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A Review on the Safety of Inhalation of Propylene Glycol in E-cigarettes

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Abstract

Electronic cigarette (e-cigarette) are being used as a safe alternative to tobacco smoking, or as a smoking cessation device. However, the FDA presumes that e-cigarettes are as hazardous as conventional cigarettes. The Tobacco Control Task Force of the American Association of Public Health Physicians instead has indicated that e-cigarettes closely resemble Nicotine Replacement Therapy products. Since Propylene glycol (PG) constitutes around 89-90% of the e-cigarettes formulation, the objective here is to review the safety of inhalation of PG. All animal and human studies that analyzed the effect of the inhalation of PG have indicated that, PG does not appear to pose a significant hazard via the inhalation route. In fact, in several of these animal studies the concentrations of PG used were higher compared to the concentration used in e-cigarettes and did not give rise to any toxic effects. However, there are no human studies at the level of e-cigarette concentrations.

This review throws some light in terms of the safety aspects of inhalation of PG particularly seen in animal studies as it relates to e-cigarette concentration. Since most of the results came from animal studies. The information gained can be used as a platform to conduct human studies to check the short term and long term effect of propylene glycol in e-cigarettes. Therefore, further human studies using PG concentrations similar to that in e-cigarettes need to be conducted to confirm the safety of inhalation of PG from e-cigarettes.

Keywords: Electronic cigarette; Propylene glycol; Inhalation; E-cigarettes; PG

Introduction

An electronic cigarette, or e-cigarette, is an electrical device that simulates the act of cigarette smoking by producing an inhaled mist bearing the physical sensation, appearance, and often the flavor and nicotine content of inhaled tobacco smoke. The primary stated use of the e-cigarette is a safe alternative to tobacco smoking, or as a smoking cessation device, while it attempts to deliver the experience of smoking without, or with greatly reduced, adverse health effects. However, the FDA in a July 22, 2009 press conference adopted the position that it will presume that e-cigarettes are as hazardous as conventional cigarettes. An opposing view is held by the Tobacco Control Task Force of the American Association of Public Health Physicians who has indicated that e-cigarettes closely resemble Nicotine Replacement Therapy (NRT) products approved by the FDA. Tests performed by the FDA have shown that e-cigarettes have similar nicotine levels and trace contaminants as NRT products. The Ruyan e-cigarettes use micro-electronics to vaporize, very small quantities of nicotine dissolved in propylene glycol into a fine aerosol with each puff.

Nicotine and Propylene Glycol are two small molecules with known safety profiles. Propylene glycol (PG) is generally recognized as safe by oral, dermal or inhalation routes and has been a common ingredient in all American made tobacco cigarettes for seven decades (AAPHP website). The cartridge liquid is tobacco-free and no combustion occurs (Ruyan cartridge report). There is a lot of literature emerging related to e-cigarettes. Most of the literature available so far related to e-cigarettes indicates.

I. Consumer based survey regarding personal view about vaping.

II. Chemical analysis of the e-cigarette cartridges, solutions and mist.

III. Nicotine content, delivery and Pharmacokinetics. Since Propylene glycol (PG) constitutes around 65-90% of the e-cigarettes formulation, the objective here is to review the safety of inhalation of PG. This was done by reviewing all the

available animal and human studies involving the inhalation of PG at concentration levels near those used in e-cigarettes.

Pharmacokinetics of propylene glycol

Metabolism: Propylene glycol is metabolized into pyruvic acid (a normal part of the glucose metabolism process, readily converted to energy), acetic acid (handled by ethanol metabolism), lactic acid- a normal acid generally abundant during digestion and propionaldehyde [1].

Half life: According to the World Health Organization (WHO) PG has a relatively short plasma half-life (4-8 hours).

Elimination: The route of elimination of PG depends on the dose administered and not on the route of exposure. It is mainly excreted in the urine as the glucuronide conjugate, but 12-45% is excreted unchanged [2]. Renal clearance decreases with dose (390mL/min/1.73m^2 at a dose of 5g/day, but only 144 mL/min/1.73m^2 at a dose of 21g/day) [3].

