THE WERC SHOP®

Enabling Innovation Through Information™

NEXUS™: NATURE'S DILUENT WHITEPAPER

OCTOBER 2016

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INTRODUCTION

Cannabis vapor "pens" represent a major advance in efforts to develop a safer, more effective cannabis delivery method. These devices provide a convenient and self-contained method for vaporizing cannabis oil using electronic heating that can reduce the tars, particulates, and other combustion products found in cannabis smoke. Despite vaporization possessing inherent safety advantages over smoking cannabis, ingredients added to vapor pen solutions may raise other issues. Safety concerns about synthetic diluents, such as propylene glycol, have emerged with the growth of the vapor pen and e-cigarette markets. At The Werc Shop®, we strive to provide scientific information to all cannabis users—whether patients or healthy adults—so informed choices can be made. In this whitepaper we examine the safety and efficacy of various ingredients used as diluents, or carriers, in vapor pens and introduce The Werc Shop's proprietary new ingredient, **Nexus™**. **Nexus** is a native cannabis terpene developed as an enhancer and carrier specifically for cannabis vapor products.

1

WHY CARRIERS?

2 WHY CARRIERS

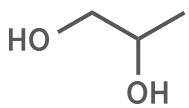
High-purity cannabis extract (e.g. +80% cannabinoids) has a consistency akin to honey. When loaded into a vapor cartridge alone, this high viscosity can impede the flow and effective wicking of the extract into the heating element. Even if effectively wicked, high-purity cannabis extract is often too potent for many patients. Adding terpenes can "thin" cannabis extracts to decrease viscosity and encourage flow. However, adding too great an amount of terpenes can result in negative and unpleasant side effects, especially when the ratio of cannabinoids to terpenes diverges from that expressed by the cannabis plant itself. In addition, mixing extracts with certain flavors can create unstable solutions that separate over time, delivering inconsistent dosing and rendering pens unreliable or inoperable. Furthermore, the potency of cannabis extracts frequently varies batch-to-batch bedeviling efforts to standardize products.

In an attempt to address this myriad of challenges, many vapor cartridge formulas are composed of a combination of three ingredients: refined extract, flavor, and a carrier.

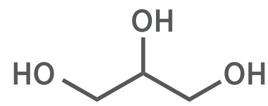
Carriers dilute the extract allowing both standardized dosing and viscosity reduction that stimulates effective vapor cartridge operation. The right carrier can also stabilize terpenes and other flavor compounds making for a more uniform product. Most commonly used carriers are synthetic derivatives of glycerin, such as propylene glycol and polyethylene glycol. Vegetable glycerin, itself, and medium-chain triglycerides (MCT oil) are also used as carriers in cannabis vapor cartridges. Each of these four carriers and some lesser known analogues confer different advantages and disadvantages.

While carrier selection requires careful consideration with respect to boiling point, viscosity, solvent properties, and taste, safety for human consumption is paramount. Since carriers can be found in high concentrations in vapor pen solutions (5-90%), it is vitally important that the safety of a carrier is properly considered.

3 PROPYLENE GLYCOL & VEGETABLE GLYCERIN



propylene glycol (PG)



glycerol, vegetable glycerin (VG)

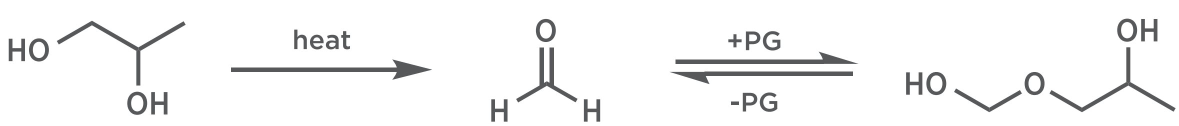
Some of the first carriers for cannabis vapor pens were propylene glycol (PG) [CAS: 57-55-6] and vegetable glycerin (VG) [CAS: 56-81-5].[1] Used as the diluents for the vast majority of nicotine-containing e-liquids,[2,3] the two related compounds were originally borrowed for cannabis vapor pens partly because of their familiarity and compatibility with existing vapor pen technology.

