INVERT SUGAR

SYNONYMS

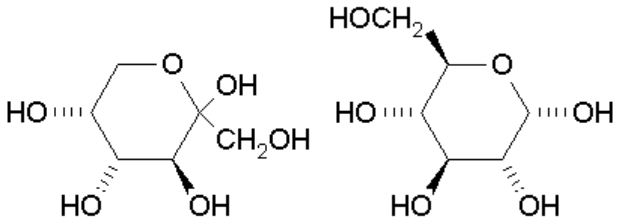
Calorose
Insubeta
Inverdex
Invertogen
Invertose
Nulomoline
Sugar invert
Travert
Invertix
Lumolinine
Metabol
Nevuline
Trimolin

CHEMICAL FORMULA

$C_6H_{12}O_6$

Invert sugar is a mixture of two monosaccharides, glucose and fructose which result from the hydrolysis of sucrose.

CHEMICAL STRUCTURES



IDENTIFIER DETAILS

CAS Number	:	8013-17-0
CoE Number	:	-
FEMA	:	-
EINECS Number	:	232-393-1
E Number	:	-

CLP CLASSIFICATION

Ingredient CLP Classification: Yes

Endpoint	Classification	Category
Acute Oral Toxicity	conclusive but not sufficient for classification	-
Acute Dermal Toxicity	data lacking	-
Acute Inhalation Toxicity	data lacking	-
Skin Corrosive/irritant	data lacking	-
Eye Damage/Irritation	conclusive but not sufficient for classification	-
Respiratory Sensitisation	data lacking	-
Skin Sensitisation	data lacking	-
Mutagenicity/Genotoxicity	data lacking	-
Carcinogenicity	data lacking	-
Reproductive Toxicity	data lacking	-
Specific Target Organ Toxicity	data lacking	-
Aspiration Toxicity	data lacking	-

REACH Statement

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints), guidance on safe use and classification and labelling. The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/.

SPECIFICATIONS

Melting Point: -

Boiling point: -

PURPOSE

Flavouring substance.

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
-	-	-	-

FDA Status:[CFR21]

Section Number	Comments
184.1859	Invert sugar

HUMAN EXPOSURE

Natural occurrence

Cane juice contains 5 – 10 % invert sugar (based on sucrose), where as in healthy beet it is 1 % [British sugar 23/08/02]. Honey is mostly invert sugar. Due to the levulose/50 % of composition of invert sugar, it is somewhat sweeter than sucrose [Budavari, 1996].

Invert sugar is widely used because it is sweeter than sucrose and begins to crystallise (harden) at much higher concentrations than glucose or sucrose syrups giving rise to more plastic foods such as icing and ice cream [British Sugar 23/08/2002].

Reported uses

Invert sugar is reportedly used in a wide variety of food products and confectioner, as a humectant to hold moisture and prevent drying out and is used in Brewing [Budavari, 1996].

TOXICITY DATA

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints), guidance on safe use and classification and labelling. The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/.

Carmines (2002), Rustemeier *et al*. (2002), Roemer *et al*. (2002) and Vanscheeuwijck *et al.* (2002) reported on a testing program designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen (Ames assay) a mammalian cell cytotoxicity assay (neutral red uptake), determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the addition of the combined ingredients, including invert sugar at levels up to 1392 ppm, “did not increase the overall toxicity of cigarette smoke” [Carmines (2002), Rustemeier *et al*., (2002), Roemer *et al*., (2002) and Vanscheeuwijck *et al.,* (2002)].
Renne *et al.*, (2006) evaluated the effects of tobacco flavouring and casing ingredients on both mutagenicity, and a number of physiological parameters in Sprague-Dawley (SD) rats. Test cigarettes containing a mixture of either 165 low-uses or eight high-use flavouring ingredients which included invert sugar at 20,000ppm, were compared to a typical commercial tobacco blend without flavouring ingredients. The Ames assay (TA 98, 100,102, 1535 and 1537 ±S9)

did not show any increase in Mutagenicity from “low” or “high” cigarette smoke condensate compared to the control. SD rats were exposed by nose-only inhalation for 1h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8mg/L from the test or reference cigarettes, or to air only. Plasma nicotine, COHb and respiratory parameters were measured periodically. Rats were necropsied after 13wk of exposure or following 13 wk of recovery from smoke exposure. Biological endpoints assessed included; clinical appearance, body weight, organ weights, and lesions (both gross and microscopic). The results of these studies did not indicate any consistent differences in toxicological effects between smoke from cigarettes containing the flavouring or casing ingredients and reference cigarettes.