Safe levels of propylene glycol: The inhaled dose of PG from normal e-cigarette use is 0.3 to 0.45g/day and if used more intensively, could result in 0.9g/day (Ruyan e-cigarette cartridge report). In terms of systemic levels, serious toxicity generally occurs only at plasma concentrations over 1g/L, which requires extremely high in takeover a relatively short period of time. Considering that the volume of blood in an average adult is 3L. Serious toxicity in an average adult can only occur at plasma amount over 3g. Thus an inhaled dose of 0.3 to 0.45g/day of PG is significantly lower compared to the concentration that can cause serious systemic toxicity.

Animal studies indicating the inhalation safety of propylene glycol

Suber et al. [4] exposed rats by nose-only inhalation to a mean target aerosol concentrations of 0.054, 0.54 or 1.2g propylene glycol/day. These exposure levels are higher compared to the inhaled dose of PG from e-cigarettes (0.3 to 0.45g/day) (Ruyan e-cigarette cartridge report). The rats in this study did not show any significant differences in terms of respiratory rates, minute volumes or tidal volumes. The mean terminal body weights for male rats did not change. However the mean body weights for female animals exposed to 1.2g/day were significantly lower than those of the female controls from day 50 onwards. This decrease in weight was consistent with a decrease in feed consumption in the female rats exposed to high concentration of propylene glycol. The nasal passages of the animals exposed to medium (0.54g propylene glycol/day) and those exposed to high (1.2g propylene glycol/day) showed a significant increase in the number of goblet cells or an increase in the mucin content of the existing goblet cells.

Most of the rats had nasal hemorrhage and ocular discharge, and this may have been caused due to the dehydration of the nares and eyes caused due to the physical irritation of propylene glycol upon the nasal epithelium in the rat. This study has shown that the rats exposed to propylene glycol by the inhalation route at the concentrations administered resulted in changes in clinical, gross pathological, histopathological or organ-weight variables that were not life-threatening. The changes thus observed in organ weight and clinical pathology parameters did not indicate a toxic effect on any single organ system or blood component. The PG exposure levels in this rat study (0.054, 0.54 or 1.2g/day) are higher when compared to the inhaled dose of PG from e-cigarettes (0.3 to 0.45g/day) and Suber et al. [4] have indicated that PG does not appear to pose a significant hazard via inhalation of either the vapor or a vapor/aerosol mixture. In addition, this study also supports previous studies indicating that propylene glycol is not a systemic toxin when administered by inhalation or by other routes [5-8]. Thus the PG concentration used in e-cigarettes appears not to have any toxic effects as shown by this *in-vivo* study but further human studies need to be conducted to confirm this.

Montharu et al. [9] in their study subjected each rat to a dose equivalent to 25mg/kg/day of propylene glycol for 4 days. The concentrations of propylene glycol used in this study are significantly higher compared to the amount of propylene glycol inhaled from-cigarettes which is in the range of 4.29mg/kg/day to 6.4mg/kg/day. In this study by Montharu et al. [9] the biochemistry and histopathology test results demonstrated that, 25mg/kg propylene glycol presented limited cellular reaction and was extremely well tolerated in a similar way to deionized water. However it was observed that during the administration of propylene glycol the respiratory arrests were the most frequent side effect and occurred on the third day of administration. As suggested by Montharu et al. [9] one explanation for this occurrence could be a rapid broncho constriction caused due to the irritating and/or inflammatory potential of the molecule.

These results indicate that with respect to inhalation of aerosols, propylene glycol may be considered as a solvent with acceptable toxicity. In fact, Propylene glycol is one of the solvents included in the FDA inactive ingredients guide for various preparations including inhalation. The concentrations of propylene glycol used in this study are significantly higher compared to the amount of propylene glycol inhaled from-cigarettes which is in the range of 4.29mg/kg/day to 6.43mg/kg/day. Secondly this study only analyzed the short term effect of propylene glycol only for 4days. Thus indicating that, the inhalation of propylene glycol in e-cigarettes at the low concentrations used appears to be safe. However further human studies to check the long term effect of inhalation of propylene glycol have to be conducted.