PG and VG are inexpensive, colorless liquids with a long history of use in the food, cosmetics, flavor, and pharmaceutical industries. Vegetable glycerin — known to chemists as glycerol — is a semi-synthetic chemical derived from natural vegetable fats,[4] while propylene glycol is produced from propylene oxide.[5] Both are considered "Generally Recognized As Safe" (GRAS) for use in food by the FDA.[6] PG and VG quickly became popular for e-liquids because of their high boiling points, mild tastes, and excellent miscibility with both nicotine and many water-soluble flavors.

However, use of the relatively polar PG and VG in cannabis vapor pens is limited by poor solubility. Vegetable glycerin is almost completely immiscible with cannabis extracts. While miscible with refined extracts, propylene glycol only partially solubilizes nonpolar native cannabis terpenes. As a result, PG or VG-based cannabis solutions tend to separate over time. Yet, despite significant drawbacks as carriers for cannabis vaporizer pens, many products still contain them.

Originally, the most compelling reason for the use of VG and PG in e-liquids was their presumed safety for human consumption. They are considered non-toxic with extremely high doses required for lethal toxicity. In animal models, acute toxicity to VG occurs at doses of 12,600 mg/kg orally (rat) and 10,000 mg/kg dermally (rabbit).[7] Propylene glycol toxicity is even lower: LD50 = 20,000 mg/kg orally (rat) and 20,800 mg/kg dermally (rabbit).[8]

Relevant research indicates that PG is largely safe for inhalation. Several studies on rat models found no signs of acute toxicity even after prolonged, repeated exposure to high levels of aerosolized propylene glycol.[9] Few studies into the effects of inhaled glycerin are available, but their use in pharmaceutical inhalers suggests minimal effects.[6]

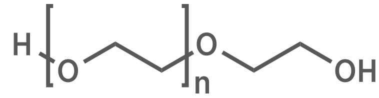


PG **formaldehyde hemiacetal** **formaldehyde hemiacetal**

In spite of the overwhelming toxicological evidence affirming the safety of VG and PG when ingested, no studies had evaluated heat-induced vaping specifically until recently. When researchers examined e-cigarette vapor, they detected varying levels of the neurotoxin and carcinogen, acrolein.[10] Other studies identified high levels of carcinogenic formaldehyde and formaldehyde-generating hemiacetals in vapor.[11] In both cases, generation of the toxins was attributed to pyrolysis: the degradation of VG or PG at the high temperatures generated by vape pen heating elements.

The discovery of formaldehyde and acrolein in e-cigarette vapor raises troubling questions about the safety of PG and VG in e-liquids. These concerns, along with their poor miscibility in cannabinoid extracts and terpenes, render propylene glycol and vegetable glycerin inferior choices as carriers for cannabis vaporizer pens.

