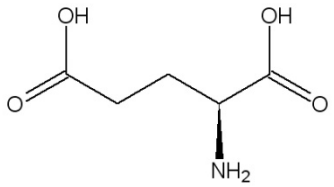
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	56-86-0
Chemical Name	L-Glutamic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical and Chemical Properties

L-Glutamic acid is a white orthorhombic, disphenoidal crystal. Melting point is 160°C and sublimation point is 175°C. Density is 1.538 g/cm^3 at 20°C and vapour pressure is 2.27×10^{-6} Pa at 25°C (extrapolated data) and 1.46×10^{-4} Pa at 20°C (estimated data). Water solubility is measured as 8,640 mg/L at 25°C. L-Glutamic acid is insoluble in methanol, ethanol, ether, acetone, cold glacial acetic acid and common neutral solvents. The octanol-water partition coefficient (log K_{ow}) is -3.69 (experimental data) and -3.83 (estimated data). Dissociation constants are measured as $pK_1 = 2.13$, $pK_2 = 4.31$ and $pK_3 = 9.67$ at 25°C.

Human Health

L-Glutamic acid, commonly found in many foods, is an amino acid and a major excitatory neurotransmitter in the central nervous system. Most free L-glutamic acid in the brain is derived from local synthesis from L-glutamine and Kreb's cycle intermediates. It plays an important role in neuronal differentiation, migration and survival in the developing brain by facilitated Ca^{++} transport. L-Glutamic acid is metabolized by enterocytes in various routes. Most L-glutamic acid delivered to the intestine of healthy volunteers is removed by the splanchnic bed on the first pass. Since L-glutamic acid is oxidized in the epithelial cells of the small intestines, its concentration in blood is relatively low compared with other amino acids.

12-13 µc (10-11 mg) of L-Glutamic acid-2-C^{14} was administered to cecum of male albino rats and observed for four hours. Carcass and liver were autopsied to identify the distribution of ^{14}C of isolated glutamic acid. During the test period, 4-5 µc of $^{14}CO_2$ was exhaled, and the distribution of ^{14}C was 11.9-12.3 mµc/mmole in the carcass and 43.6-46.0 mµc/mmole in the liver. Also, carbon 2 of L-glutamic acid was converted into methyl carbon of acetate by intestinal flora.

The acute oral LD_{50} value was greater than 5,110 mg/kg bw for male and female rats [EC standard acute method]. No mortality and body weight changes were observed.

The acute dermal LD_{50} value was greater than 2,000 mg/kg bw for male and female rats [OECD TG 402, EU Method B.3 and EPA OPPTS 870.1200]. Clinical signs included hromodacryorrhoea and scales. L-glutamic acid was non-irritant to rabbit skin [OECD TG 404 and EU Method B.4] and was not irritating to eyes in rabbits [OECD TG 405 and EU Method B.5]. L-glutamic acid was not a skin sensitizer [EU Method B.6].

The reliable repeated dose toxicity of L-glutamic acid has been investigated in 3 studies. In a repeated dose oral toxicity study in rats [OECD TG 407], L-glutamic acid was administered via gavage to 5 animals/sex/dose at 0, 62.5, 250 and 1,000 mg/kg bw/day for 7 days/week for 4 weeks. No death was observed in either sex. There were no treatment-related effects observed at any dose. Based on the results, the NOAEL for repeated dose oral toxicity was considered to be 1,000 mg/kg bw/day (the highest dose) in both sexes. In another repeated dose oral toxicity study in rats, L-glutamic acid was administered by the diet to 35-40 animals/sex/dose at 0, 0.1 and 0.4%

for 24 months. There was no evidence that L-glutamic acid caused any adverse effect on survival, weight increase, food intake, haematology or age-related pathological changes at either dose level in either sex. Motor activity and general behavioural patterns were not affected. Based on the results, L-glutamic acid did not show any toxic effects in this test condition. In the other oral repeated dose toxicity study in mice, L-glutamic acid was administered by the diet to 100 male animals/dose at 0, 1 and 4% w/w for 24 months. There were no treatment-related effects observed at any dose. L-Glutamic acid provided no evidence of toxic potential upon dietary administration.

In an Ames test with multiple strains of *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100, TA97 and TA102 and/or *Saccharomyces cerevisiae*, L-glutamic acid did not induce gene mutation in bacteria *in vitro* both with and without metabolic activation. In an *in vitro* chromosomal aberration test using Chinese Hamster Ovary K1 cells, L-glutamic acid did not induce chromosomal aberrations with and without metabolic activation. An *in vivo* micronucleus assay using mouse bone marrow cells [OECD TG 474] showed negative results up to 2,000 mg/kg bw. Based on these results, L-glutamic acid is not considered to be genotoxic.

The carcinogenic potential of L-glutamic acid has been investigated in 2 studies. In an oral carcinogenicity study in rats, the test substance was administered by the diet to 35-40 animals/sex/dose at 0, 0.1 and 0.4% (equal to 0, 199 and 542 mg/kg bw/day for males, and 0, 125 and 348 mg/kg bw/day for females) for 2 years. There was no evidence that the test substance, at any dose levels, caused tumour in both sexes. Based on the result, L-glutamic acid is considered to have no carcinogenic potential. In another oral carcinogenicity study in mice, L-glutamic acid was administered by the diet to 100 males/dose at 0, 1 or 4% (w/w) for 2 years. There were no treatment-related effects observed at any dose. Based on the result, L-glutamic acid appeared to have no carcinogenic potential upon dietary administration.