Werley et al. [10] in their study exposed rats and dogs to high concentrations of PG aerosol followed by comprehensive systemic evaluations, especially involving the respiratory system. In case of the acute and 7-day exposure studies the rats

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were exposed to a concentration of up to 214mg/kg and 174mg/kg of PG respectively, which is relatively high compared to the inhaled dose of PG from e-cigarettes of 4.29mg/kg to 6.43mg/kg. When the rats were exposed repeatedly by the inhalation route for the 7 days exposure it did not yield remarkable in-life findings. In acute inhalation studies in the rat, bleeding was observed around the eyes and from the nose when dosed at 214mg/kg. This finding was also reported by Suber et al. [4] This bleeding can be associated with one of the chemical properties of PG. PG is known to be hygroscopic, it absorbs moisture from its surroundings, and is used as humectants. When PG is deposited on the skin and mucus membranes it absorbs moisture thus causing the tissues to dry, resulting in small tissue breaks with minor bleeding.

In a 28 days inhalation toxicity study of PG in rats, rats were exposed up to 216mg/kg/day PG aerosol, which again is significantly higher, compared to the inhaled dose of 4.29mg/kg/day to 6.43mg/kg/day of PG from e-cigarettes. This high exposure gave rise to "minimal" laryngeal squamous metaplasia; this lesion is commonly observed in many different inhalation exposure studies and is probably related to the unique sensitivity of the larynx, and its capacity for efficient deposition of particles. The no-observed-effect-level (NOEL) for the 28-day rat study was determined to be approximately 20mg/kg/day. Dogs were exposed to attain up to 60mg/kg/day of PG in lungs which again is significantly higher compared to the inhaled dose of 4.29mg/kg/day to 6.43mg/kg/day of PG from e-cigarettes. It is important to note that in the dog study where the concentration administered was lower and, the tissue surfaces were much larger as compared to the rats the clinical observation of bleeding around the eyes and nose were not observed.

Safety pharmacology studies in the dogs were unremarkable. The NOEL for dogs in the 28-day study was determined to be 6.05mg/kg/day. This study indicated that when aerosol PG is administered by various dose routes including the inhalation route it has a relatively low toxic potential in dogs. In addition, no histopathological effects were observed on tissues like the larynx, trachea and lung. However, dogs treated for 28 days showed a decrease in some assessments of red blood cells. A treatment related decrease in hemoglobin level, red blood cell concentration and hematocrit were observed which were possibly attributable to red blood cell breakdown. Although the mechanism for this process is not clear, some veterinary texts suggest PG as an "oxidant" capable of producing intravascular hemolysis in animals. But these effects had no impact upon the health of the dog and were not clinically significant. The red blood cell count was still within the normal ranges for dogs for this age, strain and sex.

Overall, PG inhalation exposure in both rats and dogs produced limited toxicological findings thus indicating that CAG-PG exposures could be safely conducted in man by the inhalation route. Additionally, all the side effects were observed at PG exposure levels hundreds of times higher than the exposure levels of 4.29mg/kg/day to 6.43mg/kg/day which correspond to e-cigarette levels of PG. Although this study only analyzed the impact of short-term exposure to PG vapor and the effects of long-term (months or years) exposure are unknown. It does provide valuable information for e-cigarette users and policy makers. This study shows that no measurable harmful effects were observed with high concentrations of PG vapor and this is fully consistent with its designation by the FDA as "generally recognized as safe". Indicating that, the inhalation of PG at such low concentrations from e-cigarettes appears to be safe, but have to be confirmed with further human studies.

Heck et al. [11] performed a study to determine if subchronic exposure to smoke from cigarettes containing nonvolatile humectant ingredients like propylene glycol would influence the incidence, severity of toxicological endpoints, or persistence of respiratory-tract histopathology that were otherwise observed following exposure to similar cigarettes made without humectant ingredients. American- style tobacco blend containing propylene glycol at 2.2% w/w tobacco, were used to prepare the filtered test cigarettes used in this study. This amount to exposure levels of 95mg/kg of PG. Smoke exposures were conducted for 1h/day, 5days/wk. for 13 wk. The exposure levels in this study were higher compared to the inhaled dose of PG from e-cigarettes which are 4.29mg/kg/day to 6.43mg/kg/day.

This study shows the addition of propylene glycol to cigarettes, has no meaningful effect on the site, occurrence, or severity of respiratory-tract changes or on the measured indices of pulmonary function. It indicates that the addition of propylene glycol to cigarettes does not significantly affect the biological activity of inhaled cigarette smoke in this rat model. Thus indicating that the Inhalation of PG in rats did not have any toxic effects, however this was short term animal study conducted only for 13weeks. The effects of long-term (months or years) exposure in humans are unknown. Therefore further human studies need to be conducted to check the long-term effects of inhalation of PG.

