Final Report on the Safety Assessment of Triacetin[1]

Triacetin, also known as Glyceryl Triacetate, is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations, at concentrations ranging from 0.8% to 4.0%. It is a commonly used carrier for flavors and fragrances. Triacetin was affirmed as a generally recognized as safe (GRAS) human food ingredient by the Food and Drug Administration (FDA). Triacetin was not toxic to animals in acute oral or dermal exposures, nor was it toxic in short-term inhalation or parenteral studies, and subchronic feeding and inhalation studies. Triacetin was, at most, slightly irritating to guinea pig skin. However, in one study, it caused erythema, slight edema, alopecia, and desquamation, and did cause some irritation in rabbit eyes. Triacetin was not sensitizing in guinea pigs. Triacetin was not an irritant or a sensitizer in a clinical maximization study, and only very mild reactions were seen in a Duhring-chamber test using a 50% dilution. In humans, Triacetin reportedly has caused ocular irritation but no injury. Triacetin was not mutagenic. Although there were no available reproductive and developmental toxicity data, Triacetin was quickly metabolized to glycerol and acetic acid and these chemicals were not developmental toxins. Reports of 1,2-glyceryl diesters, which may be present in Triacetin, affecting cell growth and proliferation raised the possibility of hyperplasia and/or tumor promotion. The Cosmetic Ingredient Review (CIR) Expert Panel concluded, however, that the effects of 1,2-glyceryl diesters on cell growth and proliferation require longer ester chains on the glycerin backbone than are present when acetic acid is esterified with glycerin, as in Triacetin. On the basis of the available information, the CIR Expert Panel concluded that Triacetin is safe as used in cosmetic formulations.

INTRODUCTION

This report reviews the safety of Triacetin, an ingredient that is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations (Pepe, Wenninger, and McEwen 2002).

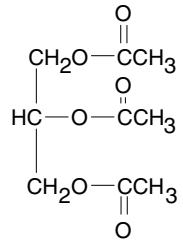
Received 4 December 2002; accepted 18 March 2003.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Monice Zondlo Fiume, former Scientific Analyst/Report Management Coordinator, Address correspondence to F. Alan Andersen, Cosmetic Ingredient Review Director, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

CHEMISTRY

Definition and Structure

Triacetin (CAS no. 102-76-1) is the triester of glycerin and acetic acid that conforms to the formula (Pepe, Wenninger, and McEwen 2002):



Triacetin is also known as Glyceryl Triacetate (Pepe, Wenninger, and McEwen 2002; National Academy of Science [NAS] 1996; United States Pharmacopeial Convention, Inc. [USP] 1995; Unichema Chemie B.V. 1994; Lewis 1993a; Budavari 1989); Glycerol Triacetate (Unichema Chemie B.V. 1994; Lide 1993; Lewis 1993a); Glycerin Triacetate (Unichema Chemie B.V. 1994); Glycerine Triacetate (Lewis 1993a); Triacetyl Glycerine (Unichema Chemie, B.V. 1994; Budavari 1989); Acetin, Tri-; 1,2,3-Triacetoxypropane (Unichema Chemie B.V. 1994); 1,2,3-Propanetriol Triacetate (Pepe, Wenninger, and McEwen 2002; USP 1995; Unichema Chemie B.V. 1994; Lewis 1993a; Budavari 1989); 1,2,3-Propanetriyl Triacetate (ChemID 1998); and Acetic, 1,2,3-Propanetriyl Ester (Pepe, Wenninger, and McEwen 2002; Unichema Chemie B.V. 1994).

Physical and Chemical Properties

Physical and chemical properties are described in Table 1. Published data on the ultraviolet radiation absorbance of Triacetin were not found.

Manufacture and Production

Triacetin is derived by the action of acetic acid on glycerol, with vacuum distillation used as the method of purification (Lewis 1993b). It can also be prepared by esterification of glycerin with acetic anhydride (Gennaro 1990), by the acetylation of glycerol, by the reaction of oxygen with a liquid-phase mixture of allyl acetate and acetic acid using bromide as a catalyst (Budavari 1989), and from glycerin and acetic anhydride