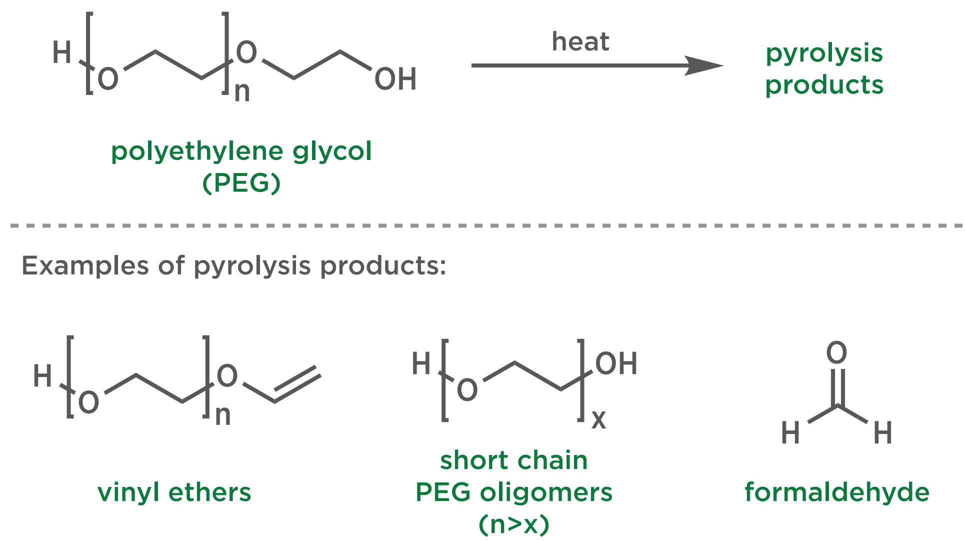
4 POLYETHYLENE GLYCOL



polyethylene glycol
(PEG)

The poor miscibility of VG and PG with cannabinoids and cannabis terpenes led to the examination of polyethylene glycol (PEG) [CAS: 25322-68-3] as a carrier for vapor pens. PEG is a water-soluble polymer of ethylene oxide available in many chain lengths. Like propylene glycol and glycerol, low molecular weight PEG preparations (such as PEG-400) are viscous, clear liquids. Some formulations of PEG are also considered GRAS for food and pharmaceutical use by the FDA,[12] and find a wide variety of uses in the cosmetics industry.[6] Available research on the inhalation of low molecular weight PEG aerosols suggests that they are non-toxic, even in very high concentrations.[13]

With respect to solubility, polyethylene glycol is superior to PG and VG as a cannabis vapor pen additive. Both cannabis extracts and nonpolar terpenes are soluble in polyethylene glycol. However, polyethylene glycol has a bitter, unpalatable taste that can overpower other flavors thus limiting the useful concentration range in any vaporizer pen. In spite of this significant drawback, PEG is still found in many vape pen products.

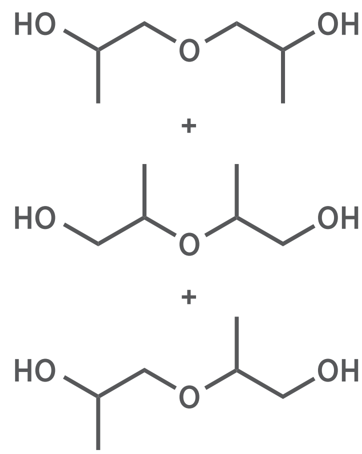


Like with propylene glycol and glycerol, research indicates PEG forms toxic byproducts through pyrolysis. Studies found that heating to just 150°C yielded degradation products including carcinogenic formaldehyde, vinyl ethers, and a variety of smaller PEG oligomers.[14] Considering the toxicity of the ethylene glycol monomer (a primary ingredient in automobile antifreeze) data describing the degradation of PEG at relatively low temperatures should raise serious concerns about the safety of the polymer as a vapor pen additive.

5 DIPROPYLENE GLYCOL AND TRIACETIN

Dipropylene glycol (DPG) is a synthetic, ether derivative of propylene glycol. Commercially manufactured DPG is actually a mixture of three related isomers. A colorless, odorless liquid with a boiling point of 233°C, DPG has low toxicity (Oral LD50 = 14.8-15.0 g/kg rats).[6] Like other glycols, DPG finds use in cosmetics, antifreeze products, as a solvent, and in plastics manufacture.[15]

Two possible alternatives to PEG, PG and V are related compounds dipropylene glycol (DPG) [CAS: 25265-71-8] and triacetin (TA) [CAS: 102-76-1].