Robertson et al. [12] performed a study to determine the safety of employing the vapors of propylene glycol in atmospheres inhabited by human beings. In this study, monkeys and rats were exposed to an atmosphere supersaturated with high concentrations of vapors of propylene glycol for periods of 12 to 18months. The concentrations of propylene glycol used were 0.23-0.35mg/liter (0.04-0.07mg/kg) and 0.17-0.35mg/liter (2-4.12mg/kg) for monkeys and rats, respectively. Thus, the dose of propylene glycol used in this study for monkeys were lower and for rats were approximately similar compared to the inhaled dose of PG from e-cigarettes which is 4.29mg/kg to 6.43mg/kg. Propylene glycol did not have any impact on growth rates, blood counts, urine examinations, kidney function tests,

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fertility and general condition of the animals, with the exception that the rats in the glycol atmospheres exhibited consistently higher weight gains.

Examination at autopsy as well failed to reveal any differences between the animals kept in glycolized air and those living in the ordinary room atmosphere. Extensive histological study of the lungs done to determine whether the glycol had produced any generalized or local irritation indicated absence of irritation. The liver, spleen, kidneys and bone marrow were also normal. Thus the results of these experiments along with the absence of any observed ill effects when patients were exposed to propyleneglycol vapors for months at a time provide assurance that air containing these vapors in amounts up to the saturation point is completely harmless. Propylene has been known to be essentially non-toxic [13,14].However since this was an animal study, further human studies need to be conducted to check the effects of inhalation of PG in e-cigarettes.

Wang et al. [15] performed studies to evaluate the potential toxicity of aerosolized cyclosporine formulated in propylene glycol when given to rats and dogs for 28days by the inhalation route. In case of rats, much higher doses of propylene glycol were evaluated (total inhaled doses of PG here were 106.2, 348.8, and 777.0mg/kg/day). The highest total inhaled dose (777.0mg/kg/day) is approximately 7times the clinical exposure based on a pulmonary deposited dose. In case of dogs, total inhaled doses of PG were 61.7, 106.9, and 133.9mg/kg/day. Thus the exposure levels in this study were significantly higher compared to the inhaled dose of PG from e-cigarettes which are 4.29mg/kg/day to 6.43mg/kg/day. The results from the propylene glycol vehicle arm of this 28 day inhalation toxicity studies in both rats and dogs demonstrated that there were no respiratory or systemic effects from high doses of propylene glycol relative to air controls.

Similarly Venitz et al. [16] in their study delivered inhaled nominal doses ranging from 3-60mg/kg/day, over a 6- to 60-minute exposure interval to dogs for 28days. The PG aerosol exposure in this study as well did not have any apparent toxicity upon lung, kidney or liver. Thus the results from these two studies indicate that the concentration of PG used in e-cigarettes will not have any respiratory or systemic and will not have any apparent toxicity upon lung, kidney or liver. However these were animal studies and were conducted only for 28days. Hence further studies to check the long term effects of PG inhalation in humans need to be conducted.

Gaworski et al. [17] performed a study to examine the biological activity and analytical smoke chemistry of mainstream smoke from cigarettes containing three different amounts (low, medium, high) (4, 7 and 10% respectively) (i.e. 28,900, 54,300 and 77,900mg/kg) of added PG. All these above mentioned concentrations are significantly higher than the inhaled dose of PG from e-cigarettes which is 4.29mg/kg/day to 6.43mg/kg/day. In this study they compared the biological activities with that of otherwise similar cigarettes, containing no added PG. It was observed that the addition of PG to the tobacco material reduced the presence and severity of some histopathological lesions (e.g., goblet cell hyperplasia in the nose, epithelial keratinization in the larynx, focal accumulation of alveolar macrophages, in females only) which are typically seen in smoke inhalation studies with rats.