International Journal of Toxicology, 22(Suppl. 2):1–10, 2003

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810390204845

TABLE 1
Chemical and physical properties of Triacetin

		Reference
Physical Characterization	Colorless, oily liquid with a slight fatty odor and taste	Lewis 1993a
	Colorless, somewhat oily liquid having a slight, fatty odor and a bitter taste	NAS 1996; Budavari 1989
Empirical formula	$C_9H_{14}O_6$	Pepe, Wenninger, and McEwen 2002
Molecular weight	218.21	NAS 1996
	218.20	Budavari 1989; Grant 1972
Melting point	−78°C	Lewis 1993a; Budavari 1989
Boiling point	258°C	Lewis 1993a; Grant 1972
	258°C–260°C	Lewis 1993b
	260°C	Gennaro 1990
	258°C–260°C; 172°C (bp_{40})	Budavari 1989
Solubility	Soluble in water; miscible with alcohol, ether, and chloroform	NAS 1996; Lewis 1993a
	Soluble in acetone, ethanol, benzene, and chloroform	Unichema Chemie B.V. 1994
	Soluble in alcohol, ether, acetone, benzene, and chloroform	Lide 1993
	Slightly soluble in water; very soluble in alcohol, ether, and other organic solvents	Lewis 1993b
	Soluble in 14 parts water and in alcohol, chloroform, and ether	Gennaro 1990
	Soluble in 14 parts water; miscible with alcohol, ether, chloroform; slightly soluble in carbon disulfide	Budavari 1989
log $P_{o/w}$	0.1, 0.368	Unichema Chemie B.V. 1994
Specific gravity	1.154–1.158 (food-grade)	NAS 1996
	1.152–1.158 (USP-grade)	USP 1995
	1.1596 (20/4)	Lide 1993
	1.161	Lewis 1993a; Grant 1972
	1.160	Lewis 1993b
	1.1562 (d_4^{25}); 1.1596 (d_4^{20}); 1.163 (d_{20}^{20})	Budavari 1989
Index of refraction	1.429–1.431 (25°C) (food-grade)	NAS 1996
	1.429–1.430 (USP-grade)	USP 1995
	1.4301 (20°C)	Lide 1993
	1.4312 (20°C)	Lewis 1993b
	1.4307 (n_D^{20})	Budavari 1989
Stability	Combustible	Lewis 1993b
Reactivity	A polar substance that is easily hydrolyzed with the liberation of acetic acid	Unichema International 1996
Flash point	280°F (COC)	Lewis 1993a; Sax 1979
	300°F	Lewis 1993b
Autoignition temperature	812°F	Lewis 1993a; Sax 1979

using phosphoric acid or zinc chloride as the condensing agent (Opdyke 1978).

Triacetin occurs naturally as an oil from cod-liver oil, butter, and other fats (Grant 1972).

Analytical Methods

Triacetin has been determined using gas chromatography (Ogawa et al. 1988, 1992; Uematsu et al. 1997), thin layer chromatography, and infrared spectroscopy (Ogawa et al. 1992).

Impurities

Triacetin contains trace moisture and acetic acid (Unichema Chemie B.V. 1994). Food-grade Triacetin must be at least 98.5% $C_9H_{14}O_6$, and it must not contain >5 mg/kg heavy metals (as Pb) or >0.2% water (NAS 1996). USP-grade Triacetin must contain not less than 97.0% and not greater than 100.5% $C_9H_{14}O_6$, calculated on the anhydrous basis (USP 1994).

USE

Cosmetic

Triacetin is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations (Pepe, Wenninger, and McEwen 2002). It is a commonly used carrier for flavors and fragrances (Unichema International 1996).

As shown in Table 2, the product formulation data reported by the cosmetics industry to the Food and Drug Administration (FDA) in 1998 indicate that Triacetin was used in a total of 13 cosmetic formulations. Concentration of use data submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicated that Triacetin was used in a number of product types at concentrations of 0.8–4% (CTFA 1999).

According to the Ministry of Health, Labor and Welfare (MHLW) in Japan, Triacetin is not restricted in any manner in cosmetic formulations (MHLW 2001).

Triacetin does not appear in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Commission 2003).

TABLE 2
Triacetin use in cosmetic formulations

Product category (total no. formulations in category) (FDA 1998)	Total no. containing ingredient (FDA 1998)	Concentration of use (%) (CTFA 1999)
Eyeliner (514)	2	1
Mascara (167)	2	2
Tonics, dressings, and other hair-grooming aids (549)	—	0.8
Makeup bases (132)	6	1
Other makeup preparations (135)	3	—
Basecoats and undercoats (manicuring preps) (48)	—	1
Nail polish and enamel (80)	—	1
Nail polish and enamel removers (34)	—	4
1998 Triacetin use	13	0.8–4

Noncosmetic

Triacetin is a generally recognized as safe (GRAS) ingredient (21 CFR 184.1901) by the FDA. It is used in foods as a flavoring agent and adjuvant, formulation aid, humectant, and solvent and vehicle; it has no limitations other than good manufacturing practice. In its determination that Triacetin was a GRAS ingredient (FDA 1983, 1989), FDA relied upon an evaluation on glycerin and glycerides prepared by the Federation of American Societies for Experimental Biology (FASEB) that included safety-test data on Triacetin. This FASEB evaluation found that Triacetin was without toxic effects in long-term feeding studies in rats that used doses that were higher than those to which consumers would be exposed (FASEB 1975). In addition, FDA contracted with a laborartory to perform a mutagenic evaluation of Triacetin, the results of which demonstrated no mutagenic activity (Litton Bionetics, Inc. 1976).

Triacetin is used in pharmaceuticals as a hydrophilic plasticizer in polymeric coatings of capsules, tablets, beads, and granules, with typical concentrations of 10% to 35% *w*/*w* (Unichema International 1996). Triacetin is used as an antifungal drug for treatment of superficial fungus infections of the skin (Gennaro 1990). However, data are inadequate to establish general recognition of the safety or effectiveness of Triacetin as an over-the-counter topical antifungal drug (21 CFR 310.545). Triacetin has been used with prostaglandin E_2 (PGE_2) to form a gel used for preinduction cervical softening (Graves et al. 1985; Noah et al. 1985). According to Yalkowsky and Roseman (1979), Triacetin stabilized PGE.

