HB

40

<TARGET><BILL>HB 40</BILL><SUBJECT>HB
40</SUBJECT><COMM>HHSS29</COMM></TARGET>

ALASKA STATE LEGISLATURE

Representative Bob Herron
State Capitol Building, Room 406
Phone (907) 465-4942
Rep.Bob.Herron@akleg.gov

HB 40: "An Act relating to the use of electronic cigarettes"

Sponsor Statement

HB 40: "An Act relating to the use of electronic cigarettes", would add electronic cigarettes to the statutory definition of smoking, thereby making it illegal state-wide to smoke e-cigs everywhere regular smoking is currently prohibited, including: public transportation vehicles, places of state employment, postsecondary educational institutions, a courtroom, a nursing home, a grocery store, a restaurant with over 50-person capacity, etc.

A May 21, 2014 Electronic Cigarette and Aerosol Emissions Product Update and Position statement from the Alaska Department of Health & Social Service clearly states:

> "Secondhand e-cigarette aerosol … contains nicotine, ultrafine particles and low levels of toxins that are known to cause cancer. The FDA's initial investigation into the content of e-cigarettes found the aerosol potentially hazardous to the public's health due to tobacco-specific nitrosamines and other volatile organic compounds."

While the airborne aerosol from e-cigs is reportedly less dangerous than second-hand cigarette smoke, it does still contain chemicals not everyone wishes to ingest. It also greatly depends on the type of e-cigarette – the industry is not yet well-regulated. The intent here is certainly not to discourage the use of e-cigarettes as a way to help quit smoking – but it's important for those users to consider the negative impacts on innocent bystanders.

Fiscal Note

State of Alaska
2015 Legislative Session

Bill Version: HB 40
Fiscal Note Number:
() Publish Date:

Identifier: HB040-DEC-FSS-03-06-15
Title: USE OF ELECTRONIC CIGARETTES AS SMOKING
Sponsor: HERRON
Requester: Health & Social Services Committee

Department: Department of Environmental Conservation
Appropriation: Environmental Health
Allocation: Food Safety & Sanitation
OMB Component Number: 2343

Expenditures/Revenues

Note: Amounts do not include inflation unless otherwise noted below. (Thousands of Dollars)

	FY2016 Appropriation Requested	Included in Governor's FY2016 Request	Out-Year Cost Estimates				
OPERATING EXPENDITURES	**FY 2016**	**FY 2016**	**FY 2017**	**FY 2018**	**FY 2019**	**FY 2020**	**FY 2021**
Personal Services							
Travel							
Services							
Commodities							
Capital Outlay							
Grants & Benefits							
Miscellaneous							
Total Operating	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Fund Source (Operating Only)							
None							
Total	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Positions							
Full-time							
Part-time							
Temporary							
Change in Revenues							

Estimated SUPPLEMENTAL (FY2015) cost: 0.0 *(separate supplemental appropriation required)*
(discuss reasons and fund source(s) in analysis section)

Estimated CAPITAL (FY2016) cost: 0.0 *(separate capital appropriation required)*
(discuss reasons and fund source(s) in analysis section)

ASSOCIATED REGULATIONS

Does the bill direct, or will the bill result in, regulation changes adopted by your agency? No
If yes, by what date are the regulations to be adopted, amended or repealed?

Why this fiscal note differs from previous version:

Not applicable, initial version.

Prepared By: Elaine Busse Floyd, Director — Phone: (907)269-7644
Division: Environmental Health — Date: 03/06/2015 02:00 PM
Approved By: Alice Edwards, Deputy Commissioner — Date: 03/06/15
Agency: Department of Environmental Conservation

FISCAL NOTE ANALYSIS

STATE OF ALASKA **BILL NO.** HB 40
2015 LEGISLATIVE SESSION

Analysis

Analysis/Assumptions:
This bill amends AS 18.35.365 to include a definition of electronic cigarettes. As written, this bill does not affect Environmental Health nor does it require any action on our part.

29-LS0232\W
Martin
3/7/15

CS FOR HOUSE BILL NO. 40( )

IN THE LEGISLATURE OF THE STATE OF ALASKA

TWENTY-NINTH LEGISLATURE - FIRST SESSION

BY

Offered:
Referred:

Sponsor(s): REPRESENTATIVE HERRON

A BILL

FOR AN ACT ENTITLED

"An Act relating to the use of electronic cigarettes; and providing for an effective date."

BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF ALASKA:

*** Section 1.** AS 18.35.365 is amended by adding new paragraphs to read:

(3) "electronic cigarette" means an electronic device that uses a heating element, battery, or electronic circuit to issue a vapor or aerosol for inhalation in a manner that simulates smoking a lighted or heated cigar, cigarette, or pipe, or other lighted or heated tobacco or plant product intended for inhalation;

(4) "smoking" includes the use of electronic cigarettes and other oral smoking devices.

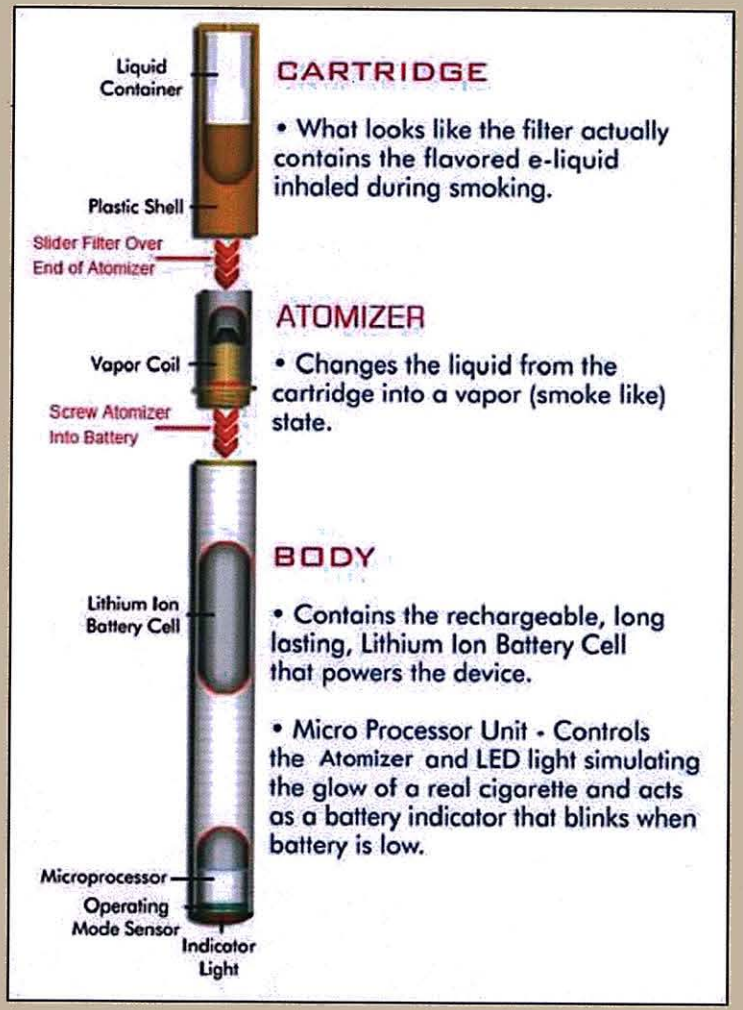
*** Sec. 2.** This Act takes effect immediately under AS 01.10.070(c).

E-CIGARETTES OVERVIEW

Rob Earl, Staff to Rep. Bob Herron
Sponsor, HB 40

What are they?

- E-cigarettes are battery-powered electronic (nicotine) delivery systems.
- They consist of a cartridge that contains the "e-juice", an atomizer that vaporizes the juice via a heating coil and the large body that is the lithium ion battery.
- There is also a small microprocessor that controls the atomizer and the LED light that lights up the end of the "cigarette".

