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Invited Review

A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient

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ABSTRACT

Transcutol® (Diethylene glycol monoethyl ether, DEGEE), CAS # 111-90-0, is commonly used as a vehicle in the formulation or manufacturing process of pharmaceuticals, cosmetics, and food additives. This paper presents unpublished nonclinical safety data using a form of DEGEE which includes a significantly decreased level of impurities, specifically ethylene glycol and diethylene glycol. It also reviews the history of use, regulatory status, and previously published toxicity data for DEGEE. The review supports that DEGEE is well tolerated across animal species and gender with toxicity occurring only at levels well above those intended for human use. At high levels of exposure, the kidney is identified as the critical target organ of DEGEE toxicity. DEGEE is negative for genotoxicity in *in vitro* and *in vivo* studies. Subchronic and chronic toxicity studies produced no reports of preneoplastic changes in organs, but the animal data is insufficient to allow a definitive opinion as to carcinogenicity. *In silico* data suggested that DEGEE is not carcinogenic or genotoxic. Developmental toxicity was seen in rats but only at levels 200 times greater than the estimated oral Permissible Daily Exposure Level of 10 mg/kg/day. The nonclinical data along with the long history of DEGEE use as a vehicle and solvent by multiple routes provide evidence of its safety. Furthermore, the novel data discussed herein provides evidence that toxicity previously associated with high levels of DEGEE in nonclinical studies conducted prior to 1990 could possibly be attributed to the presence of significant amounts of ethylene glycol or other impurities.

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1. Introduction

Transcutol®, purified diethylene glycol monoethyl ether (DEGEE, CAS No. 111-90-0), is an ethylene oxide derivative. Because of its characteristics as a strong solubilizer coupled with its low toxicity, DEGEE has a long history of safe use as a solvent in many products including pharmaceuticals, cosmetics, and food applications. Numerous independent nonclinical studies on the safety of DEGEE are available in the published literature. This paper seeks to evaluate the safety of DEGEE by reviewing the current published literature and adding previously unpublished data performed by Gattefossé to evaluate the safety of the purified compound, Transcutol®, as a pharmaceutical excipient. A brief review of the current uses and regulatory status of Transcutol® are also included.

1.1. Identity and characterization

Diethylene glycol monoethyl ether (DEGEE, CAS No. 111-90-0) is a clear, colorless, hygroscopic liquid with a mild pleasant odor (Fig. 1). It is produced by condensation of ethylene oxide and alcohol, followed by a purification distillation (USP-NF, 2013). DEGEE is soluble in water and miscible in acetone, benzene, chloroform, ethanol (95%), ether, and pyridine. It is partially soluble in vegetable oils and insoluble in mineral oils (Rowe et al., 2012). Table 1 summarizes the physiochemical properties of DEGEE.

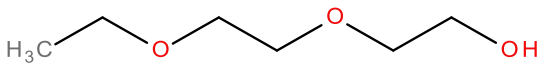

Fig. 1. Chemical structure of diethylene glycol monoethyl ether ($C_6H_{14}O_3$, CAS No. 111-90-0).

Table 1
Physiochemical properties for DEGEE[a].

Property (Unit)	Value
Empirical formula	$C_6H_{14}O_3$
Molecular weight	134.17
Boiling point (°C)	198–201
Freezing point (°C)	−105 to −103
Density (g/cm^3)	0.988
Vapor pressure (mmHg at 20 °C)	0.07–0.12
Relative vapor density (air = 1)	4.6
Flash point (°C)	90–96.1
Octanol/water partition coefficient (log P)	−0.54

[a] Rowe et al. (2012).

DEGEE has a wide variety of uses including pharmaceutical applications, as an indirect food additive for use in food, nutraceutical products and dietary supplements, and in cosmetics. The primary supplier in the US for pharmaceutical grade DEGEE is Gattefossé using the trade name Transcutol® (Osborne, 2011). Prior to 1988, Gattefossé only produced a single grade of DEGEE marketed under the trade name Transcutol® that was 99.5% pure. However, current pharmaceutical grade Transcutol® P (topical route) and Transcutol® HP (oral route) are 99.8% and 99.9% pure, respectively. A cosmetics only grade Transcutol® CG is 99.5% pure. The identified impurities for pharmaceutical- and cosmetic-grade Transcutol®, along with their identified and maximum allowable (for pharmaceutical-grade) levels, are summarized in Table 2. It is important to note that industrial grades of the solvent are at best 98% pure and contain significant levels of ethylene glycol and diethylene glycol as impurities. Toxicology studies prior to the 1990s were typically performed with the industrial grade solvent, with many of the observed adverse effects being attributable to the ethylene glycol impurity (Osborne, 2011). More recent studies with the purified material provide further evidence suggesting the attribution of effects to the impurity.