In *vivo* toxicity status

LD_{50}	[Fructose]	rat	i.v.	10 - 12 g/kg	
LD_{50}	[Glucose]	rat	i.v.	10 - 12 g/kg	[FDA, 1976]

A single dose of 1g of [5.5 g/kg] of dextrose (glucose) to rats, by oral gavage, lead to lymphopenia which was attributed to the secretion of ACTH. The treatment of weanling rats with 1g of dextrose for 14 days [14 g/kg/bw], was reported to produce atrophy of the thymus. The concurrent administration of adenine was reported to suppress both responses [FDA,1976].

Bachman *et al.,* [1938] fed rats for 10 weeks on equal calorific diets containing 68 % of either fructose or dextrose, which was equivalent to about 50 g/kg/bw. The weight gain was reported to be the same for both, with a significantly higher fat content for those rats fed on dextrose. Rats treated with fructose were reported to have increased hydration of body tissues and hypertrophy of the liver [Bachman *et al.,* 1938].

A 90-day study was conducted with 4 groups of 10 male and 10 female Sprague-Dawley rats was carried out with a high-protein feed and 10 % invert sugar from different sources instead of drinking-water. The groups were as follows: I, control invert sugar; II, glucose isomerized with *S. violaceoniger* and refined; III, as II, but not refined; IV, as III plus 2.5% *S. violaceoniger*. There were no abnormalities in growth rates, feed and drink consumption, haematology, serum biochemistry, urine analysis or organ weights (observations as specified above for a 4-week study). Histological examination of aorta, heart, stomach (rumen and fundus), pylorus, liver (including special stains, pancreas, spleen, mesenteric nodes, kidneys, prostate, thyroid, adrenals, gonads and uterus revealed only commonly occurring lesions with no clustering within any of the treatment groups [WHO 1982].

Two groups of rats received syrup containing isomerized glucose (42-43% fructose 53-56% glucose) for two years. One group was given raw isomerized glucose and the other one commercial isomerized glucose, both at 10% in drinking water. A third group (control group) received a chemically comparable product: invert saccharose at the same conditions. Each of the three groups consisted of 50 male and female OFA, Sprague-Dawley originated rats. The

sugared fluid was administered *ad libitum*, a high fluid consumption was observed. The authors suggest that the general over-consumption of energetic material had possibly induced the slightly earlier mortality than usually observed, which was comparable in the three groups. No significant differences were observed in blood and urinary parameters examined during the trial between the control and the two treated groups. No significant differences were noted in a histological examination between the groups. No toxic effect was observed when isomerized glucose was administered to rats at the dose level of about 15 g/kg/day [WHO 1984].

A study by Hansen *et al.,* (2008) assessed the effect of simple carbohydrates (sucrose, glucose and fructose) on genotoxicity in the rat colon and potential effects on the metabolome. Big Blue (Fischer) rats (11 - 13 rats/group) were fed a purified diet containing either potato starch (control, 340 g/kg feed), sucrose (340 g/kg feed), fructose (340 g/kg feed) or glucose (340 g/kg feed) for a total of 35 days. Mutation frequency was found to be elevated, but not significantly, in colon epithelium by simple carbohydrates compared to potato starch control, but not in the liver. Simple carbohydrate diet was found to increase bulky DNA adducts in both the colon and liver. Also assessed were DNA strand breaks, protein oxidation and cell proliferation, but none were significantly affected. Liver weight was increased in sucrose and fructose fed rats but not glucose, compared to controls. Simple carbohydrates increased caecal pH, and decreased concentrations of acetic acid and propionic acid. Metabolomic analysis was performed using ^{1}H NMR coupled with a multivariate analysis of the metabolites. Metabolomic analysis of the serum and urine indicated effects on amino acid metabolism and decreased acetate. The authors noted that some effects such as the liver weight were associated with the glucose or fructose content of the simple sugar included in the diet [Hansen *et al.,* 2008].

Carcinogenicity and Mutagenicity

A mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including brown invert sugar at 24000 ppm. The authors concluded that the study “did not indicate any substantive effect of these ingredients on the tumourogenicity of cigarette smoke condensate” [Gaworski *et al.*, 1999]. (It should be noted that the cigarettes contained a typical American blend humectant and sugar component (*i.e.* glycerine ≈ 20,000 ppm, and propylene glycol at ≈ 24,000 ppm)) [Gaworski *et al.*, 1999].

Groups of 5 - 6 month old rats were given daily dextrose injections subcutaneously of 25 % dextrose solution [approximating to 2.5 - 5 g per kg]. Subcutaneous fusiform and polymorphous cellular sarcomata were observed in 2/55 animals after 299 injections, with a third animal having a sarcoma of in the abdominal cavity [FDA, 1976]. In another study Heuper [1965], carried out a study in which mice and rats were dosed with 0.5 - 2.0 ml/kg of a 25 % solution of dextrin was injected 2 - 3 times a week for up to 2 years. No tumours were reportedly found at either the injection sites and no untoward effects were reported [Heuper, 1965].

