

Sodium Cyclamate

1 Nonproprietary Names

BP: Sodium cyclamate
PhEur: Natrii cyclamas

2 Synonyms

Cyclohexylsulfamic acid monosodium salt; E952; sodium cyclohexanesulfamate; *Sucaryl sodium*.

3 Chemical Name and CAS Registry Number

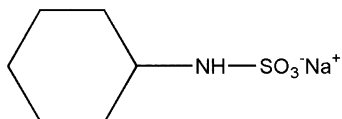
Sodium *N*-cyclohexylsulfamate [139-05-9]

4 Empirical Formula Molecular Weight

C₆H₁₂NNaO₃S

201.22

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium cyclamate is used as an intense sweetening agent in pharmaceutical formulations, foods, beverages, and table-top sweeteners. In dilute solution, up to about 0.17% w/v, the sweetening power is approximately 30 times that of sucrose. However, at higher concentrations this is reduced and at a concentration of 0.5% w/v a bitter taste becomes noticeable. Sodium cyclamate enhances flavor systems and can be used to mask some unpleasant taste characteristics. In most applications, sodium cyclamate is used in combination with saccharin.

8 Description

Sodium cyclamate occurs as white, odorless or almost odorless crystals or as a crystalline powder with an intensely sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium cyclamate.

Test	PhEur 2002
Identification	+
Characters	+
Appearance of solution	+
pH (10% w/v aqueous solution)	5.5–7.5
Absorbance	+
Sulfamic acid	+
Aniline	≤ 1 ppm
Cyclohexylamine	≤ 10 ppm
Dicyclohexylamine	≤ 1 ppm
Sulfates	≤ 0.1%
Heavy metals	≤ 10 ppm
Loss on drying	≤ 1.0%
Assay (dried basis)	98.5–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 5.5–7.5 for a 10% w/v aqueous solution.

Solubility: see Table II.

Table II: Solubility of sodium cyclamate.

Solvent	Solubility at 20°C unless otherwise stated
Benzene	Practically insoluble
Chloroform	Practically insoluble
Ethanol (95%)	1 in 250
Ether	Practically insoluble
Propylene glycol	1 in 25
Water	1 in 5
	1 in 2 at 45°C

11 Stability and Storage Conditions

Sodium cyclamate is hydrolyzed by sulfuric acid and cyclohexylamine at a very slow rate that is proportional to the hydrogen ion concentration. Therefore, for all practical considerations, it can be regarded as stable. Solutions are also stable to heat, light, and air over a wide pH range.

Samples of tablets containing sodium cyclamate and saccharin have shown no loss in sweetening power following storage for up to 20 years.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

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13 Method of Manufacture

Cyclamates are prepared by the sulfonation of cyclohexylamine in the presence of a base. Commercially, the

sulfonation can involve sulfamic acid, a sulfate salt, or sulfur trioxide. Tertiary bases such as triethylamine or trimethylamine may be used as the condensing agent. The amine salts of cyclamate that are produced are converted to the sodium, calcium, potassium, or magnesium salt by treatment with the appropriate metal oxide.

14 Safety

There has been considerable controversy concerning the safety of cyclamate following the FDA decision in 1970 to ban its use in the USA.⁽¹⁻³⁾ This decision resulted from a feeding study in rats that suggested that cyclamate could cause an unusual form of bladder cancer. However, that study has been criticized because it involved very high doses of cyclamate administered with saccharin, which has itself been the subject of controversy concerning its safety; *see* Saccharin. Although excreted almost entirely unchanged in the urine, a potentially harmful metabolite of sodium cyclamate, cyclohexylamine, has been detected in humans.⁽⁴⁾

Extensive long-term animal feeding studies and epidemiological studies in humans have failed to show any evidence that cyclamate is carcinogenic or mutagenic.^(5,6) As a result, sodium cyclamate is now accepted in many countries for use in foods and pharmaceutical formulations. *See also* Section 16.

Few adverse reactions to cyclamate have been reported, although its use has been associated with instances of photosensitive dermatitis.⁽⁷⁾

The WHO has set an estimated acceptable daily intake for sodium and calcium cyclamate, expressed as cyclamic acid, at up to 11 mg/kg body-weight.⁽⁸⁾ In Europe, a temporary acceptable daily intake for sodium and calcium cyclamate, expressed as cyclamic acid, has been set at up to 1.5 mg/kg body-weight.