2. Economic uses in marketed products with human exposure

DEGEE has a long history of use in pharmaceutical applications worldwide in the United States of America, Asia, and Europe. It is an effective solubilizer and is used in oral, topical, transdermal and injectable human and veterinary pharmaceutical products. In recent years it has been widely used as a solvent for topical products on account of three main properties: firstly, it has been shown to solubilize actives that are insoluble in common solvents such as propylene glycol and ethanol. Secondly, it modifies the skin penetration properties of active ingredients allowing different drug delivery outcomes to be obtained including enhanced local absorption, a prolonged release depot effect or systemic absorption for transdermal applications (Osborne, 2011); lastly it provides functionality at concentrations which avoid safety and tolerability issues.

Table 2
Characterization of the impurities or accompanying contaminants for Transcutol®.

Substance	CAS No.	ICH Q3C (ppm)	USP36-NF31 (ppm)	Max level in Transcutol® Grades[a] (ppm)		
				CG	*P*	HP
Ethylene Glycol	107-21-1	Class 2 (⩽620)	⩽620	⩽620	⩽100	⩽20
Diethylene Glycol	111-46-6	–	⩽150	⩽250	⩽150	⩽50
Ethylene oxide	75-21-8	–	⩽1	⩽1	⩽1	⩽1
2-Methoxyethanol	110-80-5	Class 2 (⩽50)	⩽50	⩽50	⩽50	⩽20
2-Ethoxyethanol	109-86-4	Class 2 (⩽160)	⩽160	⩽160	⩽100	⩽50

ppm: parts per million; CG is the cosmetics only grade Transcutol® and is 99.5% pure; P and HP are pharmaceutical grade Transcutol® and are 99.8% and 99.9% pure,

Table 3
DEGEE use as a vehicle in nonclinical studies.

Species	Route	Duration	Dose	Comments
Cat	Intravenous	1 month	DEGEE 2 mL/kg	Well tolerated, no evidence of hemolysis or hematotoxicity
Rabbit	Dermal	Skin irritation	Transcutol®5 mL over 2 cm^2 area	50%; Non-irritant
		28 days	Transcutol® 0, 300, 1000, 3000 mg/kg/day	Undiluted; NOEL > 1000 mg/kg/day
	Ocular	Eye irritation	Transcutol® 0.1 mL	30%; Slight irritation
		Eye irritation	Transcutol® 0.1 mL	Undiluted; Slight irritation
Rat	Oral	90 days	DEGEE 0%, 0.25%, 1% and 5%	NOEL is 1%
		Acute	Transcutol® 5.0 g/kg	LD 50 > 5000 mg/kg
		Fertility and embryo toxicity range-finding study	DEGEE 500, 1000, 2000, 4000 mg/kg/day	NOEL > 500 mg/kg/day
Mouse	Oral	Acute	DEGEE	6.6 g/kg tested toxic
		Chronic (12 months)	DEGEE	NOEL: 850–1000 mg/kg
Dog	Oral	90 days	DEGEE	NOAEL: 1500 mg/kg/day

Source: Gad et al. (2006).

In topical products DEGEE is often used in an aqueous gel. ACZONE, the 5% dapsone gel for the treatment of acne was the first prescription drug product containing DEGEE as Transcutol® approved by the FDA (Osborne, 2011). Transcutol® has also been formulated in solutions, ointments and creams (emulsions and microemulsions) for the delivery of hormones, anti-inflammatory, anti-fungal, anesthetic, analgesic and antiseptic agents in prescription products approved in numerous countries around the world (USFDA CDER, 2013; Gattefossé SAS).