As suggested by Gaworski et al. [17] one reason for this decrease in severity of some histopathological lesions could be that when PG is added to experimental cigarette tobacco this consequently reduced the concentrations of several of the major smoke constituents, including nicotine. These reductions in smoke constituents are probably the result of a dilution effect by PG displacing nicotine, as well as an increase in water content of the particulate phase from the burned tobacco, rather than an effect of PG. However, the responses shown from the cigarette with no added PG and the three cigarettes with added PG were very similar, and more importantly did not indicate any substantial increase in toxicity related to the levels of PG. Since the exposure levels in this study were higher than the inhaled dose of PG for e-cigarettes and the results did not indicate any toxic effects, it indirectly indicates that the concentration of PG used in e-cigarettes is safe for inhalation.

Human studies indicating the inhalation safety of propylene glycol

\Wieslander et al. [18] performed a study to evaluate the effects of exposure to a PG mist, at exposure levels occurring during normal aviation emergency training. The physiological effects studied included tear film stability, nasal patency and lung function, as well as subjective symptoms. The design was experimental and showed acute effects on ocular and throat symptoms, and decreased tear film stability in non asthmatic subjects after 1 minute exposure to PG mist from an artificial smoke generator. The exposure concentration of PG (geometric mean 309mg/m^3) (99.29mg/kg) was quite high, compared with other exposure measurements of this compound in work environments.

Exposure measurements in house painters who used water based paints showed exposure concentrations of PG ranging from <0.1 to 12.7mg/m^3 (mean 2.6mg/m^3) (0.84mg/kg), but no measurable exposure to PG was found in motor servicing work [19]. These studies showed that exposure to PG can be high from smoke generators, compared to other occupational applications. It was concluded from the results that short exposures to PG mist from smoke generators may cause acute irritative ocular and upper airway effects in non-asthmatic subjects, and some symptoms were more common in women and subjects with atopy. Some subjects may present with minor lower airway obstruction, cough, and mild dyspnoea.

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Thus, sensory hyper reactivity could be one mechanism behind the development of a combination of cough, slight airway obstruction, and mild dyspnoea in a few of those exposed to PG mist. However, when children were exposed to, airborne PG (mean concentration 22.17mg/kg, maximum 30.21mg/kg) for air sterilization, continuously during several weeks. The mucous membranes in the upper respiratory tract did not show any negative effects. It was observed that the concentrations of PG used in these studies were higher than the inhaled dose of PG for e-cigarettes which is 4.29mg/kg/day to 6.43mg/kg/day. Indicating that the concentration of PG used in e-cigarettes may be at safe levels [20].

Greenbaum et al. [21] in their study observed that the use of the new formulation of 0.025% Rhinalar containing a reduced amount of propylene glycol (5%) (0.04g/day) considerably reduced nasal burning and stinging and throat irritation compared with the original formulation which contained 20% (0.16g/ day) propylene glycol. The dose (gram/day) used in this study are lower than the inhaled dose of PG from e-cigarettes which is 0.3 to 0.45g/day.

Environmental protection agency (EPA) report

General toxicity observations: The EPA upon reviewing the available toxicity information has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to propylene glycol. In these studies, dose levels near or above testing limits (as established in the OPPTS 870 series harmonized test guidelines) were employed in experimental animal studies and no significant toxicity was observed. However the report did not mention the concentration of the dose administered. The acute toxicology profile for propylene glycol in case of oral exposure in rats resulted in LD50 range of 8000-46000mg/kg [22,23].

Based on the EPA report as a result of the Phase IV review of propylene glycol for reregistration under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), ecological effects data requirements were waived due to its high volatility, known low toxicity, and available data. Data obtained from published studies related to propylene glycol provide an additional confirmation of the low toxicity of the compound to fish and aquatic invertebrates (Table 1).

Table 1: Studies Indicating the Inhalation Safety of Propylene Glycol.