L-Glutamic acid has been investigated in a reproduction and developmental toxicity screening test in rats [OECD TG 421]. L-Glutamic acid was administered by oral gavage to 14 animals/sex at 0, 250, 500 or 1,000 mg/kg bw/day. Male rats were administered for 2 weeks prior to mating, mating period and 2 weeks post mating period (at least 28 or more days) and female rats were administered from 2 weeks prior to mating, to day 3 of lactation including the mating and gestation period. During the observation period, there were no dose-related effects on clinical signs, body weight, food consumption, mating, gestation, delivery, organ weights, necropsy and histopathology in parents. No dose-related changes in clinical signs, body weight, viability index, external malformations and sex ratios were noted in pups. This study found no indication of any reproductive toxicity in parent animals or developmental toxicity in pups at the highest dose of 1,000 mg/kg bw/day. Therefore, the NOAEL for reproduction and developmental toxicity was 1,000 mg/kg bw/day.

In another reproduction study, 0.1 and 0.4% (equal to 199 and 542 mg/kg bw/day for males, and 125 and 348 mg/kg bw/day for females) L-glutamic acid were administered to Sprague-Dawley male and female rats aged 12 weeks for up to 2 years. There were no treatment-related changes in clinical signs, motor activity, food consumption, body weight, fertility, survival, organ weights or histopathological findings compared with the control group. Therefore, there were no reproductive toxicity effects of L-glutamic acid.

In a multigeneration and teratogenicity study, rats receiving 2% L-glutamic acid did not show any adverse effects such as skeletal malformations of fetuses.

In a neurotoxicity study, L-glutamic acid was administered by the diet to 6 male animals/dose at dose levels of 0 or 174,000 mg/kg bw/day for 5 weeks. Repeated oral administration of the test substance did not show specific neurological defects at 174,000 mg/kg bw/day in rats.

L-Glutamic acid does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

In a stability in water test, L-glutamic acid was stable for 96 hours. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.261 day by AOPWIN ver. 1.92. A test for ready biodegradability was conducted with L-glutamic acid with activated sludge for 28 days [OECD TG 301E]. The concentration of the test substance was 50 mg/L corresponding to a carbon content of 20.4 mg C/L. The test result showed 97 % degradation by DOC removal. Based on this result, L-glutamic acid is considered

to be readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that L-glutamic acid will be distributed mainly to the soil (73%) and water (26.9%) compartments with minor distribution to the sediments compartment (0.06%) and a negligible amount in the air compartment. A Henry's law constant of 1.49×10^{-9} Pa-m^3/mole (1.47×10^{-14} atm-m^3/mole) suggests that volatility of L-glutamic acid from the water phase is expected to be low. A soil adsorption coefficient of log K_{oc}=1.13 indicates that L-glutamic acid has negligible sorption to soil and sediment. Since the ionisation state of L-glutamic acid is sensitive to pH, the K_{oc} may vary with pH.

Using an octanol-water partition coefficient (log K_{ow}) of -3.69, a bioconcentration factor of 3.162 was calculated with BCFBAF, version 3.01. This chemical is not expected to bioaccumulate.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oryzias latipes*, OECD TG 203]	96 h LC_{50} >100 mg/L (nominal; static), >99.47 mg/L (measured; static)
Invertebrate [*Daphnia magna*, OECD TG 202]	48 h EC_{50} >83.14 mg/L (measured; static)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]	
	72 h E_rC_{50} = 68.5 mg/L (growth rate, nominal; static)
	72 h E_yC_{50} = 54.4 mg/L (yield, nominal; static)

L-Glutamic acid possesses properties indicating a hazard for the environment (acute aquatic toxicity between 10 and 100 mg/L for algae). However, the substance is readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the environmental hazard for the purpose of the Cooperative Chemicals Assessment Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volumes of L-glutamic acid were 190, 2,382 and 2,494 tonnes in 2010, respectively. In Sweden estimated use volumes of L-glutamic acid were approximately 14, 9, 24 and 15 tonnes in 2007, 2008, 2009 and 2010, respectively. In the United States the estimated production volume of L-glutamic acid was below 225 tonnes in 2005.

L-Glutamic acid is used as a food additive and foodstuff condiment due to its flavour-enhancing properties. It is used as an intermediate in pharmaceuticals and synthetics, semiconductors, cosmetics and fertilisers. It is also used as a salt substitute, flavour enhancer, in nutrients, dietary supplements and fortified dietary supplements. In the sponsor country, L-glutamic acid is mainly used as additives of food and a foodstuff condiment, and is accepted for general use in food. According to JECFA no ADI is needed for L-glutamic acid, which is in agreement with the opinion of the sponsor country and Scientific Commitee for Food (SCF) of the European Commission. According to CODEX, for fortified dietary supplements of vegetable juice, Maximum Permitted Levels (MPL) is managed by Good Manufacturing Practice (GMP). Also, the use of fortified dietary supplements of infant milk formula is restricted to improving nutrient value for infants only. In addition, FCC reports that it is used as a salt substitute and in nutrients with no established MDL.

The industrial manufacture and use process of a condiment in a commercial formulation is as follows: L-glutamic acid is produced by adding sulfuric acid to raw sugar/molasses to remove inorganic matter and fermented using microorganisms. L-Glutamic acid produced by the above process is then separated by sulfuric acid or hydrochloric acid, and evaporated. Wet crystals are then dried and packed as an article.

In the sponsor country, L-glutamic acid is handled in closed systems, and workplaces are under control in accordance with the occupational safety and health acts. Occupational exposure is managed by sealed containers, filter facilities and personal protective equipment such as gas masks, waterproof clothes, rubber gloves, rubber boots and goggles in the workplace. Occupational exposure is considered to be negligible in the sponsor country. Exposure of humans via natural food and food additives was estimated to be up to approximately 3 g/day (International Food Information Council Foundation, 2011). Exposure through consumer products is expected to be negligible.