In Europe, Transcutol® HP (the high purity DEGEE) has been used in a number of oral prescription drugs including the oral drop product 'Lysanxia', and the oral solutions 'Pilosuryl' and 'Urosiphon' as well as a sublingual solution 'Natispray'. In emerging Asia Pacific countries, notably South Korea, Transcutol® is used in soft gelatin capsules in approved antiviral, anti-inflammatory, and immune suppressant medicines (source Gattefossé SAS).

Historically, Transcutol® has been used in injectable products, although its use in marketed human medicines remains limited to a few examples. In 1977 it was used in an intravenous injectable (IV) product 'Trombovar' approved in Europe for the treatment of varicose and spider veins in the leg; this product is no longer available. More recently, it has been formulated in an IV and IM injection of sodium diclofenac and an alpha beta-arteether intramuscular (IM) injection for the treatment of severe/cerebral malaria approved in India (source Gattefossé SAS).

The aforementioned uses of high purity DEGEE in the form of Transcutol® are associated with human medicine. Veterinary medicines require the same level of purity of excipients as human medicines, and as such, Transcutol® is also widely used in veterinary applications including topical solutions, sprays and spot-on's, often containing anti-parasitic agents which are formulated for transdermal delivery (source Gattefossé SAS). It is also used in injectable veterinary products including the anti-inflammatory SC and IM product 'Tolfedine' and a 'Vitamin E' IV injection (Strickley, 2004).

DEGEE is used as an indirect food additive for use in food, nutraceutical products and dietary supplements. The safety of use of this substance in such applications has been evaluated and is largely confirmed by many years of use.

DEGEE has a long history of use in cosmetic and personal care applications. Currently, it can be found in over 740 cosmetic products including eye makeup, fragrances, nail preparations, sunless tanning products, hair coloring products, and skin care preparations (Elder, 1985; Osborne, 2011). The safety of use of this substance in such applications has been evaluated and is largely confirmed by many years of use (CIR Expert Panel, 2006; Elder, 1985; Osborne, 2011).

conducted a data mining project to determine the safe dosing level of drug delivery vehicles for *in vivo* animal studies. The results included information on 65 different vehicles and 9 animal species. The use of Transcutol® as a vehicle was reported for five species of animals and across four routes of exposure as shown in Table 3.

3. Regulatory status

The United States Food and Drug Administration (Center for Drug Evaluation and Research (CDER)) maintains an Inactive Ingredients Database (USFDA CDER, 2013). This database provides a partial listing of excipients being used in authorized medicinal products in the USA. This information can be used by industry as an aid in developing drug products. Once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is considered qualified at the approved level and may require a less extensive review the next time it is included in a new drug product. For example, after an inactive ingredient has been approved for a specific dosage form and potency, a sponsor could consider it safe for use in a similar manner for a similar type of product. DEGEE is listed in the FDA Inactive Ingredient Database for topical use in a gel (25% maximum potency), transdermal use in a gel (5% maximum potency) and for use in a transdermal patch (maximum potency not reported). It is important to note that the approved maximum potency is not a limit for inactive ingredients, as higher levels may be approved with justification, but merely lists the amount of such ingredients that are currently approved for use in drug products.

Similarly, DEGEE is listed in the Australian Register of Therapeutic Goods (Australian Therapeutic Goods Administration, 2013) which includes all therapeutic goods, including medicines and medical devices, approved for use in Australia. Health Canada (2013) maintains a repository of approved medicinal and non-medicinal ingredients approved for use in Canada. DEGEE is listed in the Canadian natural health products ingredients database.

US FDA has approved DEGEE as an inactive ingredient for use as a component of adhesives for use in packaging, transporting, or holding food (21 CFR 175.105). US FDA has also approved DEGEE for use as a component of paper and paperboard in contact with dry food (21 CFR 176.180) and as a sanitizing agent for food-processing equipment and utensils (21 CFR 178.1010). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) have evaluated the use of DEGEE in food. The JECFA concluded that an Acceptable Daily Intake (ADI) for DEGEE could not be established due to the absence of adequate long-term (chronic/carcinogenicity) feeding studies in rats and mice and the absence of adequate

