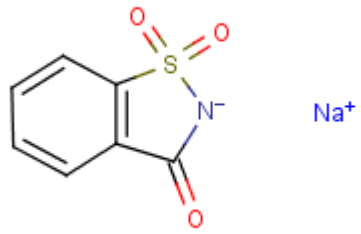
Sodium Saccharinate

SYNONYMS

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, sodium salt
Saccharin sodium anhydrous
Sodium saccharin
Sodium saccharide
Soluble saccharin
Sodium saccharinate
Saccharine

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_7H_4NO_3S.Na$

IDENTIFIER DETAILS

CAS Number	:	128-44-9, 6155-57-3
CoE Number	:	-
FEMA	:	2297
EINECS Number	:	204-886-1
E Number	:	-

SPECIFICATIONS

Melting Point: 228.8 – 229.7^{o}C

Boiling point: >200^{o}C

PURPOSE

Flavouring agent and Sweetener

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
0-5	JECFA	1993	Sweetening agent

FDA Status:

Section Number	Comments
Part 180	Food additives permitted in food or in contact with food on an interim basis pending additional study
180.37	Saccharin, ammonium saccharin, calcium saccharin and sodium saccharin
145.116; 150.141; 150.161; 145.126; 145.131; 145.136; 145.171; 145.181	See 'Reported Uses' section below.

HUMAN EXPOSURE

Reported Uses: Saccharin and its salts have been used as sweeteners for over a century now. Saccharin in its acid form is not water-soluble. The named salts of saccharin are produced by the additional neutralization of saccharin with the proper base to yield the desired salt. The form used as an artificial sweetener is usually its sodium salt. As a sweetening agent, sodium saccharinate (SS) is reportedly used as follows: in beverages (0.39 ppm); fruit juice drinks (0.41 ppm); baked goods (0.69 ppm); condiments and relishes (160 ppm); hard candy (1.83 ppm) and sugar substitutes (25.00 ppm) to name a few food categories. SS can also be used to reduce the bulk and enhance flavours in chewable vitamin tablets (Fenaroli, 2005).

The average daily dietary intake is generally less than 1 mg/kg bw (IARC, 1999)

TOXICITY DATA

In Vivo Toxicity

In 1999, IARC evaluated and summarised the available data at the time on saccharin and its salts. They concluded that there is inadequate evidence in humans for the carcinogenicity of saccharin salts used as sweeteners. Therefore they reclassified saccharin and its salts as Group 3 (not classifiable as to their carcinogenicity to humans) There is sufficient evidence for the carcinogenicity of sodium saccharin in experimental animals. It should be

noted that the working group concluded that sodium saccharin produces urothelial bladder tumours in rats by a non-DNA-reactive mechanism that involves the formation of a urinary calcium phosphate-containing precipitate, cytotoxicity and enhanced cell proliferation. This mechanism is not relevant to humans because of critical interspecies differences in urine composition (IARC, 1999).

Species	Test Type	Route	Reported Dosage
Mouse	LD_{50}	Intraperitoneal	6000 mg/kg
Mouse	LD_{50}	Oral	17500 mg/kg
Rat	LD_{50}	Intraperitoneal	7100 mg/kg
Rat	LD_{50}	Oral	14200 mg/kg

(Toxnet 2010)

Carcinogenicity and Mutagenicity

In a study conducted by Sasaki et al., (2002) the genotoxicity of 39 food additives, including sodium saccharinate was tested in the Comet assay with 8 mouse organs. Groups of four male ddY mice were fed orally one dose of sodium saccharinate up to 200 mg/kg. After 3 and 24 h, the animals were sacrificed and eight organs were removed: liver, kidney, lung, brain, stomach, colon, urinary bladder and bone marrow. Appropriate slides were prepared from each of the organs and analysed. An increase in DNA damage was indicated by an increase in nuclear DNA migration. Sodium saccharinate induced dose-related DNA damage in the colon and glandular stomach with the lowest dose inducing damage being 1000 mg/kg.

Epidemiological case-control studies of the carcinogenicity of artificial sweeteners have been reported only for the urinary bladder or lower urinary tract. Most studies were published between 1975 and 1985, so the association would be to sweeteners that were on the market over 25 years ago. The studies varied widely in the detail with which information on the source and nature of artificial sweeteners was identified, collected and presented. Terms used in the study included ‘artificial sweeteners’, ‘dietetic beverages’ and ‘table-top’.