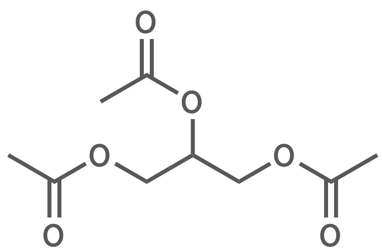


DPG
dipropylene glycol

DPG has excellent properties as a carrier. It is tasteless and exhibits excellent solubility for nonpolar compounds, such as cannabinoids and terpenes. DPG also produces stable vapor pen solutions with acceptable shelf life.

The downside is that only scant toxicological data exists for DPG. One investigation found DPG to be benign at low doses when ingested with abnormalities reported only after chronic exposure to very high concentrations.[16] Studies on other glycol ethers have found the class of chemicals to be largely innocuous when ingested. However, no groups have investigated the safety of inhaled DPG or its pyrolysis products to date. Due to incomplete toxicological data, DPG is not currently used in pharmaceutical preparations.[17,6]

Triacetin (TA) is a simple synthetic triglyceride which is used as a solvent and biocide in cosmetic formulations and as a plasticizer in other industries.[18] It is a colorless, oily liquid with a fatty taste occasionally described as bitter. It has a very high boiling point (259°C).[19] Triacetin is non-toxic and considered GRAS for food use by the FDA. Research has indicated that daily ingestion of as much as 5g TA/kg body weight is generally safe.[20]



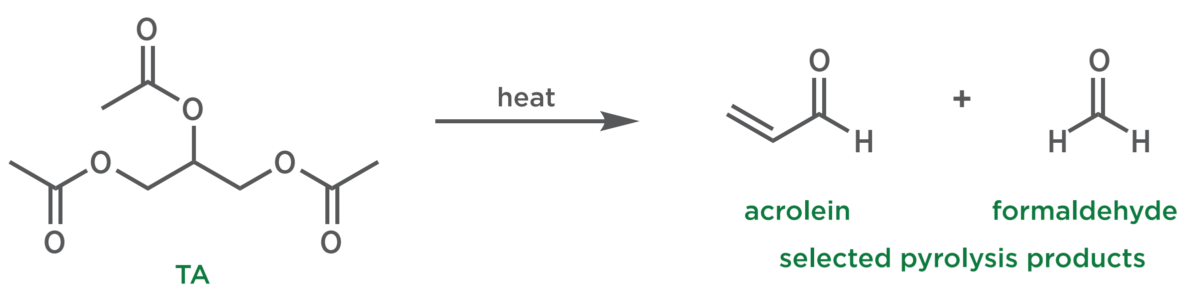
triacetin
TA

TA is nonpolar and is readily soluble in other nonpolar solvents. As a result, TA is very miscible in both cannabis extracts and terpenes, producing long-lived, stable solutions. Not unlike PEG however, these excellent enhancer properties are limited somewhat by the potentially unpalatable taste.

Inhalation studies on TA are limited, but short-term exposure studies have not revealed any toxicity concerns. In fact, concerns about the safety of triacetin ingestion appear limited to the possibility of carcinogenic contaminants imparted by manufacturing processes.[18]

Like the related glycols and glycerols, recent pyrolysis studies raise questions about the safety of TA for use in e-liquids. Using both direct measurement and computational simulations, Laino and coworkers compared the pyrolysis of TA to PG. The group found that at high temperatures, TA readily decomposes into a constellation of byproducts including carcinogens like acrolein and formaldehyde. The authors concluded that PG was "intrinsically more stable to pyrolysis," and should substitute for TA "whenever there is a choice to be made...and [the substance] is potentially exposed to high temperatures."[21]

