Sucrose

(CAS No: 57-50-1)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

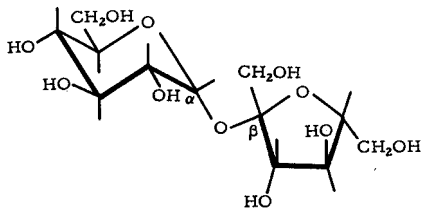
The present document contains the assessment of the health hazard of sucrose by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

In April 1999, literature was searched in the databases Medline, Toxline, and Chemical Abstracts, starting from 1966, 1981, and 1937, respectively, and using the following key words: saccharose; sucrose; α-D-glucopyranoside, ß-D-fructofuranosyl-; and 57-50-1.

In July 2000, the President of the Health Council released a draft of the document for public review. No comments were received.

An additional search in Toxline and Medline in September 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	sucrose
synonyms	:	saccharose; α-D-glucopyranoside, ß-D-fructofuranosyl-; beet sugar; cane sugar; confectioner's sugar; ß-D-fructofuranoside, α-D-glucopyranosyl-; sugar
molecular formula	:	$C_{12}H_{22}O_{11}$
structural formula	:	
CAS number	:	57-50-1

3 Physical and chemical properties

molecular weight	:	342.30
melting point	:	decomposes at 160-186°
boiling point	:	-
flash point	:	-
vapour pressure	:	negligible
solubility in water	:	very soluble
log $P_{octanol/water}$	:	-3.70 (experimental); -4.27 (estimated)
conversion factors	:	not applicable

Data from ACG92, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

Sucrose is a disaccharide composed of D-glucosyl and D-fructosyl moieties. It forms hard, white, dry crystals, lumps, or powder. It has a sweet taste and is odourless (ACG92).

Sucrose is a normal ingredient of the human diet. The human body can metabolise the compound and use its energy. A high intake can cause caries. Sucrose is present in large quantities in sugar beet and sugar cane. Occupational exposure occurs mainly in sugar factories and sugar refineries. Certain, not well-known circumstances in storage can cause severe explosions of the dust (Kop39).

4 Uses

Sucrose is used as a sweetening agent and food. It is the starting material in the fermentative production of ethanol, butanol, glycerol, and alcoholic beverages. It is used in pharmacy as a preservative, in the plastics and cellulose industry, and in the manufacture of ink and transparent soaps (ACG92).

5 Biotransformation and kinetics

Based on physical and chemical constants, Barratt calculated a human skin permeability coefficient of 5.25 x 10^{-6} cm/hour (Bar95). The committee concludes that skin penetration of sucrose is negligible.

The absorption of sucrose from animal lung was investigated by intratracheal (cannula) administration of ^{14}C-labelled compound as an aerosol or as a solution. Following administration of an aerosolised solution containing 1 mM sucrose

and 100 mM *p*-aminohippuric acid (mass mean aerodynamic diameter: 2.55±0.04 µm; geometric standard deviation: 2.49±0.02 µm) to anaesthetised rats, mice, and rabbits, for 5 minutes, the time to absorb 50% of the sucrose administered was calculated to be 41.5, 11.5, and 69.3 minutes, respectively (Sch86). When injected dissolved in Krebs-Ringer phosphate solutions, the absorption half-lives were 84-87, 23.6, and 173 minutes in rats, mice, and rabbits, respectively. The finding that the absorption rates of injected solutions in rats were directly proportional to the concentration over a range of 0.1-100 mM suggested that sucrose was absorbed by simple diffusion (Enn72, Sch83, Sch86).

6 Effects and mechanism of action

Human data

Dermal effects

Skin problems have been observed in sugar artists. These workers form decorative objects from sugar, heated to around 53ºC. The main skin problems at the hands were increased sweating, seen in 20 of a group of 30 (67%), and burning with erythema and blistering, seen in 12 out of 30 (40%). Four suffered from a relapsing type of chronic eczema (13.3%). The authors conclude that skin problems in sugar artists are mainly heat related and that allergic contact dermatitis is rare (Ban96).

Also, in a group of 71 female confectioners exposed to flour dust and aerosols of sugar, starch, egg powder, nuts, cocoa, cacao, and chocolate, the incidence of allergic reactions to sugar, measured with a skin prick test, was low: 2% (Zus94).

Respiratory effects

In a sugar cane production plant in Nigeria, no increase in respiratory diseases was found among the workers (n=335), compared with a control group (n=300) consisting of male inhabitants of the same area, who never worked in the sugar factory, viz., mainly traders, office workers, and teachers. On the contrary, the frequency of occurrence of cough alone, cough with sputum, morning phlegm, nasal catarrh, and chest pain was higher in the control group than in the exposed group ($p<0.05$). No data on exposure levels were presented (Tan96).