Triacetin had wide use in foundry applications as a curing agent for phenol resins used in the manufacture of sand molds (Unichema International 1996). It is used as a cellulose acetate plasticizer in the manufacture of cigarette filters, a tobacco humidifier, a plasticizer for cellulose nitrate, and a solvent for basic dyes and in the manufacture of celluloid and photographic films, as well as in the paint, lacquer, and varnish industries (Unichema Chemie B.V. 1994). Triacetin is also used in removal of carbon dioxide from natural gas (Lewis 1993b). According to Budavari (1989), technical Triacetin (a mixture of mono-, di-, and small quantities of Triacetin) is used as a solvent for basic dyes, particularly induline dyes, and tannin in dyeing.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

In an in vitro study by Stoughton (1970), the penetration of Triacetin into the corium of human skin was determined by topical application of Triacetin to the epidermis (which was later separated from the corium), and then measuring the antimicrobial activity. Using leg skin, a plastic cylinder was attached to the epidermis, and 0.01 cc Triacetin was applied for 20 to 24 h. The skin was then washed and the epidermis removed. Six-millimeter punches of the corium were taken and implanted on the culture medium, with the epidermal side in contact with the medium. When inhibition of growth around the corium

occurred, the radius of inhibition was measured. There was no average inhibition of positive responses with Triacetin cream. The researchers speculated that an antimicrobial agent may penetrate into the corium and not diffuse into the surrounding medium when assayed, and that this might give a false-negative report of its ability to penetrate the epidermis.

von Oettingen (1960) stated that Triacetin is absorbed from the gastrointestinal tract, but no experimental details were provided.

Pharmacological Effects

In a series of studies, the use of Triacetin in total parenteral nutrition was examined.

Six female mongrel dogs were used to determine the effect of Triacetin on serum phosphorus, calcium, and magnesium metabolism (Bailey, Heath, and Miles 1989). A 5% *v*/*v* aqueous solution of Triacetin was infused intravenously at a rate of 47 μmol/kg/min for 3 h. Arterial blood was sampled at 15 to 30-min intervals, and urine was collected during infusion. No significant changes in total serum calcium or phosphorus concentrations were observed; however, serum magnesium concentrations were statistically significantly decreased 90 min after the initiation of dosing and remained decreased until the end of the study. During Triacetin infusion, the plasma acetate concentration increased from 0.13 to 1.32 mmol/L at 30 min; the concentration gradually declined to ~1 mmol/L during the last hour of the study. No change was observed in the fractional excretion of calcium, magnesium, or phosphorus. The authors speculated that the decrease in serum magnesium was probably because of cellular uptake rather than accelerated excretion. Baseline blood pH was not significantly altered.

Bailey, Haymond, and Miles (1991) also used groups of female mongrel dogs to study the metabolic effects of isocaloric and hypercaloric infusions of 5% *v*/*v* aqueous Triacetin. A primed, continuous infusion of ~5 μmol/kg (0.3 μCi/kg/min) [^{13}C]-acetoacetate and ~1.0 μCi/kg (0.01 μCi/kg/min) [^{3}H]-glucose was continued for 6 h. Three hours after the start of the isotope infusion, dosing with Triacetin was started. Six animals were infused at a rate of 47 μmol/kg/min and seven were infused at a rate of 70 μmol/kg/min Triacetin for 3 h. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 μmol/kg/min glycerol and used as the control for the hypercaloric infusion.

During isocaloric infusion of Triacetin, plasma acetate and free fatty acid concentrations were significantly increased at 30 and 60 min, respectively, and remained elevated. During hypercaloric infusion, plasma acetate concentration increased progressively throughout the study, whereas the plasma free fatty acid concentration did not change. Plasma pyruvate and lactate concentrations were significantly decreased after 30 and 90 min, respectively, and throughout the study with both isocaloric and hypercaloric infusion. The plasma insulin concentrations were modestly increased during both infusions. Plasma glucose concentration was significantly decreased during isocaloric Triacetin infusion; a slight but significant increase was observed with hypercaloric infusion. Glucose clearance decreased significantly in both groups during the last hour of Triacetin infusion. Plasma ketone body concentrations increased significantly by 60 min, and they remained elevated with isocaloric infusion and increased progressively with hypercaloric infusion of Triacetin; the increased concentrations were due to increased ketone body production. During the last hour of infusion, resting energy expenditure was significantly increased with isocaloric Triacetin (Bailey, Haymond, and Miles 1991).

In a study examining the effect of Triacetin on nitrogen balance, whole-body kinetics, and muscle and liver fractional protein synthetic rates, Bailey, Barker, and Karlstad (1992) infused male Sprague-Dawley rats with isovolemic, isocaloric, and isonitrogenous parenteral diets. Thirty percent of the nonprotein energy of the diets was lipid energy, and for groups of 6, 10, and 6 animals, the lipid energy was composed of 0%, 50%, and 90% Triacetin, respectively. No difference was observed in the plasma acetate concentration of animals that received Triacetin compared to those that did not. The liver weight was significantly decreased in the animals given Triacetin. Protein concentration in the liver and rectus muscle was similar for all three groups. Cumulative nitrogen balance was positive for all animals, and no significant difference in nitrogen balance was observed on days 6 and 7. Lipid composition had very little effect on plasma leucine kinetics. Also, fractional protein synthetic rates in the rectus muscle and liver were similar for all animals.