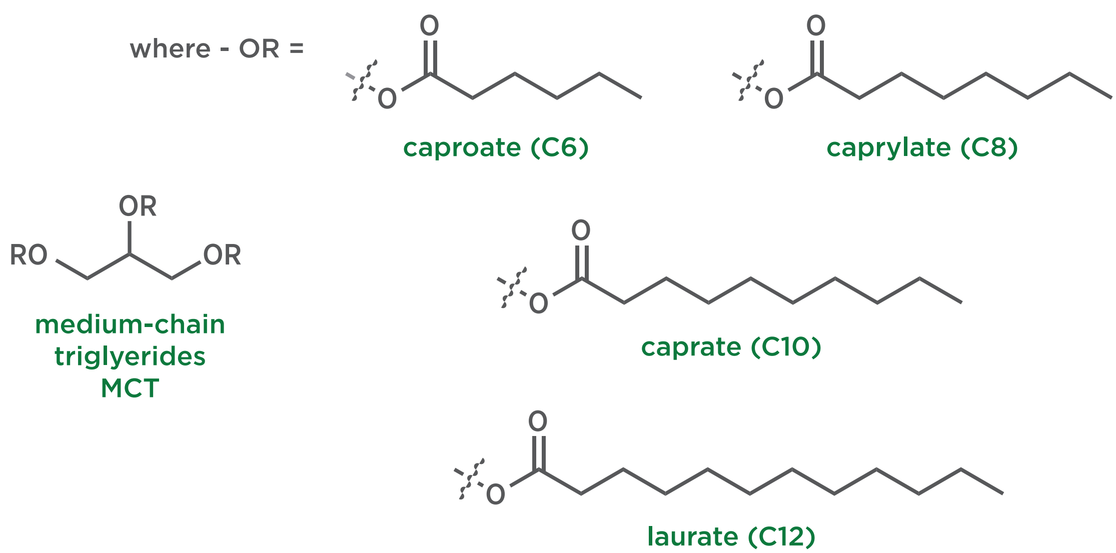
Given current concerns about PG, inclusion of TA in any vapor pen formulation should be viewed as a potential hazard.



selected pyrolysis products

6 MEDIUM-CHAIN TRIGLYCERIDES

Medium-chain triglycerides (MCTs or MCT oil) refer to a combination of triglycerides with fatty acid chains of intermediate length. MCTs are naturally produced and can be extracted from a variety of sources, most notably coconut oil.[22] Preparations may contain different proportions of several medium-chain fatty acid substituents such as caproic acid (C6), caprylic acid (C8), capric acid (C10) and lauric acid (C12).[23] As a result of this variety, MCT oils are available in a range of forms—from less viscous liquid oils to solid fats.



The components of MCT oil are part of the human diet and are metabolized normally in the body. MCTs are considered unequivocally safe and limits have not been placed on their inclusion in food products. Recent reports even suggest benefits to weight-management and neuroprotection. [23,24]

MCT has many excellent qualities as a carrier. The oil dissolves readily in the fat-soluble cannabinoids and terpenes found in the cannabis plant. MCT generally lacks the fatty odor or taste associated with other food oils and is less prone to oxidation. The diversity of MCT oil preparations allows formulators to select optimal viscosities, boiling points, and a plant-derived carrier for use in vaporizer pens.

Unlike glycols (PG), glycerol or synthetic triglycerides (TA), MCT use in food has been vetted by millennia of human consumption. Little inhalation data exists for MCT oil, however, which is "not expected to present a significant inhalation hazard."[25] Sparse medical reports associate MCT oil with pulmonary complications, especially in children. In agreement with earlier reports, Wolfson and coworkers noted symptoms of lipid aspiration pneumonia leading to significant pulmonary abnormalities in one infant fed MCT oil through a feeding tube.[26]

Unsurprisingly, no direct study on the inhalation of heat-vaporized MCT has been performed. Nevertheless, MCTs are derivatives of glycerol and a triglyceride similar to triacetin so despite natural origins they are expected to suffer similar toxic pyrolysis. Indeed, studies on the pyrolysis of closely related food oils have indicated the generation of many different decomposition products, including the carcinogenic acrolein.[27] While it remains unclear what risk is posed by its inclusion in cannabis vapor cartridges, the use of MCT oil as a carrier should be treated with some caution.