Pathogenic spores can be present in the air of sugar-processing plants (For89). On the other hand, the number of spores of the bacteria

Thermoactinomyces sacchari in 2 Australian cane sugar mills was too low to cause bagassosis (a form of allergic alveolitis) (Daw96).

In the beet sugar industry, workers are also overexposed to calcium oxide, carbon monoxide, respirable coal dust, and sulphur dioxide. In the packaging area, the sugar dust concentration exceeded the TLV of 10 mg/m^3 for nuisance dust (Man90).

There was a high prevalence of acute respiratory symptoms in confectioners (n=71) during the work shift, especially cough, dyspnoea, eye burning, and dryness of the throat and nose. However, no significant association with immunological tests was found (Zus94). Therefore, the committee concludes that there was no evidence of sensitisation.

Workers exposed to sugar dust in a sugar-cube manufactory (n=40) had significantly lower forced expiratory volume in one second (FEV_1) compared with workers not involved in sugar-cube manufacturing (n=98; p=0.02) or with the 'pooled remaining groups' (non-exposed workers, laboratory and office workers; n=116; p=0.009) after adjustment for smoking. Forced vital capacity (FVC), FEV_1/FVC, and the maximal flow at 50% of the FVC (V_{max50}) were not affected. The proportion of subjects complaining of cough and/or phlegm was higher in the exposed group (28%) than in the non-exposed group (16%); however, the difference was not statistically significant, even after comparison between exposed workers and the 'pooled remaining groups' after adjusting for smoking in a logistic regression (p=0.25). The sugar dust concentration was not measured (Boh96).

A single case of occupational asthma has been reported in a 33-year-old worker in a beet sugar-processing plant. In a bronchoprovocation test, the patient responded positively to mouldy but not to fresh beet sugar pulp (Ros92).

Dental effects

Caries was already recognised as an occupational disease at the beginning of the 20th century. It occurred among bakers, confectioners, and workers in the chocolate and honey biscuit industry. In these occupations, there was not only exposure to sugar, but also to flour. Kunert visited 150 workshops in Wroclaw (Poland; at that time Germany), and examined the dental health status of 726 workers. Part of these workers were divided into 4 categories of expected low to high exposure to sugar: I: bakers, baking only brown and white bread (n=67), II: bakers not further specified, having little exposure to sugar (n=67), III: confectioners within bakeries (n=28), and IV: confectioners (n=104). Further, there were 3 control groups: millers (n=70), shoemakers (n=51), and butchers

(n=44). The percentages of healthy teeth in the exposed groups decreased from 69.1, 55.1, 42.4% to 36.9%, respectively, and those of caries increased from 14.0, 20.5, 24.2% to 28%, respectively. In the control groups, incidences of healthy teeth were 62.5, 70.2, and 71.8%, respectively, and of caries 9.6, 9.7, and 9.3%, respectively. The concentration of sugar dust in the air was not measured (Kun01). The committee could not make statistical calculations because of lack of individual data.

A statistically significant increase in caries was found in a group of workers of a biscuit-production line (n=49) when compared with a control group of employees not exposed to sugar or flour dust (n=74) after age adjustment (73.0% vs. 60.7%; $p<0.05$). No increase in caries was found in a group of workers of a sweet- or bakery-production line (n=117 and 58, respectively). The levels of airborne sugar dust were 3 mg/m^3 or lower in 25/27 samples. In the 2 other samples, sugar concentrations were 18 and 21 mg/m^3. Masalin et al. concluded that these low sugar dust concentrations do not represent a danger to dental health, and, therefore, other factors must be the cause of the increase in dental caries. Since caries is multifactorial in nature, it is impossible to give a specific threshold value above which caries might appear. Consumption levels of 2.5-3.0 g/day or of 15 kg/year might be 'cut-off' points for high-caries and low-caries incidence. The average sugar consumption of American and European children is between 110 and 160 g/day (Mas88, Mas90).

In a group of 59 workers in a chocolate factory in Denmark, one third claimed to have had trouble with their teeth (many cavities, gingival bleeding). Upon examination, the workers had lost more teeth, had more untreated dental decay, and a higher caries incidence than a control group consisting of shipyard workers matched with respect to age, urbanisation, education, occupation, shift work, and dental care. Similar results were found when chocolate workers who confessed often consuming chocolate at work (about 25%) were excluded from analyses. Before starting the examination, high organic dust levels of 16-205 mg/m^3 were found in two departments, but the proportion of sucrose was not reported. From his studies, Petersen considered chocolate workers at high risk for dental problems (Pet84a, Pet84b).