Reference point: inhaled dose of PG from e-cigarettes of 4.29mg/kg to 6.43mg/kg (per day)						
Author	**Study**	**Average Weight (Grams)**	**Exposure Levels**	**Mg/Kg Of PG**	**Exposure Duration**	**Findings**
Suber et. al.		rats	nose-only inhalation to a mean target aerosol concentrations of 0.054, 0.54 or 1.2 g propylene glycol /day			This study has shown that the rats exposed to propylene glycol by the inhalation route at the concentrations administered resulted in changes in clinical, gross pathological, histopathological or organ-weight variables that were not life-threatening. The changes thus observed in organ weight and clinical pathology parameters did not indicate a toxic effect on any single organ system or blood component.
Jerome Montharu et al.		rat		25mg/kg/day	4 days	The biochemistry and histopathology test results demonstrated that, 25mg/kg propylene glycol presented limited cellular reaction and was extremely well tolerated in a similar way to deionized water.
						However it was observed that during the administration of propylene glycol the respiratory arrests were the most frequent side effect and occurred on the third day of administration.
Werley et al.	Acute inhalation toxicity study of PG in rats	210 (rat)	45mg/L(liquid PG)	upto 214	4 hours	bleeding was observed around the eyes and from the nose
Werley et al.	7-Day inhalation toxicity study of PG in rats	235 (rat)	41mg/L(liquid PG)	upto 174	4hrs/day for 7 days	Did not yield remarkable in-life findings

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Werley et al.	28-Day inhalation toxicity study of PG in rats	195 (rat)		Up to 216	per day for 28 days	Gave rise to “minimal” laryngeal squamous metaplasia, The NOEL for the 28-day rat study was determined to be approximately 20 mg/kg/day
Werley et al.	28-Day inhalation toxicity study of PG in Beagle dogs	7200 (beagle dog)		Up to 60	per day for 28 days	No histopathological effects were observed on tissues like the larynx, trachea and lung,
						Decrease in hemoglobin level, red blood cell concentration and hematocrit were observed,
						The red blood cell count was still within the normal ranges for dogs for this age, strain and sex ,
						The NOEL for dogs in the 28-day study was determined to be 6.05mg/kg/day
Heck et al.	Subchronic exposure to smoke from cigarettes	210 (rat)	2.2% w/w tobacco, tobacco weight=0.9 gm/cigarette,	95	1 h/day, 5 days/wk for 13 wk	Does not induce changes in respiratory-tract or indices of pulmonary function
						Does not significantly affect the biological activity of inhaled cigarette smoke
Robertson et al.		85 (rat)	0.17-0.35mg/L	2 to 4.12	12 months	Did not have any effect on growth rates, blood counts, urine examinations, kidney function tests, fertility and general condition of the animal,
						The rats in the glycol atmospheres exhibited consistently higher weight gains.
		• 5300 (Rhesus Monkey)	0.23 - 0.35mg/L			Autopsy examination also did not reveal any differences between the animals kept in glycolized air and those living in the ordinary room atmosphere.
				0.04 to 0.07	12 -18 months (saturation of chambers)	Extensive histological study of the lungs indicated absence of irritation.
						The liver, spleen, kidneys and bone marrow were also normal.
Wang et al.		Sprague-Dawley Rat		106.2, 348.8, and 777.0	per day for 28 days	There were no respiratory or systemic effects from high doses of propylene glycol
		Beagle Dog		61.7, 106.9, and 133.9	per day for 28 days	There were no respiratory or systemic effects from high doses of propylene glycol
J. Venitz et al.		Dogs		Mar-60	per day for 28 days	It was observed that the addition of PG to the tobacco material reduced the presence and severity of some histopathological lesions (e.g., goblet cell hyperplasia in the nose, epithelial keratinization in the larynx, focal accumulation of alveolar macrophages, in females only) which are typically seen in smoke inhalation studies with rats.
						Did not indicate any substantial increase in toxicity related to the levels of PG

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Gaworski et al.	To examine the biological activity and analytical smoke chemistry of mainstream smoke from cigarettes containing three different amounts (low, medium, high) of added PG.	210 (rat)		28,900, 54,300 and 77,900 mg/kg		The addition of PG to the tobacco material reduced the presence and severity of some histopathological lesions (e.g., goblet cell hyperplasia in the nose, epithelial keratinization in the larynx, focal accumulation of alveolar macrophages, in females only).
						However, the responses shown from the cigarette with no added PG and the three cigarettes with added PG were very similar, and more importantly did not indicate any substantial increase in toxicity related to the levels of PG.
Wieslander et al.	To evaluate the effects of exposure to a PG mist, at exposure levels occurring during normal aviation emergency training.	82000 (Human Adults)		99.29 mg/kg	1 minute exposure to PG mist	The design was experimental and showed acute effects on ocular and throat symptoms, and decreased tear film stability in nonasthmatic subjects after 1 minute exposure to PG mist from an artificial smoke generator.
						It was concluded from the results that short exposures to PG mist from smoke generators may cause acute irritative ocular and upper airway effects in non-asthmatic subjects, and some symptoms were more common in women and subjects with atopy. Some subjects may present with minor lower airway obstruction, cough, and mild dyspnoea.
Wieslander et al.		Children		mean concentration 22.17mg/ kg, maximum 30.21mg/kg		The mucous membranes in the upper respiratory tract did not show any negative effects.
Greenbaum et al.			0.04g/day			The new formulation of 0.025% Rhinalar containing a reduced amount of propylene glycol (5%) (0.04g/day) considerably reduced nasal burning and stinging and throat irritation compared with the original formulation which contained 20% (0.16g/ day) propylene glycol.