Further work by Bailey, Miles, and Haymond (1993) reported the effect of a 5% *v*/*v* aqueous solution of Triacetin on leucine metabolism using female mongrel dogs. A primed, continuous infusion of L-[1-^{14}C]-leucine was continued for 6 h. Three hours after the start of the isotope infusion, administration of Triacetin was started. Six animals were infused at a rate of 47 μmol/kg/min and seven were infused at a rate of 70 μmol/kg/min Triacetin for 3 h. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 μmol/kg/min glycerol and a group of five animals was infused with saline; both were used as control groups. During the last hour of dosing, plasma acetate concentrations increased from 0.13 to 0.99 and from 0.10 to 11.8 for the animals infused with 47 and 70 μmol/kg/min Triacetin, respectively. Plasma glucose concentration decreased slightly but significantly for the animals given 47 μmol/kg/min Triacetin. Plasma leucine concentration decreased significantly in the animals given 70 μmol/kg/min Triacetin. Plasma α-ketoisocaproate concentration and specific activity increased with both doses. $^{14}CO_2$ excretion was increased with the low dose and decreased with the high dose of Triacetin.

The conclusion of this series of studies was that due to the water solubility, minimal effect on mineral metabolism, improved nitrogen balance, lack of toxicity, and favorable effects

on protein metabolism, Triacetin warranted further study as a parenteral nutrient.

Bleiberg et al. (1993) used mongrel dogs to determine the systemic, hindlimb, gut, hepatic, and renal uptake of acetate during infusion of a 5% *v*/*v* aqueous solution of Triacetin. A primed, continuous infusion of [1-^{14}C]-acetate was continued for 7 h with 10 animals. Three hours after the start of the tracer infusion, the animals were infused with Triacetin at a rate of 47 μmol/kg/min for 4 h. Blood and breath samples were taken at 15-min intervals for the last 30 min. Steady-state conditions were achieved in plasma acetate concentrations and specific activity and in expired $^{14}CO_2$. Plasma acetate concentrations were $\approx$1180, $\approx$935, $\approx$817, $\approx$752, and $\approx$473 μmol/L in the aorta, renal vein, portal vein, femoral vein, and hepatic vein, respectively. The acetate turnover rate during Triacetin infusion was 2214 μmol/min; systemic acetate turnover accounted for 68% of Triacetin-derived acetate. The researchers concluded that the majority of triacetin undergoes intravascular hydrolysis, and the majority of the resulting acetate is oxidized.

Lynch, Miles, and Bailey (1994) determined the metabolic effect of Triacetin on intestinal mucosa cells and plasma substrates in a 30-day feeding study in which male Sprague-Dawley rats were given a diet that contained Triacetin. Groups of eight animals were fed a diet in which 30% of the energy was supplied as lipids, and Triacetin composed either 0 or 95% of the lipids (long-chain triglyceride [LCT] or Triacetin group, respectively); the remainder of the lipid was a long-chain triglyceride. (In the Triacetin-containing feed, Triacetin composed 19% of the diet by weight.) A control group of eight animals was fed chow that supplied 5% of the energy as LCTs. Body weights and feed consumption were measured throughout the study.

At study termination, animals of the LCT group weighed more than the animals of the Triacetin or control groups. Feed consumption was not statistically significantly different between the Triacetin and LCT groups; however, during week 2 for the Triacetin group and weeks 2 to 4 for the LCT group, feed consumption was significantly greater than that of controls. No significant differences in lactate, ketone body, or glucose concentration were observed among the groups. Plasma pyruvate concentration in the Triacetin group was significantly decreased compared to the LCT group, and plasma free fatty acids were significantly decreased and the plasma triglyceride concentration was significantly increased in the Triacetin group compared to animals of the control and LCT groups. Total intestinal DNA, RNA, protein, and protein: DNA ratio were measured. No significant difference in mucosal protein concentration was observed in the jejunum and colon. Jejunal and colonic DNA content was significantly increased (and therefore protein: DNA ratio decreased), whereas jejunal RNA was significantly decreased in animals fed Triacetin. No significant differences in crypt depth or mean villus height were observed (Lynch, Miles, and Bailey 1994).

Lynch and Bailey (1995) fed groups of eight male Sprague-Dawley rats the diets described in the preceding paragraph for 30 days, and the effect on total adiposity, fat distribution, and body composition was determined. At study termination, animals of the LCT group weighed more than the animals in the Triacetin or control groups. Feed consumption was not significantly different between the Triacetin and LCT groups; however, the controls ate less than animals of the test groups. Also, energy intake was not significantly different between animals of the Triacetin and LCT groups, but it was significantly less in animals of the control group during weeks 2 to 4. Animals of the Triacetin group had the least adipose tissue mass (measured in three depots) compared to the other groups; animals in the LCT group had the greatest adipose tissue mass. Triacetin decreased adipocyte size, but total fat cell number did not differ among the groups.

ANIMAL TOXICOLOGY

Table 3 summarizes the acute toxicity findings as a function of the route of administration and animals used.

Acute Oral Toxicity

Gast (1963) stated that the oral LD_{50} of Triacetin for male and female mice was 1.8 and 1.1 g/kg, respectively, although study details were not provided.

The acute oral toxicity of Triacetin was determined using a group of 10 mice (Lawrence, Malik, and Autian 1974). The animals were given a single dose and observed for 7 days. The calculated oral LD_{50} for mice was 8.0 ml/kg.