LD₅₀ (mouse, IP): 1.15 g/kg⁽⁹⁾
 LD₅₀ (mouse, IV): 4.8 g/kg
 LD₅₀ (mouse, oral): 17 g/kg
 LD₅₀ (rat, IP): 1.35 g/kg
 LD₅₀ (rat, IV): 3.5 g/kg
 LD₅₀ (rat, oral): 15.25 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

The use of cyclamates as artificial sweeteners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in the UK and some other countries owing to concern about the metabolite cyclohexylamine. However, this is no longer the case, and cyclamates are now permitted for use as a food additive in Europe.

The use of cyclamates in the USA is currently not permitted although this position is under review. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Calcium cyclamate; cyclamic acid.

Calcium cyclamate

Empirical formula: C₁₂H₂₄CaN₂O₆S₂·2H₂O

Molecular weight: 432.57

CAS number:

[5897-16-5] for the dihydrate

[139-06-0] for the anhydrous form

Synonyms: calcium *N*-cyclohexylsulfamate dihydrate; *Cyclan*; cyclohexanesulfamic acid calcium salt; cyclohexylsulfamic acid calcium salt; E952; *Sucaryl calcium*.

Appearance: white, odorless or almost odorless crystals or a crystalline powder with an intensely sweet taste.

Acidity/alkalinity: pH = 5.5–7.5 for a 10% w/v aqueous solution.

Solubility: freely soluble in water; practically insoluble in benzene, chloroform, ethanol, and ether.

Cyclamic acid

Empirical formula: C₆H₁₃NO₃S

Molecular weight: 179.23

CAS number: [100-88-9]

Synonyms: cyclamate; cyclohexanesulfamic acid; *N*-cyclohexylsulfamic acid; E952; hexamic acid; *Sucaryl*.

Appearance: white, odorless or almost odorless crystals or a crystalline powder with an intensely sweet taste.

Melting point: 169–170°C

Solubility: slightly soluble in water.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace the bulk, textural, or preservative characteristics of sucrose if sucrose is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g., sodium cyclamate with saccharin sodium or acesulfame potassium.

Sodium cyclamate has also been used to increase the solubility of neohesperidin dihydrochalcone in sweetener blends.⁽¹⁰⁾

19 Specific References

- 1 Nabors LO, Miller WT. Cyclamate: a toxicological review. *Commun Toxicol* 1989; 3(4): 307–315.
- 2 Lecos C. The sweet and sour history of saccharin, cyclamate and aspartame. *FDA Consumer* 1981; 15(7): 8–11.
- 3 Anonymous. Cyclamate alone not a carcinogen. *Am Pharm* 1985; NS25(9): 11.
- 4 Kojima S, Ichibagase H. Studies on synthetic sweetening agents VIII. Cyclohexylamine, a metabolite of sodium cyclamate. *Chem Pharm Bull* 1966; 14: 971–974.
- 5 D'Arcy PF. Adverse reactions to excipients in pharmaceutical formulations. In: Florence AT, Salole EG, eds. *Formulation Factors in Adverse Reactions*. London: Wright, 1990: 1–22.
- 6 Schmähl D, Habs M. Investigations on the carcinogenicity of the artificial sweeteners sodium cyclamate and sodium saccharin in rats in a two-generation experiment. *Arzneimittelforschung* 1984; 34: 604–606.
- 7 Yong JM, Sanderson KV. Photosensitive dermatitis and renal tubular acidosis after ingestion of calcium cyclamate. *Lancet* 1969; ii: 1273–1274.
- 8 FAO/WHO. Evaluation of certain food additives and contaminants. Twenty-sixth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1982; No. 683.
- 9 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 3241–3242.

- 10 Benavente-Garcia O, Castillo J, Del Bano MJ, Lorente J. Improved water solubility of neohesperidin dihydrochalcone in sweetener blends. *J Agric Food Chem* 2001; 49(1): 189–191.

20 General References

- Anonymous. Saccharin is safe. *Chem Br* 2001; 37(4): 18.
Schiffman SS, Sattely-Miller EA, Graham BG, *et al.* Effect of temperature, pH, and ions on sweet taste. *Physiol Behav* 2000; 68(4): 469–481.

21 Authors

G Russell, DM Thurgood.

22 Date of Revision

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