The EPA report has clearly mentioned that there is a reasonable certainty no harm will result to the general population or any subgroup from the use of propylene glycol. The agency arrived to this conclusion based on all available information on the toxicity, use practices and exposure scenarios, and the environmental behavior of propylene glycol and dipropylene glycol. Because no toxicological endpoints were identified for propylene glycol, by oral, dermal, or inhalation exposure, the agency determined that exposure to it does not result in human health effects of concern [24,25].

Conclusion

Suber et al. [4], Werley et al. [10] Venitz et al. [10] and Wang et al. [15] through their studies indicated that rats and dogs did not exhibit any respiratory or systemic toxicological effects due to inhalation of high doses of propylene glycol relative to air

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controls. In addition, these studies also support previous studies indicating that propylene glycol is not a systemic toxin when administered by inhalation Robertson et al. [12] or by other routes [5-8]. Heck et al. [11] demonstrated that the addition of glycerin and propylene glycol to cigarettes, has no meaningful effect on the site, occurrence, or severity of respiratory-tract changes or on the measured indices of pulmonary function. It indicates that the addition of glycerin and propylene glycol to cigarettes does not significantly affect the biological activity of inhaled cigarette smoke in the rat model. Similarly several cigarette analysis conducted by Gaworski et al. [17] indicated that cigarettes with no added PG and cigarettes with added PG were very similar, and more importantly did not indicate any substantial increase in toxicity related to the high levels of PG inclusion.

Gaworski et al. [17] observed that the addition of PG to the tobacco material reduced the presence and severity of some histopathological lesions (e.g., goblet cell hyperplasia in the nose, epithelial keratinization in the larynx, focal accumulation of alveolar macrophages, in females only) these are typically seen in smoke inhalation studies with rats. As suggested by Gaworski et al. [17] one reason for this decrease in severity of some histopathological lesions could be that when PG is added to experimental cigarette tobacco this consequently reduced the concentrations of several of the major smoke constituents, including nicotine. In addition, the EPA report has also clearly mentioned that there is a reasonable certainty no harm will result to the general population or any subgroup from the use of propylene glycol.

The agency arrived at this conclusion based on all available information on the toxicity, use practices and exposure scenarios, and the environmental behavior of propylene glycol. Because no toxicological endpoints were identified for propylene glycol by oral, dermal, or inhalation exposure, the EPA determined that exposure to it does not result in human health effects of concern. It is important to note that this EPA report was published prior to the advent of the e-cigarettes. All the animal studies show that no measurable harmful effects were observed with high concentrations of PG vapor and this is fully consistent with its designation by the FDA as "generally recognized as safe". In fact, propylene glycol is one of the solvents included in the FDA inactive ingredients guide for various preparations including inhalations. Several of the animal studies employed concentrations of PG higher than the concentrations used in e-cigarettes and did not give rise to any toxic effects. Based on animal studies that are testing at higher levels it is safe to use PG in humans. However, there are no human studies at the level of e-cigarette concentrations. Therefore, further human studies using PG concentrations similar to that in e-cigarettes need to be conducted to confirm the safety of inhalation of PG from e-cigarettes.

This review throws some light in terms of the safety aspects of inhalation of PG particularly seen in animal studies as it relates to e-cigarette concentration. There are not many human studies checking the inhalation safety of PG. Since most of the results came from animal studies. The information gained can be used as a platform to conduct human studies to check the short term and long term effect of propylene glycol in e-cigarettes.

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