In a population-based study a statistically significant relative risk of the order 1.6 for the association between use of artificial sweeteners (including saccharin salts) and bladder cancer was found for men but not for women in Canada. However, in subsequent population-based studies including several thousand people in the USA, this association could not be confirmed (IARC, 1999).

Sodium saccharin (SS) has been tested by oral administration in numerous experiments in rats, mice and in a few studies in hamsters, guinea-pigs and monkeys some studies were considered to be inadequate in design. SS produced urinary bladder tumours in male rats in 4 two-generation studies, with SS administration commencing at birth or at 30 days of age. Conversely,

SS was not carcinogenic for the urinary bladder in several one-generation studies in male and female rats or in mice (IARC, 1999)

Takayama et al., (1998) conducted a 23 year study in monkeys. Twenty monkeys of three species (six African green; seven rhesus, six cynomolgus and one hybrid – rhesus male and cynomolgus female) were treated with SS at 25 mg in the diet/kg body weight daily for 5 days a week. The study began within 24 hrs after the birth of the monkeys and continued for up to 24 years. Sixteen monkeys served as controls. During their last two years of life, urine was collected from controls and treated animals. On death, urinary bladders were examined by light microscopy and by scanning electron microscopy. Results showed that SS had no effect on the urine or the bladders of treated animals, leading the authors to conclude that SS is without carcinogenic effect on the primate urinary tract.

Dermal Toxicity

A total dose of saccharin (the exact form is not specified) was applied as an 8% solution in acetone three times a week to the skin of 'S' strain mice. Twenty-five days after the start of treatment the animals were given 18 weekly applications of the tumour-initiator croton oil in acetone at 0.17%. At the end of the treatment 15 skin papillomas were observed in 7 of the 20 saccharin-treated animals by comparison with 4 papillomas in 4 of 19 controls treated with croton oil only. The increase was not statistically significant (Salaman and Roe, 1956).

Reproductive and Developmental Toxicity

Saccharin, generally as the sodium salt, has been tested for developmental and reproductive toxicity in mice, rats, hamsters and rabbits. The effects have generally been limited to reductions in body weights at high dietary concentrations (IARC, 1999).

Inhalation Toxicity

No data identified

Other Relevant Studies

All of the published studies with the exception of one, indicate that saccharin is not metabolized and is excreted in the unchanged form. The elimination half-life is longer in humans (70 min) than in rats (30 min; IARC, 1999).

Since its discovery, saccharin use has been a matter of controversy due to its tumour promoting abilities in second generations of rats. As a result, saccharin was thought to be unfit for human consumption and was banned before the First World War. Later on, various studies focused on the possible mechanism of carcinogenic effects of saccharin on different animals. Several epidemiological studies were conducted to find out the relation of saccharin with cancer promotion. But, no significant association was found between

saccharin intake and cancer in humans. It was found that urinary bladder cancer is a high dose phenomenon and is species specific, which occurs only in rats. Lastly, in 2000, saccharin was removed from the list of human carcinogens by National Toxicology Programme, USA and International Agency for Research on Cancer (IARC). (Singh 2013).

Behavioural data

No data identified

***In Vitro* Toxicity Status**

Carcinogenicity and Mutagenicity

The genotoxic activity and potency of 135 compounds was investigated in the Ames reversion test in the presence and absence of a 10% liver S9 mix from Aroclor-treated Sprague-Dawley rats. *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were tested. The chemicals were also tested in a bacterial DNA-repair test (3 isogenic *E. coli* strains were used; WP2, WP67 and CM871). Amongst the chemicals tested was saccharin sodium salt which was found to be negative in all *S. typhimurium* strains tested. It was also negative in the DNA-repair test leading the authors to conclude that saccharin sodium salt is not genotoxic in the two *in vitro* tests conducted in this paper (De Flora et al., 1984).

Sodium saccharin was not mutagenic to S. typhimurium strains TA100, TA1535, TA1537, TA1538, TA98, TA92 or TA94 in the presence or absence of an exogenous metabolic activation system.
Sodium saccharin did not cause DNA damage and did not bind covalently to DNA of rat liver or bladder. The IARC working group concluded that overall the results of the genotoxicity tests do not support a mechanism for the induction of urothelial-cell tumours in rats involving a direct interaction of sodium saccharin with DNA (IARC, 1999).

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