

SUMMARY OF DATA FOR CHEMICAL SELECTION

Dihydroxyacetone
96-26-4

BASIS OF NOMINATION TO THE CSWG

As consumers have become more mindful of the hazards of a "healthy tan," more individuals have turned to sunless tanning. Sunless tanning products represent about 10% of the \$400 million market for suntan preparations, and these products are the fastest growing segment of the suntanning preparation market. All sunless tanners contain dihydroxyacetone.

Information on the toxicity of dihydroxyacetone appears contradictory. A mutagen that induces DNA strand breaks, dihydroxyacetone is also an intermediate in carbohydrate metabolism in higher plants and animals. Such contradictions are not unprecedented, and it has been suggested that autooxidation of α -hydroxycarbonyl compounds including reducing sugars may play a role in diseases associated with age and diabetes (Morita, 1991).

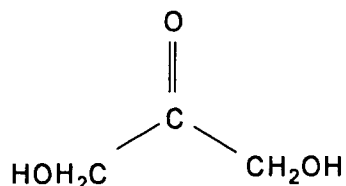
When dihydroxyacetone was applied to the skin of mice, no carcinogenic effect was observed. It is unclear whether this negative response was caused by a failure of the compound to penetrate the skin. If so, extrapolating the dermal results to other routes of exposure would not be appropriate. NCI is nominating dihydroxyacetone to the NTP for dermal penetration studies in rats and mice to determine whether dihydroxyacetone can penetrate the skin. This information will clarify whether additional testing of dihydroxyacetone is warranted.

FEB 21 1998

CHEMICAL IDENTIFICATION

<u>CAS Registry Number:</u>	96-26-4
<u>Chemical Abstracts Service Name:</u>	1,3-Dihydroxy-2-propanone (9CI; 8CI)
<u>Synonyms and Tradenames:</u>	1,3-Dihydroxydimethyl ketone; Chromelin; CTFA 00816; Dihyxal; Otan; Oxantin; Oxatone; Soleal; Triulose; Viticolor
<u>Structural Class:</u>	Ketone, ketotriose compound

Structure, Molecular Formula, and Molecular Weight:



$\text{C}_3\text{H}_6\text{O}_3$

Mol. Wt.: 90.08

Chemical and Physical Properties:

<u>Description:</u>	Crystalline powder; fairly hygroscopic; characteristic odor; sweet, cooling taste. Normal form is a dimer; freshly prepared dihydroxyacetone everts rapidly to monomer in solution (Budavari, 1996)
<u>Melting Point:</u>	90°C (Lide, 1995)
<u>Solubility:</u>	Dimer: slowly sol. in 1 part water, 15 parts alcohol. Monomer: very soluble in water, alcohol, ether, acetone (Budavari, 1996)

Technical Products and Impurities: Dihydroxyacetone (DHA) is available in all grades and in 55-gallon drums; 1- and 5-gallon pails; and 1-, 5-, 10-, and 25-lb quantities from Penta Manufacturing Co. Tri-K Industries offers 25-kg drums and 1- and 5-kg pails (Rodnan, 1997).

DHA dimer is available at purities of 97% and >99% from Aldrich and Fluka, respectively (Aldrich Chemical Co., Inc. 1996; Fluka Chemical Co., 1997).

EXPOSURE INFORMATION

Production and Producers: DHA is produced from glycerol by *Acetobacter* sp. under aerobic conditions (Budavari, 1996). According to recent chemical catalogs and directories, DHA is manufactured and/or distributed by Aldrich Chemical Co., Inc.; Biddle Sawyer Corp.; Chemapol USA, Inc.; Davos Chemical Corp.; Eastern Chemical Corp.; EM Industries, Inc.; Fluka Chemical Corp.; Gemchem, Inc.; Girindus Corp.; K3 Corp.; Penta Manufacturing Co.; Protameen Chemicals, Inc.; R.W. Greef & Co., L.L.C.; Schweizerhall, Inc.; Sigma Chemical Co.; Spectrum Bulk Chemicals; and Tri-K Industries, Inc. (Aldrich Chemical Co., Inc., 1996; Fluka Chemical Corp., 1997; Hunter, 1997; McCoy, 1997; Rodnan, 1997; Sigma Chemical Co., 1997).

No data were reported for DHA by the US International Trade Commission (USITC) *Synthetic Organic Chemicals, US Production and Sales*, for the years 1983-1993. This source is no longer published. No other quantitative information on annual production was found in the available literature.

DHA is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1997).

Use Pattern: DHA was first used as an active ingredient in the pharmaceutical field. In the 1920s, researchers used DHA as a substitute for glucose in the treatment of diabetes. In 1957, a doctor discovered the tanning properties of DHA while investigating the effects of its oral administration on a childhood glycogen storage disease. Today, all self-tanning preparations contain DHA and these products provide the primary market for DHA (Kurz, 1994).