Inhalation Toxicity

A study investigated the effect of cigarettes, containing various additives in three combinations, in a 90 day nose-only smoke inhalation study in rats [Vanscheeuwijck *et al.*, 2002]. These ingredients included Invert Sugar at 1392 ppm, a level described as a multiple of its typical use in a US cigarette. The data from this study along with that from a number of other biological and chemical studies indicate that the addition of the combined ingredients "did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used" [Vanscheeuwijck *et al.*, 2002].

When tested at 24000 ppm in cigarettes, in a 13-week inhalation study, the presence of brown invert sugar "…had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats" [Gaworski *et al.*, 1998]. (However, it should be noted that the cigarettes had been spiked with a number of flavour ingredients in combination prior to smoking, and they contained a typical American blend humectant and sugar component (*i.e.* glycerine ≈ 20,000 ppm, and propylene glycol at ≈ 24,000 ppm)) [Gaworski *et al.*, 1998].

A total of 31 ingredients were tested in 90-day nose-only rat inhalation studies using mainstream cigarette smoke. Studies were designed following conventional toxicity testing methods employed for food additives and other consumer products. The authors concluded that these ingredients, which included invert sugar applied at levels up to 100,000 ppm on cigarettes produced minimal changes in the overall toxicity profile of mainstream cigarette smoke, and in some cases, the addition of high levels of an ingredient caused a small reduction in toxicity findings, probably due to displacement of burning tobacco [Gaworski *et al*., 2011].

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including invert sugar at levels up to 19975 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Reproductive / Developmental Toxicity

Isomerized glucose (42 – 43 % fructose 53 – 56 % glucose) was administered in drinking water to three successive generations of rats. The results have been compared to those obtained on animals receiving inverted saccharose under the same conditions. The test substance was administered in the drinking water as an aqueous solution at 10 % to two groups. Each group

consisted of 10 males and 20 females (F0 generation) which after 10 weeks were mated twice in order to obtain F1a and F1b generations. At weaning of F1a, 10 males and 20 females per group were retained and mated, when adult, to produce, the F2a and then the F2b generations. F3a and F3b were produced from the F2a generation, for which, at weaning, 10 males and 20 females were selected. F3b was observed until 8 weeks of age and sacrificed. The growth of the F3b generation during the 8 weeks of treatment after weaning was normal in the two groups. Main organs of 10 males and 10 females per group were examined histologically. Results obtained with inverted saccharose (group I) and with Isomerized glucose (group II) were comparable. The occasional differences observed between groups I (inverted saccharose) and II (Isomerized glucose) during the production of 6 litters (2 in each of the three generations) were incidental. No behavioural changes were observed during the three generations study. The production of two successive litters of the F0, F1 and F2a generations showed no abnormalities in the reproductive process. No adverse effect of the co administration of either carbohydrate was observed on fertility, reproductive performance, birth weight (growth in utero). The no effect level on reproduction was observed when isomerized glucose was administered at the dose level of 20 g/kg/day [WHO 1984].

Other relevant studies

Invert sugar is routinely administered intravenously to treat the painful ferbril crisis of sickle cell anaemia [Kraus *et al.,* 1974].

Intracutaneous injections of 3 glucan contaminants of invert sugar, have been reported to produce localised wheals and erythema reactions. These glucans with molecular weights between 12,00 - 1,400,000 have been reported to be active on intradermal injection into both dextran sensitive and dextran non sensitive rats [West, 1978].

Invert sugar injection (containing equal parts of dextrose and fructose): fructose offers no advantages and some disadvantages over dextrose injection. It may increase serum levels of lactate and urate if given rapidly. The infusion of fructose has been associated with increased production of uric acid and hyperuricemia. Invert sugar injection in patients with hereditary fructose intolerance (aldolase deficiency), can cause severe reactions (hypoglycaemia, nausea, vomiting, tremors, coma, convulsions) and its use is contraindicated [American Medical Association, 1973].

Less than 2 % of sugar is excreted in urine when 1 litre of 10 % invert sugar solution was infused in 1 hr. When given over a longer period of time invert sugar is completely utilised by the body and none is excreted in urine [American Hospital Formulary Service, 1984].

Behavioural data

Berlin *et al*., (2004) reported that ‘glucose attenuates tobacco craving and withdrawal symptoms in temporarily abstinent smokers’. The researcher

concluded that ‘further studies assessing the direct effect of glucose on brain serotonin are needed to ascertain whether a glucose induced reduction in craving is associated with an increase in brain serotonin [Berlin *et al*., 2004].

Glucose and caffeine are reported to improve cognition and mood (caffeine). The effects on both substances in combination were studied in a double-blind study with 20 participants. The researchers concluded that ‘the data suggested that there is some degree of synergy between the cognition-modulating effects of glucose and caffeine which merits further investigation [Scholey and Kennedy, 2004].