DEGEE has been evaluated by the Cosmetic Ingredient Review (CIR) expert panel (CIR Expert Panel, 2006; Elder, 1985). The panel noted that DEGEE was used in 80 different cosmetic preparations in 1981 (0.1 to greater than 50%) with the largest uses found in hair dyes and colors as well as skin cleansing creams, lotions, liquids, and pads. By 2002, DEGEE was used in 622 preparations at concentrations ranging from 0.0004% to 80%. The panel concluded that based on the available data DEGEE is safe as presently used in cosmetics (2006; Elder, 1985). The Scientific Committee on Consumer Safety (SCCS, 2013) issued an opinion on the safety of DEGEE in cosmetic products. The SCCS concluded that DEGEE in cosmetic products (excluding oral hygiene and eye products) does not pose a risk to consumer health at concentrations up to 10% in rinse-off products, up to 7.0% in hair dye formulation and up to 2.6%, pro in all other cosmetic products provided that the level of ethylene glycol in DEGEE used is <0.1%.

4. Safety evaluation

A number of toxicity studies have been conducted with DEGEE by multiple routes of administration in a variety of species for a period of up to two years. Additionally, Gattefossé has completed a full battery of additional studies on DEGEE (as Transcutol®), including those evaluating toxicokinetics, local tolerance, skin sensitization, reproductive effects, teratogenicity, genotoxicity, and systemic toxicity. The new data for DEGEE generated within Gattefossé, in combination with the preexisting data, are presented here and serve to provide a dataset sufficient for determining the safety of DEGEE in humans.

4.1. Toxicokinetics

The absorption of DEGEE *in vitro* has been evaluated in human abdominal, whole skin. The rate of absorption was 0.125 ± 0.103 mg/cm^2/h, the permeability constant was 1.32×10^{-4} cm/h, and the damage ratio (a measure of integrity of the skin) was 1.20 ± 2.62. Among numerous glycol ethers tested in this study, including ethylene glycol monomethyl, monoethyl and monobutyl ethers, and DEGEE and diethylene glycol butyl ether, DEGEE had the lowest damage ratio and the second lowest permeability constant and rate of absorption, suggesting a decreased absorption rate with increasing molecular weights of glycol ethers (Dugard et al., 1984).

Unlike monoethylene glycol ethers, diethylene glycol ethers (including DEGEE) are poor substrates for alcohol dehydrogenase and expected to be good substrates for cytochrome P-450 based on experiments that measured induction of P-450. In an *in vitro* system using equine liver alcohol dehydrogenase, the V_{max} (μmol) K_m (μM) and V_{max}/K_m were 6.94, 6.31×10^{-2}, and 0.11, respectively (Miller, 1987). In an adult human volunteer (sex and age not reported) given a single oral dose of 11.2 mmol DEGEE, approximately 68% of the dose was recovered in the urine as (2-ethoxyethoxy) acetic acid within 12 h (Kamerling et al., 1977).

A number of studies have been completed in which multiple parameters were measured to further evaluate the toxicokinetic profile of purified DEGEE as Transcutol®. In an *in vitro* study performed to determine the metabolism profile of DEGEE (as Transcutol®) and ethylene glycol monoethyl ether (EGEE) formed by rat and human hepatocytes, EGEE was readily metabolized by both rat and human hepatocytes to ethoxy acetic acid (EAA) and ethylene glycol (EG), and the rat liver cells metabolized EGEE at a higher rate than human liver cells. However, contrasting results were seen approximately 1–17% of the total radioactivity. DEGEE was not significantly metabolized by human hepatocytes (Gattefossé, 2001a).

In vivo, the absorption, distribution and excretion of DEGEE (as Transcutol®) was investigated comparably in Sprague–Dawley and BDIX rats after a single oral or intravenous dose of 20 mg ^{14}C-DEGEE/kg bw each. The GLP-compliant study was performed according to internal laboratory methodology comparable to OECD 417. Rapid excretion of radioactivity occurred in the urine, regardless of sex and route of administration. The maximum plasma concentration of the radioactivity was observed 0.25 h following intravenous injection, while after oral administration it was observed at 0.25–0.50 h post dose. The plasma half-life corresponded to 37–84 h with measurable concentrations observed in most of the tissues 168 h following administration. The absolute bioavailability of the radioactivity was very high (79–95%). The distribution of radioactivity in tissues was characterized by high concentrations detected in pituitary, thyroid, adrenals and bone marrow with regards to the concentrations observed in blood/plasma (100–1000 times less) at the same sampling time. The radioactivity levels in tissues was significantly decreased at 48 h. No biologically relevant differences were observed between the two rat strains (Gattefossé, 2002a).