Groups of five mice and five rats were used to determine the acute oral toxicity of Triacetin (Anstadt 1976). The dose ranges tested were 1.6 to 25.6 and 0.8 to 12.8 g/kg for mice and rats, respectively. The approximate LD_{50} was 3.2 to 6.4 g/kg for mice and 6.4 to 12.8 g/kg for rats.

Additional oral LD_{50} values were 3.2 to 6.1 g/kg for mice, 3.0 and $>$2.0 g/kg for rats, and $>$2.0 g/kg for rabbits (Unichema Chemie B.V. 1994).

Groups of eight Long-Evans rats were given as a continuous nasogastric infusion 462 kJ/kg of a diet containing either 16% or 32% Triacetin (Robertson et al. 1992). No adverse effects, such as diarrhea or change in normal activity, were observed.

Acute Dermal Toxicity

The acute dermal LD_{50} of Triacetin was determined using groups of five albino rabbits (Food and Drug Research Laboratories, Inc. 1976). A dose of 5 g/kg was applied to intact and abraded skin. The animals were observed for 7 days after dosing. None of the animals died. The dermal LD_{50} of Triacetin for rabbits was $>$5 g/kg. Additional dermal LD_{50} values were $>$20 ml/kg for guinea pigs and $>$2 g/kg for rabbits (Unichema Chemie B.V. 1994).

Acute Inhalation Toxicity

Unichema Chemie B.V. (1994) stated that, using five male and five female rats and a 4-h exposure, the LC_{50} of Triacetin was $>$1.721 mg/L. The particle size was not specified.

TABLE 3
Triacetin acute toxicity studies

Route of administration	Animal	LD_{50}	Reference
Oral	Mice (male)	1.8 g/kg	Gast 1963
Oral	Mice (female)	1.1 g/kg	Gast 1963
Oral	Mice (sex not given)	8 ml/kg	Lawrence, Malik, and Autian 1974
Oral	Mice (sex not given)	3.2–6.4 g/kg	Anstadt 1976
Oral	Mice (sex not given)	3.2–6.1 g/kg	Unichema Chemie B.V. 1994
Oral	Rats (sex not given)	6.4–12.8 g/kg	Anstadt 1976
Oral	Rats (sex not given)	3.0 and >2.0 g/kg	Unichema Chemie B.V. 1994
Oral	Rabbits (sex not given)	>2.0 g/kg	Unichema Chemie B.V. 1994
Dermal	Rabbits (sex not given)	>5 g/kg	Unichema Chemie B.V. 1994
Dermal	Rabbits (sex not given)	>2 g/kg	Unichema Chemie B.V. 1994
Dermal	Guinea pigs (sex not given)	>20 ml/kg	Unichema Chemie B.V. 1994
Parenteral	Mice (sex not given)	2.3 cc/kg	Li, Sah, and Anderson 1941
Parenteral	Mice (sex not given)	1.6 g/kg	Wretlind 1957
Parenteral	Mice (male)	1.7 g/kg	Gast 1963
Parenteral	Mice (female)	1.4 g/kg	Gast 1963
Parenteral	Mice (sex not given)	1.52 ml/kg	Lawrence, Malik, and Autian 1974
Parenteral	Mice (sex not given)	~0.8–1.6 g/kg	Anstadt 1976
Parenteral	Mice (sex not given)	1.2 ml/kg	Tarr, Sambandan, and Yalkowsky 1987
Parenteral	Rats (sex not given)	2.8 cc/kg	Li, Sah, and Anderson 1941
Parenteral	Rats (sex not given)	~0.8–1.6 g/kg	Anstadt 1976
Parenteral	Rabbits (sex not given)	0.75 ml/kg	Opdyke 1978
Parenteral	Guinea pigs (sex not given)	1.5 cc/kg	Lipschitz et al. 1942
Parenteral	Dogs (sex not given)	1.5–2.0 ml/kg	Opdyke 1978
Parenteral	Dogs (sex not given)	>70 μmol/kg/min	Bailey, Haymond, and Miles 1991
Inhalation	Rats (male and female)	>1.721 mg/L (LC_{50})	Unichema Chemie B.V. 1994

Acute Parenteral Toxicity

Li, Sah, and Anderson (1941) determined the subcutaneous (SC) LD_{50} of Triacetin for inbred white mice and inbred albino rats. Groups of 10 mice were dosed with 1.0 to 3.0 cc/kg and groups of 10 rats were dosed with 2.0 to 10.0 cc/kg aqueous Triacetin. The mice and rats were observed for 5 and 15 days after dosing, respectively. Two, 2, 7, and 10 mice of the 1.0-, 2.0-, 3.0-, and 3.5-cc/kg groups and 1, 6, and 10 rats of the 2.0-, 3.0-, and 4–10-cc/kg groups died, respectively. The animals usually died within 20 min to 3 or 4 h after injection. The authors noted marked depression, weakness, prostration, and in some animals, labored respiration just before death. Hemorrhagic areas in the lungs and some swelling of the convoluted tubules of the kidney were observed, along with hydropic degeneration and necrosis of the tubules in some areas. Also, the authors stated that the liver appeared to be congested. The SC LD_{50} was calculated to be 2.3 and 2.8 cc/kg for mice and rats, respectively. Diacetin was slightly less toxic than Triacetin, and the researchers concluded that the order of toxicity of the acetins appears to increase with the degree of acetylation.