7 NEXUS

As a leader in cannabis vapor pen technology, The Werc Shop is excited to introduce **Nexus** - the first Native terpene carrier and enhancer designed specifically for cannabis vapor applications (patent pending). **Nexus** provides a potentially safer alternative to other carriers currently in use and improves upon their short-comings.

(E)-phytol
Nexus

Nexus is comprised of naturally occuring terpenes, including phytol, a viscous diterpene alcohol produced by the cannabis plant.[28] A component of chlorophyll, phytol is ubiquitous throughout the plant world and is one of the "most abundant acyclic [terpene] compounds in the biosphere."[29] In its pure form, phytol is a nearly colorless, viscous liquid with a virtually undetectable "floral" aroma.[30]

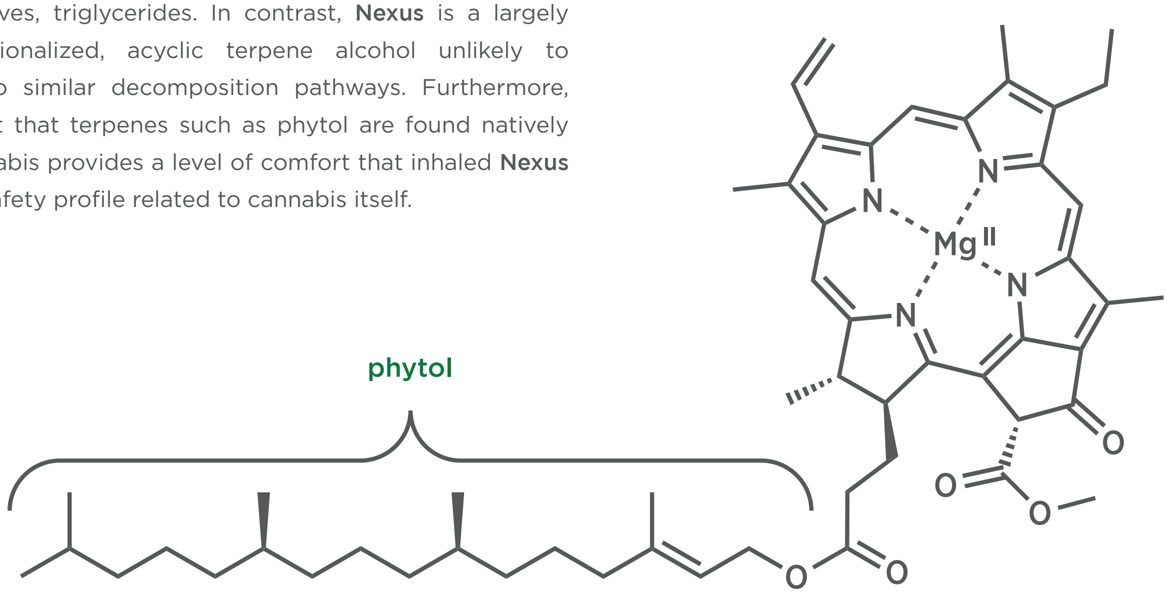
Phytol may also enter the human diet at low levels in leafy greens, beans, asparagus and other raw vegetables. Ruminant animals can metabolize chlorophyll into phytol, leading to elevated levels in dairy products, beef, and other meats. Tea contains high levels of phytol as well.[31]

Phytol exhibits very low toxicity. In multiple rat and rabbit studies, oral and dermal LD50s were greater than the maximum dose studied (LD50 reported as >10.0 g/kg oral [rats] and >5 g/kg dermal [rabbits]).[30] No studies on the effects of inhaled phytol have been published.

Due to its low toxicity, phytol is GRAS for food use in the U.S. and considered safe for use as a flavoring agent by the Flavor and Extract Manufacturers Association. The diterpene is a component of fragrances found in soaps, lotions, perfumes and other cosmetics.[30] Preliminary research has indicated potential as an anticonvulsant,[32] but phytol is not found in any currently marketed pharmaceuticals.