In studies evaluating the metabolic fate and excretion of DEGEE (as Transcutol®) results indicated that following a single oral administration, the large majority (90%) of the administrated radioactivity was rapidly excreted (within the first 24 h) in the urine and ^{14}C-DEGEE was intensively metabolized as Ethoxyethoxyacetic acid (83%) and Diethylene glycol (5.4%) with only 3% of the urinary excreted radioactivity corresponding to unchanged compound. In plasma, only Ethoxyethoxyacetic acid and unchanged ^{14}C-DEGEE were detected, which was consistent with urinary results. The GLP-compliant study was performed according to internal laboratory methodology comparable to OECD 417 (Gattefossé, 2003).

4.2. Local tissue tolerance (skin, eye, intravenous, and mucosal irritation, sensitization, hematocompatibility, and parenteral irritation)

The current published data has shown that DEGEE is not a skin irritant in rabbits even after prolonged and repeated contact under normal study conditions while being only slightly irritating to rabbit skin with the use of an occlusive wrap (Cragg, 2012; Rowe, 1947; Krasavage and Terhaar, 1981). In rabbits, ocular administration of 500 mg DEGEE has produced moderate irritation

Table 4
DEGEE acute toxicity summary (external publications).

Route	Species	Effect
Oral	Rabbit	LD_{50} = 3620 mg/kg
	Mouse	LD_{50} = 7250 mg/kg
	Rat	LD_{50} = 7500 mg/kg
	Guinea Pig	LD_{50} = 3000 mg/kg
Intravenous	Cat	LD_{Lo} = 1000 mg/kg
	Dog	LD_{50} = 3000 mg/kg
	Rat	LD_{50} = 4000 mg/kg
	Mouse	LD_{50} = 4300 mg/kg
	Rabbit	LD_{50} = 2500 mg/kg
Intraperitoneal	Rat	LD_{50} = 6300 mg/kg
	Mouse	LD_{50} = 3900 mg/kg
		LD_{50} = 2300 mg/kg
Subcutaneous	Rat	LD_{50} = 6000 mg/kg
	Mouse	LD_{50} = 5500 mg/kg
	Rabbit	LD_{50} = 2000 mg/kg

Table 5
Acute toxicity studies conducted with Transcutol® (previously unpublished data from studies conducted by Gattefossé).

Study type/duration	Route	Species	Test article	Results/conclusion
Acute toxicity	Oral (gavage)	Rat	Transcutol® Pure (undiluted) Dose levels: 5000 mg/kg	$LD50_{(oral)}$ > 5000 mg/kg
Acute toxicity (Dose escalating)	Oral (gavage)	Dog	Transcutol® Pure (undiluted) Dose levels: 500, 1000, 1500, 2000 mg/kg	$MTD_{(oral)}$ > 2000 mg/kg
Acute toxicity (Dose escalating)	IV bolus (tail vein)	Mouse	Transcutol® Vehicle: Physiological saline solution M: 25, 50, 100, 200, 400, 800, 1600, 6400, 3200 and 4800 mg/kg F: 25, 50, 100, 200, 400, 800, 1600, 8000, 6400, 4800 and 3200 mg/kg	$MTD_{(IV)}$: 3200 mg/kg

(Cragg, 2012; Union Carbide Corporation, 1968). When used as in vaginal and nasal gels and emulsions in rabbits with repeat doses, it has not shown itself to be an irritant (Mourtas et al., 2010; Elshafeey et al., 2009).

GLP-compliant primary irritation single patch and a repeat insult patch tests in human performed by Gattefossé (1992, 1993) showed that undiluted DEGEE (as Transcutol®) applied under occlusive conditions was well tolerated and did not lead to any classifiable primary or cumulative skin irritation. A skin irritation study in rabbits, using an older, less pure form of DEGEE (as Transcutol®), which was not performed under GLP conditions but exceeded the current guideline requirements (OECD 404) in respect to animal numbers and can be considered as scientifically valid, showed that a 50% aqueous solution was not a skin irritant (Gattefossé, 1974). Guideline-conforming (OECD 405, EEC 92/69) eye irritation studies in rabbits performed under GLP conditions, revealed only a slight irritant effect to the eyes, when tested neat or as 30% aqueous solution (Gattefossé, 1996a). However, as the observed findings were only slight and transient in nature, and were not sufficient to be considered an eye irritant according to EU classification criteria (mean score of 2.00 for acute ocular irritation), it is concluded that DEGEE (as Transcutol®) is not an eye irritant.