A single case of dental caries in a worker in the confectionary industry has been described more recently (Par95).

The human data indicate that the teeth may be the target 'organ' following occupational exposure to sucrose. However, it is not clear to what extent additional oral intake contributed to the effects observed. In addition, exposure levels are lacking. Therefore, the commission is of the opinion that these that

cannot be used for the derivation of a health-based recommended occupational exposure limit (HBROEL).

Carcinogenicity

In a case-referent study, no relationship was found between bladder cancer and exposure to sugar dust (8 cases in a group of 116 cases with urinary bladder cancer). The referent group consisted of ward personnel (n=116) and general persons (n=116). The number of cases in the referent groups was not given, but the crude Odds Ratios varied from 1.6 to 3.9, with the lower 95% confidence interval below unity, at all calculations (Hou94).

Animal data

Sucrose was not a primary skin irritant in intact and abraded skin of guinea pigs and rabbits (Rou65).

Oral LD_{50} values of 35.4 and 29.7 g/kg bw were reported for male and female rats, respectively. The initial clinical signs of toxicity were hypokinesia, prostration, cyanosis, clonic-tonic convulsions, abdominal bloating, and diarrhoea. Sublethal doses giving for 1-3 days produced anorexia, polydipsia, hypothermia, diarrhoea, and weight loss. Death was the result of respiratory failure (ACG92).

A single oral dose of 30 g/kg bw caused very severe intoxication in sheep (Del59).

A single intravenous injection of 2.0 mL of a 60% sucrose solution caused nephrosis in rats. It produced vacuolisation and loss of enzyme activity in the kidneys (Sch65).

The LD_{50} (100 days) - the daily dose that killed 50% of the animals during 100 days of administration - was 28.5 g/kg bw/day for rats. Signs of toxicity were inhibition of growth, diuresis, polydipsia, aciduria, diarrhoea, soiling, ataxia, hepatitis, nephritis, and degeneration of many organs. No mortality occurred at daily doses of 19.8 g/kg bw (Con68).

Groups of 32 male and 32 female mice (*Acomys cahirinus*, spiny mice) received a 50% sucrose diet for 18 months, which resulted in a daily sucrose intake of roughly 57 g/kg bw*. The diet was isocaloric with the regular rat chow

* Calculation based on a weekly mean food consumption of 74.1 g per pair and mean initial and final body weights of 48.4 and 47.7 g, respectively, for males and of 43.9 and 44.6 g, respectively, for females.

that was given to a control group. Both male and female mice gained significantly less weight than the control group ($p<0.01$). These changes could not be attributed to differences in the dietary intake. The greater mortality in both parents and pups was not statistically significant. According to the number of pups born and number of productive pairs, the sucrose-fed mice were also less fertile. The litter size and the number of pups born per productive pair were slightly but not significantly lower (Sha84). Due to the singular strain used, the outcome cannot be used for the risk assessment.

A group of 50 female mice (Swiss) received oral (diet) doses of 10% sucrose in polyethylene glycol for 18 months while a second group of 50 mice was pre-treated with a single oral (gavage) dose of benzo[*a*]pyrene of 50 µg in polyethylene glycol followed 7 days later by diets containing 10% sucrose. When compared to vehicle-treated controls (n=100), the mice fed 10% sucrose gained more weight. Sucrose did not show carcinogenic or tumour-promoting activity (Roe70).

Subcutaneous injection of 25% sucrose solutions into rats (Bethesda black; n=30/sex) or mice (C57BL; n=30/sex) for up to 2 years did not induce increases in tumour incidences when compared to controls (Hue65).

Mutagenicity and genotoxicity

- *In vitro* tests:
  - Gene mutation assays. Sucrose was exclusively negative when tested for forward and reverse mutations in a variety of strains, including normal, excision-repair-deficient, and plasmid-carrying strains, of *S. typhimurium* and *E. coli* under a great number of different experimental conditions in more than 15 separate laboratories (Bri81, Fal85, Ish80).
    Sucrose did not induce reversions in *S. cerevisiae* strain XV185-14C when tested with and without rat liver metabolic activation (Meh81).
    Sucrose was negative in the L5178Y mouse lymphoma cell forward mutation assay both in the absence and presence of a rat liver metabolic activation system (McG87, Mit88, Myh88).
  - Cytogenicity assays. Sucrose did not induce SCEs when tested with and without metabolic activation in CHO cells (Per81).
    Sucrose produced a dose-related increase in the frequency of chromosomal aberrations in CHO cells. However, this phenomenon was ascribed to hyperosmolarity of the solution, because other hyperosmotic solutions (NaCl, KCl) induce the same effect (Gal87). Ishidate et al. reported an increased frequency of chromosomal aberrations in a Chinese

hamster lung cell line, which can be ascribed to the osmolarity of the solution as well (Ish80).
Sucrose did not induce mitotic aneuploidy when tested in *S. cerevisiae* strain D6 with and without rat liver metabolic activation (Par81).