7 NEXUS

Like many other carriers, studies on the use of phytol in vaporizer pens have not been performed. Further, researchers have not examined phytol pyrolysis or identified possible byproducts of the process. However, phytol is chemically dissimilar to other discussed diluents. All other cannabis vapor pen carriers belong to a related family of molecules: glycols, glycerol, or its substituted derivatives, triglycerides. In contrast, **Nexus** is a largely unfunctionalized, acyclic terpene alcohol unlikely to undergo similar decomposition pathways. Furthermore, the fact that terpenes such as phytol are found natively in cannabis provides a level of comfort that inhaled **Nexus** has a safety profile related to cannabis itself.



chlorophyll a

Nexus has excellent characteristics as a base for vaporizer cartridges. It is nonpolar and is fully miscible with cannabinoids and terpenes. The taste of **Nexus** is very mild and does not contribute significantly to the overall aroma of the product. Like many other terpenes, **Nexus** is believed to have a specific synergy with cannabinoids when consumed together. Termed the Ensemble Effect, reports suggest that high levels of phytol in smoked cannabis material is notably calming.[28]

Nexus is the only naturally occurring carrier and enhancer for cannabis vapor cartridges formulated from terpenes native to the cannabis plant. It has optimal miscibility with the cannabinoids and other terpenes in vapor cartridge formulations to go along with a pleasing odor. In light of these qualities, **Nexus** is the apparent superior choice as a carrier for cannabis vapor cartridges.

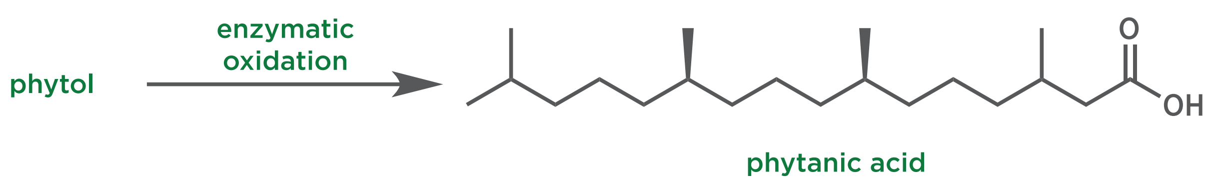
8 REFSUM DISEASE

While allergies to phytol have not been identified, patients with Refsum disease should not use Nexus™ vapor cartridges to avoid potentially serious complications.

Heredopathia atactica polyneuritiformis or **Refsum disease (RD)** is a hereditary, neurological condition thought to effect fewer than 1 in 250,000 in the general population, though exact figures are unknown.[33] RD is caused by inherited mutations that reduce the ability of the body to metabolize phytanic acid, a type of branched fatty acid found in certain foods.[31] Over time, toxic levels of phytanic acid can accumulate in tissues such as the blood and brain in those with RD, causing deleterious effects such as night blindness from retinal degeneration (retinitis pigmentosa), loss of smell (anosmia), weakness or numbness of extremities (peripheral neuropathy), deafness, loss of balance or coordination (ataxia), dermatological symptoms and irregular heartbeat (cardiac arrhythmia).[34] While RD frequently begins in adolescence, sporadic diagnoses in adults 40 years old or older have been reported.[33]

Patients suffering from RD can effectively control their symptoms by avoiding foods containing phytanic acid, such as meat and dairy. While humans absorb nearly all of their phytanic acid directly from their diet, phytol is converted by enzymes in the body to phytanic acid, so patients with RD must limit their intake of phytol as well.

Phytol does not cause deleterious effects in patients without RD. However, patients suffering from RD or those with a family history of the condition should not consume products containing **Nexus**. If you experience any of the symptoms of RD while using a product containing **Nexus**, please discontinue use and contact a physician immediately.



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