A paper reviewing advances in pharmacotherapy for treatment of tobacco dependence reported the rapid increase in non-nicotine pharmacotherapies (including glucose) [Foulds *et al*., 2004].

Messier, (2004) reported the memory enhancing properties of glucose have been studied for a period of almost 20-years and glucose memory improvement occurs at two optimal doses in animals (100 mg/kg and 2 g/kg), which is thought to correspond to two physiological mechanisms underlying glucose effects in memory. However, dose-response studies in humans are reported to be rare with glucose being reported to facilitate tasks where are difficult to master or involve divided attention rather than easier tasks. There is reported evidence that impaired glucose regulation is associated with impaired cognition (episodic memory in particular). Results of a few studies have revealed that treatments that improve glucose regulation also improve cognition, (in diabetic patients), [Messier, 2004].

In *vitro* toxicity status

Carcinogenicity and Mutagenicity

Roemer *et al.* (2002) reported on a study in which cigarettes containing various additives in three different combinations were produced. Smoke condensates prepared from these cigarettes were then tested in two different *in vitro* assays. The mutagenicity of the smoke condensate was assayed in the Salmonella plate incorporation (Ames) assay with tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of an S9 metabolic activation system. The cytotoxicity of the gas/vapour phase and the particulate phase was determined in the neutral red uptake assay with mouse embryo BALB/c 3T3 cells. The authors concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients which included Invert Sugar at levels up to 1392 ppm (a multiple of its typical use in a US cigarette) [Roemer *et al.,* (2002)].

A total of 95 ingredients were tested individually through addition at different concentrations to the tobacco of experimental cigarettes. Mainstream cigarette smoke chemistry analysis, bacterial mutagenicity testing, and cytotoxicity testing were conducted. The authors concluded that these ingredients, which included invert sugar applied at levels up to 100000 ppm on cigarettes produced minimal changes in the overall toxicity profile of

mainstream cigarette smoke, and in some cases, the addition of high levels of an ingredient caused a small reduction in toxicity findings, probably due to displacement of burning tobacco [Gaworski *et al*., 2011].

There was reported to be no mutagenicity of dextrose when tested with the Ames *Salmonella typhimurium* strain TA98 with metabolic activation [Concentration not specified, CCRIS 23/08/02].

Additional information concerning the in vitro mutagenicity of this material may be found in "An Interim report on data originating from Imperial Tobacco Limited's Genotoxicity testing programme September 2003" or "An updated report on data originating from Imperial Tobacco Limited's external Genotoxicity testing Programme – Round 2, August 2007".

The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with the tester strain TA98 in the presence of an S9 metabolic activation system. The cytotoxicity of the cigarette condensate was determined in the neutral red uptake assay and the (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt assay (MTS assay) with the human hepatocellular liver carcinoma cell line, HEP-G2. It was concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included invert sugar at levels up to 25000 & 50000 ppm.

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including invert sugar at levels up to 19975 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other relevant studies

Dextrose was reported to be positive in the mouse lymphoma assay with L5178Y (TK+and TK-), without metabolic activation at concentrations between 0.179-0.235 mol/l^{-1} [CCRIS 23/08/02].

Sugars, such as sucrose or invert sugar, have been used as tobacco ingredients in American-blend cigarettes to replenish the sugars lost during curing of the Burley component of the blended tobacco in order to maintain a balanced flavour. Chemical-analytical studies of the mainstream smoke of research cigarettes with various sugar application levels revealed that most of the smoke constituents determined did not show any sugar-related changes in yields (per mg nicotine), while ten constituents were found to either increase

(formaldehyde, acrolein, 2-butanone, isoprene, benzene, toluene, benzo[k]fluoranthene) or decrease (4-aminobiphenyl, N-nitrosodimethylamine, N-nitrosonornicotine) in a statistically significant manner with increasing sugar application levels. Such constituent yields were modelled into constituent uptake distributions using simulations of nicotine uptake distributions generated on the basis of published nicotine biomonitoring data, which were multiplied by the constituent/nicotine ratios determined in the current analysis. These simulations revealed extensive overlaps for the constituent uptake distributions with and without sugar application. Moreover, the differences in smoke composition did not lead to relevant changes in the activity in in vitro or in vivo assays. The potential impact of using sugars as tobacco ingredients was further assessed in an indirect manner by comparing published data from markets with predominantly American-blend or Virginia-type (no added sugars) cigarettes. No relevant difference was found between these markets for smoking prevalence, intensity, some markers of dependence, nicotine uptake, or mortality from smoking-related lung cancer and chronic obstructive pulmonary disease. In conclusion, thorough examination of the data available suggests that the use of sugars as ingredients in cigarette tobacco does not increase the inherent risk and harm of cigarette smoking [Roemer *et al*., 2012].

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