DHA imparts color to the skin through a "browning reaction." The DHA, as a simple sugar, reacts with the amino acids provided by sweat and keratin and perhaps as well by free amino acids on the skin. The first DHA tanning preparations which were introduced in the 1960s, included QT Quick Tanning Suntan Lotion and Man-Tan. The early products resulted in an unacceptable off-orange skin color. Recent formulations have overcome this problem partly through the use of lower DHA concentrations (3-5%) (Debrovner, 1992; Anon., 1993; Gerry, 1997).

The 1996 sales of suncare products were estimated at about \$390 million and sunless tanning products represented about 10% of these US sales. The market for self-tanning products is growing at about 10% a year (Anon., 1993; Gerry, 1997).

Additional uses cited for DHA include intermediate, emulsifier, humectant, plasticizers, and fungicides (Lewis, 1993).

Human Exposure: There is potential for widespread, low-level exposures to DHA in consumer populations resulting from its use in self-tanning products.

An adult's average single application of tanning lotion was estimated to be 10 ml. This volume of QT suntan lotion contains 350 mg DHA (Pham *et al.*, 1980). Since the color begins to fade after a few days, repeated applications of the self-tanning preparations are required (Anon., 1993).

No reports of occupational exposure to DHA during its production or processing were found in the available literature. No listing was found for DHA in the National Occupational Exposure Survey (NOES).

Environmental Occurrence: No information on the environmental occurrence of DHA was identified in the available literature.

DHA is an intermediate in carbohydrate metabolism in higher plants and animals (Anon., 1993). Raffi and coworkers (1981) identified DHA in irradiated maize starch.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or work place allowable levels of DHA. DHA was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

The FDA (1997) has approved DHA as a permanently listed colorant exempt from certification for drugs and cosmetics. It may only be used in externally applied drugs and cosmetics intended solely or in part to impart a color to the human body.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to dihydroxyacetone (DHA) and cancer risk were identified in the available literature. DHA has been used to treat diabetic coma, has been administered to diabetics instead of glucose, and has been tested as a diagnostic tool for glycogen storage diseases (Akin & Marlowe, 1984). Topically applied DHA in combination with lawsone has been used to treat patients with severe photosensitivity (Rice, 1976).

DHA was reportedly detected in the blood after topical application (Goldman & Blaney, 1962).

Animal Data: *Carcinogenicity Studies:* Akin and Marlowe (1984) described the results of a lifespan skin painting study of DHA in mice. Once a week for 80 weeks, 0.1 ml of 5% or 40% DHA in aqueous solution was placed on the clipped backs of Swiss-Webster mice, 100 animals per group, equally divided by sex. Fresh DHA solutions were prepared for each application. All mice that died and those killed in moribund condition were examined for tumors and other abnormalities. Tissues examined included skin, liver, spleen, stomach, small and large intestines, kidney, bladder, adrenals, gonads, uterus, pituitary, thyroid, thymus, salivary glands, axillary lymph nodes, lung, and brain. Grossly observable tumors were fixed for microscopic examination. The authors did not provide details regarding the disposition of animals still surviving after the final compound administration at 80 weeks.

The authors reported that no significant differences were seen between control mice dosed with distilled water and those treated with DHA. Except for the brown color on the DHA-treated mice, no differences in physical appearance, behavior, weight gains, or survival were observed. The number of tumors identified in male mice were 22, 16, and 16, respectively, in the 0, 5%, and 40% DHA groups. Corresponding figures for the female mice were 26, 27, and 26 tumors in the 0, 5%, and 40% DHA groups, respectively.

Microscopic findings were also reported, with no significant differences observed between treated animals and controls. The number of mice examined microscopically were 26 males and 30 females in the control group, 26 males and 26 females in the 5% DHA group, and 18 males and 25 females in the 40% DHA group.

Short-Term Tests: Table 1 presents data on the genotoxicity of DHA. This compound has generally shown mutagenic activity vs. *Salmonella typhimurium* TA100, a strain sensitive to base-pair mutagens and TA104, a strain sensitive to carbonyl compounds. It is generally negative in other tester strains.