Lipschitz et al. (1942) determined the intramuscular (IM) toxicity of Triacetin using guinea pigs. The lethal dose was 1.5 cc/kg, and dyspnea followed by death was observed. The researchers stated that the behavior of the animals suggested to them that the lethal effect might be attributable to the large amount of the acids liberated by relatively rapid hydrolysis.

Wretlind (1957) determined the intravenous (IV) LD_{50} of a 25% emulsion of Triacetin. Six groups of 10 animals were dosed with 1 to ~2.5 g/kg Triacetin. The IV LD_{50} of Triacetin was 1.6 g/kg for mice. Injection with Triacetin produced almost immediate convulsions, failure of the righting reflexes, and respiratory arrest.

von Oettingen (1960) reported a study using rabbits in which a SC injection of 0.8 g/kg of Triacetin given in three fractional doses caused a temporary stimulation of respiration with no narcosis. This author also reported that a slow IV injection of 1.48 g/kg Triacetin given in three fractional doses of 2.4 g/kg given in two fractional doses, and of 1.46 g/kg given as a single dose caused deep sleep, reduction of the tendon reflexes, and reduction of sensitivity to pain in rabbits. Respiration became slow and labored, and the authors stated that animals died from respiratory arrest.

Gast (1963) reported that the intraperitoneal (IP) LD_{50} of Triacetin for male and female mice was 1.7 and 1.4 g/kg, respectively. Based on a study using a limited number of adult rats,

this author also stated that the IP LD_{50} was 2.1 g/kg, although no study details were provided.

Lawrence, Malik, and Autian (1974) determined the acute IP toxicity of Triacetin using a group of 10 mice. The animals were given a single injection and observed for 7 days. The calculated IP LD_{50} for mice was 1.52 ml/kg.

Anstadt (1976) used groups of five mice and five rats to determine the acute IP toxicity of Triacetin. The dose ranges tested were 0.4 to 6.4 and 0.8 to 6.4 for mice and rats, respectively. The approximate LD_{50} was 0.8 to 1.6 g/kg for both mice and rats.

The IV LD_{50} of Triacetin for rabbits and dogs has been reported as 0.75 and 1.5 to 2.0 ml/kg, respectively (Opdyke 1978).

Tarr, Sambandan, and Yalkowsky (1987) determined the IV LD_{50} of an emulsion consisting of 50% Triacetin, 1.5% soy lecithin, 1.5% pluronic F68, and 2.0% ethyl oleate for Swiss-Webster mice. Groups of eight animals were dosed intravenously with 0.8 to 2.0 ml/kg of the emulsion. The IV LD_{50} for mice of the Triacetin emulsion was 1.2 ml/kg.

Bailey, Barker, and Karlstad (1991), in a study described earlier, infused female mongrel dogs with 47 or 70 μmol/kg/min Triacetin for 3 h, reported no evidence of acute toxicity.

Short-Term Oral Toxicity

According to Opdyke (1978), rats fed diets containing 55% Triacetin instead of fat gained weight.

Shapira et al. (1969) stated that, in 3-month feeding studies, rats tolerated up to 20% Triacetin without weight loss as compared to control values; but that diets containing 60% Triacetin were associated with a large loss in weight and considerable mortality. The authors stated that the type and quantity of protein present influenced weight gain.

Shapira, Vann, and Furst (1975) stated that, in groups of eight male Sprague-Dawley rats that were fed diets containing 30% Triacetin (and 30% glycerin or propylene glycol) as a starch substitute for 3 to 4 or 12 to 13 weeks, growth was relatively poor. Liver enlargement was observed in all animals.

In a study by Lynch, Miles, and Bailey (1994) described previously, the metabolic effect of Triacetin on intestinal mucosal cells and plasma substrates in male Sprague-Dawley rats was assessed. Rats were fed for 30 days a diet in which 28.5% of the total calories were supplied by Triacetin. No overt signs of toxicity were observed.

Short-Term Inhalation Toxicity

Anstadt (1976) stated that no toxicity was observed when rats were exposed to 8200 ppm Triacetin (saturated vapor) for 6 h per day for 5 days.

Unichema Chemie B.V. (1994) exposed a group of three rats to 250 ppm Triacetin for 6 h per day, 5 days per week, for 64 days. The no-observed-effect level (NOEL) was 250 ppm. Three rats were also exposed to 8271 ppm Triacetin for 6 h per day for 64 days. The NOEL was 8271 ppm.

Short-Term Parenteral Toxicity

Bailey, Barker, and Karlstad (1992) infused rats intravenously with 0%, 50%, or 90% (15.2 and 27.2 g/L) Triacetin for 7 days. No overt signs of toxicity were observed.

Subchronic Oral Toxicity

Blumenthal (1964) stated that Triacetin was not toxic to groups of five male rats fed a diet containing 1%, 2%, 4%, or 8% Triacetin for 16 weeks. A control group was fed basal diet.

Subchronic Inhalation Toxicity

Unichema International (1996) exposed rats to concentrations of 250 ppm Triacetin, which was produced by using heated vapor, 5 days per week for 13 weeks. No changes in liver and kidney weight, blood counts, or urinalysis were observed.

Chronic Toxicity

Published data on the chronic toxicity of Triacetin were not found.