Intravenous administration of 1 mL/kg or less of aqueous solutions containing concentrations of 5% or less is not hemolytic. *In vitro* hemolysis studies of a range of excipients showed no hemolysis caused by DEGEE (as Transcutol®) at concentrations up to 80 µl/ml (Aparicio et al., 2005.) Intramuscular injection of 30% oily solution and 50% aqueous solutions of DEGEE (as Transcutol®) causes moderate but reversible irritation. Microemulsions containing DEGEE (as Transcutol®) have been shown to not be irritating to veins when given intravenously (He et al., 2010).

4.3. Acute toxicity studies

Both external publications (see Table 4) and studies conducted by Gattefossé (see Table 5) indicate that the acute toxicity of DEGEE after oral, intraperitoneal, intravenous, and subcutaneous application can be regarded as very low in all species investigated. The LD_{50} values for acute toxicity were generally much higher than 2000 mg/kg bw, and the available LC_{50} value for acute inhalation was >5 mg/L (i.e. 5.24 mg/L).

4.4. Repeat-dose toxicity studies

4.4.1. Previously published oral data

A six week study was conducted in which groups of 10 male Sprague–Dawley rats were administered DEGEE by oral gavage at doses of 1340, 2680, and 5360 mg/kg/day. In the high dose group, throughout the study. Several other hematological and clinical chemistry signs were observed. One death also occurred at the intermediate dose prior to study termination. Lethargy was noted during the first week of treatment. However, there were no significant effects of treatment with the intermediate dose on hematology or clinical chemistries. Increased organ weights seen include the relative liver, heart, and kidney weights (but not absolute weights of these organs) with respect to control. Microscopic changes included hyperkeratosis of the stomach (2/10), and splenic congestion (1/9). Because no effects were seen at the lowest dose, the NOAEL was established as 1340 mg/kg/day (European Chemicals Bureau, 2000; OECD, 2005).

In a further study, groups of 15 male and female CFE rats were fed DEGEE at doses 250 and 2500 mg/kg bw (0.5% and 5.0% in the diet, respectively) for 90 days. Effects observed at the high dose included reductions in growth rate and food consumption as well as the average male final body weight. Decreased hemoglobin concentration of high dose males was seen at 90 days and the hemoglobin concentration and red blood cell count were decreased in females at 45 days. In high dose males and females, oxalate crystals in urine were observed. Increased relative kidney weights were seen in high dose males and females and the spleen and thyroid of high dose females were increased. Advanced intracellular edema (hydropic degeneration) of the kidney was reported in 6 high dose males and 1 high dose female. Calcification of the renal cortex was reported in three high dose males and 1 high dose female. Based on these effects, the NOAEL was determined to be 250 mg/kg bw (Gaunt et al., 1968).

Groups of 12 male and 12 female Wistar rats received diet containing 0%, 0.25%, 1.0%, and 5.0% DEGEE for 13 weeks. Decreased growth of male and female rats, which was associated with a reduction in food consumption, was seen in high-dose rats. No hematological changes were seen in any dose group. Males and females given 5% test material had elevated urinary glutamic-oxaloacetic transaminase and kidney weights compared to controls. High dose males also had proteinuria. Hydropic degeneration was seen in the kidneys of two high dose males and one high dose female. Slight to moderate fatty changes in the liver were seen in most high dose animals (incidences not provided). Because no treatment-related effects were seen in 0.25% or 1.0% dose groups, the NOAEL in this study was 1.0% in the diet corresponding to about 800 mg/kg bw (Hall et al., 1966).

Wistar rats were exposed orally to a blend of Labrasol, Labrafil, and Transcutol® (L/L/T) at dose levels of 0, 5, 10, or 20 mL/kg/day (approximately 0, 1000, 2000, and 4000 mg/kg/day Transcutol®) for four weeks to evaluate the safety of the formulation for use in *in vivo* non-clinical safety assessment studies for poor water soluble drugs. The blend was well tolerated at 5 mL/kg/day. In the mid-dose group, changes in appearance and behavior were seen.

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