Table 1. *In vitro* genotoxicity of dihydroxyacetone

Test system/strain or cell line (locus)	Dose: study details (activation, solvent, schedule)	Result	References
Endpoint: Mutation			
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1536, TA1537, & TA1538	Paper disks saturated with QT suntan lotion (7.5% DHA), Sudden Tan suntan lotion (3.5% DHA) and 8% aqueous soln. of DHA.	+ (TA100) weak (TA98) - (others)	Pham <i>et al.</i> , 1980
<i>S. typhimurium</i> TA100	Agar overlay technique; QT lotion, Sudden Tan lotion, and DHA; 1 mg/plate; +/- S9 rat hepatic microsomes	+	Pham <i>et al.</i> , 1980
<i>S. typhimurium</i> TA 100	No data provided	+	Kasai <i>et al.</i> , 1985
<i>S. typhimurium</i> TA100	5 concentrations \leq 300 μ g/plate +/- S9 mix	+ (S9-no effect)	Yamaguchi, 1982
<i>S. typhimurium</i> TA100	Standard assay of DHA pretreated for 60 min. at 37°C with oxygen radical scavengers	mutagenic activity reduced	Yamaguchi, 1985
<i>S. typhimurium</i> TA100	1, 50, & 100 μ g/ml, +/- UV irradiation	-	Pathak <i>et al.</i> , 1982
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, & TA1538	Plate incorporation test +/- S9 mix, DHA in DMSO	-	Bonin <i>et al.</i> , 1982
<i>S. typhimurium</i> TA104	Liquid preincubation procedure	maximum non-toxic dose >111 μ moles; 5 revertants/ μ mole	Marnett <i>et al.</i> , 1985

Test system/strain or cell line (locus)	Dose: study details (activation, solvent, schedule)	Result	References
<i>E. coli</i> PQ37 SOS chromotest	Colorimetric detection of lacZ gene expressed upon induction of DNA damage	+	Mersch-Sunderman <i>et al.</i> , 1994
<i>E. coli</i>	3.3 mmol/l	+	NLM, 1997
Endpoint: DNA Damage			
<i>Bacillus subtilis</i> M ₄₅ & H ₁₇	Rec assay, 0.1 ml Sudden Tan or QT lotions or 2, 4, or 8% DHA on paper disk over agar overlay	primary DNA damage	Pham <i>et al.</i> , 1980
DNA repair synthesis/ mouse embryo fibroblast 10T1/2 cells	30 min. pretreatment with 1% DHA with subsequent exposure to 10 J/m ² of UV light	-	Long & Little, 1984
Cell transformation assay/ mouse fibroblast 3T3 cells	No details reported	induced significant no. of type-3 foci	Pathak <i>et al.</i> , 1982
DNA strand breakage/ bacteriophage ϕ X174	DHA (10 ⁻⁴ or 10 ⁻⁵ M) in presence of Cu ²⁺ , 3 hr. incubation	+ single strand breaks (31.5 and 0.74, respectively, per ϕ X174 DNA)	Morita, 1991
Isopropylideneinosine (IPG) adducts	DHA and DHA phosphate reacted with IPG under physiological conditions	adducts identical to methylglyoxal-IPG adducts formed	Kasai <i>et al.</i> , 1985

+ = positive results; - = negative results

Other Biological Effects: DHA phosphate is an intermediate in the Embden-Meyerhof pathway for the oxidation of glucose to carbon dioxide and water. Thus, DHA can be readily metabolized by entering directly into the glycolytic pathway at the triose-phosphate level (Burch *et al.*, 1970).

The aerobic xanthine oxidase reaction causes the cooxidation of DHA in a process strongly inhibited by superoxide dismutase but not by catalase, peroxide scavengers, or

iron-inactivating chelating agents. Several molecules of the sugar can be oxidized for each oxygen radical introduced. A free radical chain mechanism, in which oxygen radicals act as an initiator and a chain propagator is proposed. Thus simple sugars capable of tautomerizing to enediols are biologically relevant targets for oxygen radicals (Mashino & Fridovich, 1987).

Structure/Activity Relationships: DHA, acetol, acetylmethylcarbinol, glycolaldehyde, glyoxal, and dihydroxyfumaric acid were mutagenic in the Ames assay. α -Methoxyacetone, 3-hydroxy-3-methyl-2-butanone, and 4-hydroxy-3-methyl-2-butanone were not. The mutagens are easily oxidized and the nonmutagens are difficultly oxidized, suggesting that mutagenicity is dependent on reactive oxygen metabolites (Garst *et al.*, 1983). Of these chemicals, only glyoxal has been tested extensively.

In cellular systems glyoxal reacts readily with proteins, RNA, and DNA. It binds preferentially to guanosine in RNA or DNA to form stable adducts (Lundberg, 1995). In addition to mutagenic activity in the Ames assay, glyoxal has produced mutations in *E. coli*, sister chromatid exchanges in human lymphocytes and hamster ovary cells, DNA damage in rats administered 500 mg/kg doses orally, DNA damage in mouse lymphocyte cultures, and unscheduled DNA synthesis in rats administered 300 mg/kg oral doses (NLM, 1997). Glyoxal has demonstrated tumor promoting activity in the glandular stomach of rats following initiation with N-methyl-N'-nitro-N-nitrosoguanidine (Lundberg, 1995).

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