Dermal Irritation

Anstadt (1976) determined the dermal irritation potential of Triacetin using two guinea pigs. Doses of 5 and 10 cc/kg were applied under an occlusive patch for 24 h. Slight erythema was observed. Occlusive patches with 5 to 20 cc/kg were tested using three animals. Slight edema and "1-3 erythema" were observed. Slight skin irritation was observed in the high dose animals.

Unichema Chemie B.V. (1994) stated that groups of three, three, and two guinea pigs were used to determine the irritation potential of Triacetin, but no study details were provided. At the end of a 14-day observation period, erythema, slight edema, alopecia, and desquamation were observed. They also stated that another study found no skin irritation in guinea pigs, but no details were available.

Other reports stated that Triacetin was not a skin irritant in guinea pigs (Unichema International 1996; Opdyke 1978) or rabbits (Unichema Chemie B.V. 1994).

Dermal Sensitization

Anstadt (1976) reported that no sensitization was observed using the "drop-on method" in a test using five guinea pigs.

Unichema Chemie B.V. (1994) evaluated the sensitization potential of Triacetin in acetone, dioxane, and guinea pig fat (7:2:1) using guinea pigs. The animals were initially dosed three times over 5 days and challenged after 1, 2, or 3 weeks. A vehicle and positive control were used. Triacetin was nonsensitizing.

Other reports found that Triacetin was not a sensitizer in guinea pigs (Unichema International 1996; Unichema Chemie B.V. 1994; Opdyke 1978).

Ocular Irritation

Li, Sah, and Anderson (1941) stated that application of 50% Triacetin (and diacetin) into the conjunctival sac of the eyes of rabbits resulted in "marked congestion and moderate edema."

In the original work of Draize, Woodard, and Calvery (1944), undiluted Triacetin, 0.1 ml, instilled into the conjunctival sac of the eyes of rabbits yielded average scores of 2.1 and 1.5/110 after 1 and 24 h, respectively.

Conquet et al. (1977) determined the ocular irritation potential of Triacetin using albino rabbits. In the first study, 0.1 ml undiluted Triacetin was instilled into the conjunctival sac of the eyes of six rabbits, and the eyes were scored according to the methods of Draize; corneal thickness was also measured. In a second study using groups of four rabbits, in which ocular tissue sampling was done, 0.1 ml was instilled into both eyes. A control group of four rabbits was not treated. Animals were killed after 2 or 24 h. In the Draize test, Triacetin had a total Draize score of 1 after 2 h (0 for the cornea and 0.7 for the conjunctiva); corneal thickness did not change. After 2 h, the corneal percentage of dry weight/wet weight was significantly decreased, but not after 24 h, compared to controls. No difference was observed for conjunctival percentage of dry weight/wet weight or Evan's blue concentration/dry weight at 2 or 24 h.

Unichema Chemie B.V. (1994) reported a study in which one drop of Triacetin was placed into the eyes of two rabbits; the eye of one rabbit was washed. The eyes were evaluated after 1, 24, and 48 h. Triacetin was slightly irritating. The authors stated that Triacetin, as tested using rabbits according to Organization for Economic Cooperation and Development (OECD) guidelines, was reported to be nonirritating.

In other reports, Triacetin, 100 μl, was a low-to-moderate irritant in rabbit eyes (Unichema International 1996). No damage was observed when a rabbit eye was irrigated continuously for 6 min (Unichema International 1996; Opdyke 1978).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of Triacetin were not found.

GENOTOXICITY

In Vitro

Several laboratories have reported results from different versions of the Ames test for bacterial genotoxicity.

Litton Bionetics, Inc. (1976) evaluated the mutagenic potential of Triacetin in a plate test using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 with and without metabolic activation. Test concentrations were 0.0013%, 0.00065%, and 0.000325% and the solvent was dimethyl sulfoxide (DMSO). A negative control (solvent) and appropriate positive controls were used and gave expected results. Triacetin was not mutagenic with or without metabolic activation.

The mutagenic potential of Triacetin was also evaluated in a suspension test with and without metabolic activation. Test concentrations were 0.0013%, 0.00065%, and 0.000325% with *S. typhimurium* strains TA1535, TA1537, and TA1538 and 1.25%, 2.5%, and 5.0% with *Saccharomyces cerevisiae* strain D4. DMSO was used as the solvent. Appropriate negative and positive controls were used and gave expected results. Triacetin was not mutagenic in the suspension tests with or without metabolic activation (Litton Bionetics, Inc. 1976).

Unichema Chemie B.V. (1994) reported that Triacetin was not mutagenic at 50 to 5000 μg/plate in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without metabolic activation.

In Vivo

The mutagenic potential of Triacetin was determined using adult *Drosophila melanogaster* (Efremova 1962). A dose of 0.2 to 0.3 mg Triacetin had a spontaneous mutation rate of approximately one mutation per 750 chromosomes.

CARCINOGENICITY

Published data on the carcinogenicity of Triacetin were not found.