- Other tests. Sucrose was negative when tested with and without metabolic activation in differential killing tests in *E. coli* (Gre81, Hym80, Twe81) and in the rec-assay in *B. subtilis* (Kad81). No induction of the prophage lambda in a lysogenic strain of *E. coli* was observed (Tho81).
  Using different strains of *S. cerevisiae*, sucrose was concluded to be negative upon testing for induction of mitotic gene conversion, mitotic crossing-over, or differential inhibition (Jag81, Kas81, Sha81a, Sha81b, Zim81). Weakly positive results in tests for gene conversion and differential inhibition at relatively high dose levels (Sha81a, Sha81b) were thought to be the consequence of chemical changes following dissolving high concentrations of sucrose in DMSO at elevated temperatures (Ash81).
  Sucrose was negative in UDS tests in HeLa cells (with and without S9 mix) (Mar81) or rat hepatocytes (Nov85).
  Sucrose was positive in a degranulation test that assays for the dissociation of ribosomes or polysomes from endoplasmatic reticulum derived from rat liver. Fey et al. considered the outcome thoroughly anomalous, arisen due to chemical changes consequent upon dissolving sucrose in DMSO at high concentrations at 40ºC. In a subsequent test using water as a vehicle, sucrose produced a negative response (Fey81).

- *In vivo* tests:
  No increase in the incidence of micronuclei was found in bone marrow sampled from male B6C3F_1 mice 36, 48, or 72 hours after the final of two intraperitoneal injections, given 24 hours apart, of sucrose of 2000 mg/kg bw each (Sal81), or from CD-1 mice 6 hours after the final of two intraperitoneal injections of doses of 2000, 4000, or 8000 mg/kg bw (Tsu81).

- Other tests:
  Sucrose was negative in a cell transformation test using BHK21 C13/HRC (baby hamster kidney) cells with and without rat liver metabolic activation (Dan81, Sty81).
  It did not enhance MLV (mouse leukaemia virus) infection in contact inhibited C3H2K (mouse kidney) cells (Yos81).

Reproduction toxicity

Daily oral sucrose doses of 2000-10,000 mg/kg bw to pregnant rats on gestational days 6-15 had no detectable adverse effects on embryos or fetuses (Fri68).

A diet containing 35 parts sucrose and 65 parts Purina Chow was given to mice during gestation and lactation. The offspring was given Purina Chow after weaning. The offspring had a lower growth rate and a different disposition of glucose after a glucose-tolerance test, compared with a control group (Dav73).

7 Existing guidelines

The current occupational exposure limit (MAC) for sucrose in the Netherlands is 10 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for sucrose in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Oral intake of sucrose causes caries. There are suggestions that a consumption level of 2.5-3.0 g/day or of 15 kg/year is a cut-off point between high-caries and low-caries incidence. Occupational exposure to sucrose may cause dental problems. However, since there were no data available on the relationship between exposure and effect or on the contribution of additional oral intake, the commission cannot use them for derivation of a HBROEL.

Sucrose was not irritating to the skin of rabbits or guinea pigs. The oral LD_{50} in rats was 30-35 g/kg bw. The compound had no mutagenic, genotoxic, carcinogenic, or tumour-promoting activity. High dietary intake caused a reduced fertility in mice (50% of the diet) and a lower growth rate in the offspring of mice (35% of the diet).

The committee considers the toxicological database on sucrose too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes there is insufficient information to comment on the level of the present MAC-value.

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Annex

Occupational exposure limits for sucrose in various countries.

country - organisation	occupational exposure limit	time-weighted average	type of exposure limit	note[a]	reference[b]

	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	10[c]	8 h	administrative		SZW04
Germany						
- AGS	-	-				TRG04
- DFG MAK-Kommission	-	-				DFG04
Great Britain						
- HSE	-	10	8 h	OES		HSE02
		20	15 min			
Sweden	-	-				Swe00
Denmark	-	-				Arb02
USA						
- ACGIH	-	10	8 h	TLV	A4[f]	ACG04b
- OSHA	-	15[d]	8 h	PEL		ACG04a
	-	5[e]	8 h			
- NIOSH	-	10[d]	10 h	REL		ACG04a
	-	5[e]	10 h			
European Union						
- SCOEL	-	-				EC04

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Inhalable dust.

[d] Total dust.

[e] Respirable fraction.

[f] Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.