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

A maximization test for undiluted Triacetin was completed using 33 subjects (Epstein 1976). Triacetin was applied under an occlusive patch to the volar aspect of the forearm for 48 h on 5 alternate days. Because a pretest indicated the Triacetin was not an irritant, the test site was pretreated for 24 h with 2% sodium lauryl sulfate (SLS) under an occlusive patch prior to application of the initial test patch. After a 10 to 14-day nontreatment period, challenge patches were applied to a previously unexposed site on the right side of the back. Prior to challenge, 2% SLS was applied for 30 min under an occlusive patch to the left side of the back. Additional SLS control patches and petrolatum patches were placed on the left and right sides, respectively, and used as controls. Undiluted Triacetin did not produce an irritant or sensitization reaction.

A Duhring-chamber test was performed using 20 subjects (Unichema Chemie B.V. 1994). Triacetin was applied as a 50% dilution for 24 h. No further details were available. The authors stated that only very mild skin reactions were observed.

Ocular Irritation

According to Unichema Chemie B.V. (1994), commercial Triacetin, which can contain diacetin and monoacetin, caused severe burning, pain, and much redness of the conjunctiva, but no injury. The authors claimed that diacetin causes considerably more discomfort than pure Triacetin.

Toxicity

The safety and effectiveness of a mucosa-adhesive polymer film used to alleviate acute radiation-induced oral mucositis and prevent infections was analyzed using 25 patients (Oguchi et al. 1998). The film contained 24 mg Triacetin, 600 mg hydroxypropylcellulose, 5 mg each of tetracaine hydrochloride, ofloxacine, and miconazole nitrate, 0.6 mg guaiazulene, and 100 ml ethyl alcohol. No acute or chronic adverse effects on the oral mucosa or gastrointestinal tracts were observed, and no allergic dermal reactions were reported. No changes in liver or renal function and no hematological toxicity were noted.

Unichema Chemie B.V. (1994) stated that Triacetin "appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals."

SUMMARY

Triacetin, also known as Glyceryl Triacetate, is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations. In 1998, it was reported to FDA that Triacetin was used in a total of 13 cosmetic formulations. Industry reported that it was used at concentrations of 0.8% to 4%. Triacetin was affirmed as a GRAS human food ingredient by FDA.

The acute dermal LD_{50} of Triacetin was >5 g/kg for rabbits and >20 ml/kg for guinea pigs. The oral LD_{50} for mice has been reported as 1.8 and 1.1 g/kg for males and females, respectively, and as 3.2 to 6.4 g/kg; it has been calculated as 8.0 ml/kg. For rats, the oral LD_{50} was 6.4 to 12.8 g/kg. The inhalation LC_{50} was >1.721 mg/L for rats. The SC LD_{50} was 2.3 cc/kg for mice and 2.8 cc/kg for rats. For mice, the IV LD_{50} values of 25% and 50% emulsions of Triacetin were 1.6 g/kg and 1.2 ml/kg, respectively. For rabbits, the IV LD_{50} of Triacetin was 0.75, and for dogs, it was 1.5 to 2.0 ml/kg. The IP LD_{50} for Triacetin in mice was determined to be 1.7 and 1.4 g/kg for males and females, respectively, and 0.8 to 1.6 g/kg; it was also calculated as 1.52 ml/kg for mice. The IP LD_{50} for rats was 2.1 g/kg; in another study, it ranged from 0.8 to 1.6 g/kg. The IM lethal dose was 1.5 cc/kg for guinea pigs.

In short-term feeding studies, Triacetin affected weight gain. Triacetin was not toxic in short-term studies when administered via inhalation or parenterally or in subchronic studies when administered via feed or inhalation.

Triacetin was, at most, slightly irritating to guinea pig skin. However, in one study, it caused erythema, slight edema, alopecia, and desquamation. Triacetin was not sensitizing in guinea pigs; however, test concentrations were not stated. Triacetin caused some irritation in rabbit eyes.

Triacetin, with and without metabolic activation, was not mutagenic in the Ames assay or a suspension test. It was also not mutagenic in an in vivo assay using *Drosophila*.

Triacetin (test concentrations not provided) was not an irritant or a sensitizer in a clinical maximization study, and only very mild reactions were seen in a Duhring-chamber test using a 50% dilution. In humans, commercial Triacetin has caused ocular irritation but no injury.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the safety of Triacetin for use as a cosmetic ingredient. The Expert Panel considered the FDA affirmation of glycerides, including Triacetin, as a GRAS human food ingredients to be supportive of the overall safety of this ingredient.

The Expert Panel did recognize that reproductive and developmental toxicity data on Triacetin are absent from the report. Because Triacetin is thought to be hydrolyzed to glycerol and acetic acid and these chemicals are not developmental toxins, the Expert Panel concluded that the use of Triacetin in cosmetics does not present a risk of reproductive or developmental toxicity.

The Expert Panel also noted that there are reports indicating that 1,2-glyceryl diesters (also known as 1,2-diacylglycerols) can affect cell growth and proliferation, raising the possibility of hyperplasia and/or tumor promotion. This was an issue for discussion because, although Triacetin is a glyceryl triester, it is recognized that there would be some small amounts of glyceryl diesters present, some of which could be 1,2-glyceryl diesters. The Panel concluded, however, that the effects of 1,2-glyceryl diesters on cell growth and proliferation require ester chains longer than two carbon atoms on the glycerin backbone. Thus, any glyceryl 1,2-diacetyl esters present in Triacetin would be inactive in hyperplasia and tumor promotion.

CONCLUSION

On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that Triacetin is safe as used in cosmetic formulations.

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