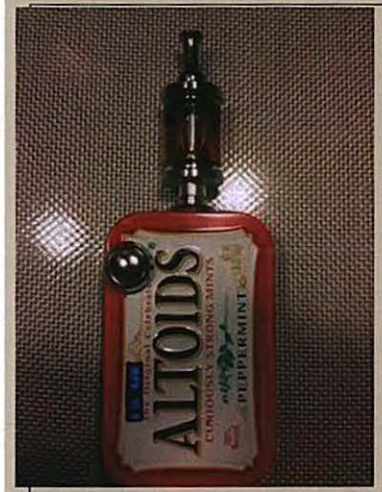


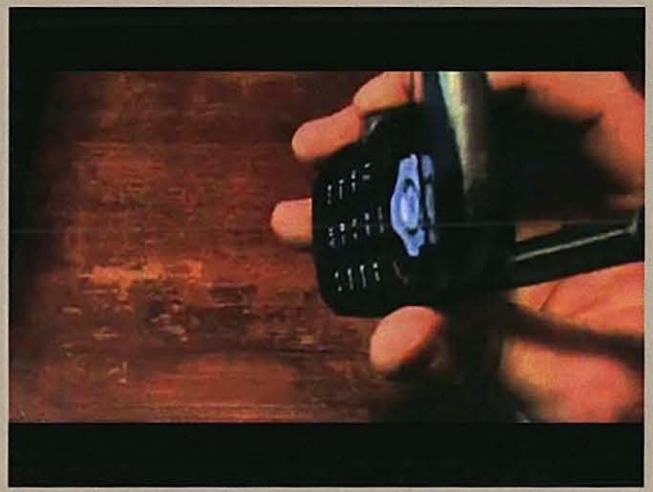
A cigarette by any other name still does not smell sweet…

- E-cigarettes deliver nicotine, produce "smoke" and imitate the practice of smoking.
- First generation devices also termed, "Cigalikes".
- The subsequent generations of the product have been-rebranded as vape-pens, e-hookah's, or hookah-pens.

Tank Systems

- The refillable tank system is the more popular device now.
- The "tank", also known as a cartomizer is the cartridge and atomizer in one piece.
- You can refill the tank with customized e-juice.
- These devices can be hacked and modified


ALTOIDS
CURIOUSLY STRONG MINTS
PEPPERMINT




voltage
Billet
BOX


TOOLMATE

Dry/Whole "Herb"

- You can use these devices to smoke marijuana and other drugs.
- They do not smell like tobacco smoke nor pot which makes their use hard to detect.
- People use them indoors, kids are using them in schools.

E-juice

- Propylene glycol or vegetable glycerin, nicotine, flavorings.
- Propylene Glycol:
  - generally recognized as safe to be used in cosmetics, pharmaceuticals and is commonly used in stage smoke.
  - causes eye and respiratory irritation and exposure should be limited according to the FDA safety data sheet.
  - safety has never been assessed for daily, deep inhalation into the lungs.
  - Studies show that heating propylene glycol creates carcinogens (Henderson et al., 1981)

Second-Hand Aerosol?

- Today's batteries are stronger, the liquid is heated to a higher temperature which aerosolizes more toxins in smaller more dangerous particles.
- The aerosol that is exhaled from the lungs is not "harmless water vapor" it contains nicotine, ultra-fine particles and chemicals and other carcinogenic toxins.
- Some research shows equal and even higher concentrations of toxicants in e-cigarette aerosol compared to tobacco smoke (Williams et al., 2013).
- Williams et al., found elevated levels in aerosol for tin, silver, iron, nickel aluminum and silicate nanoparticles (Williams et al., 2013).

Cessation Research

- Though studies show a reduction in cigarette consumption initially, after a year of using e-cigarettes as a cessation device, 89%, had not quit and were still using traditional cigarettes. (Adkison, et al., 2013).
- People using e-cigarettes were significantly *less* likely (by about 1/3) to have quit cigarettes at follow-up.
- There is no difference between placebo e-cigs and nicotine e-cigs in quit rates (Vansickle, AR, 2010)
- Smoking 1–4 cigarettes per day was associated with a significantly higher risk of dying from ischemic heart disease and from all causes, and from lung cancer in women (Bjartveit and Tverdal, 2005).

Harms?

- E-cigs could serve as an initiation tool for nicotine addiction and tobacco use in youth.
- E-cigs could re-normalize cigarette smoking in public.
- E-cigs could discourage or delay tobacco cessation because they are viewed as "safer".
- E-cigs could tempt former smokers to return to nicotine and relapse into smoking.
- E-cigs can be used to discretely "vape" THC oil.

Conclusion

- E-cigarettes should be considered a tobacco product and should be subject to all laws and regulations that govern tobacco products.
- More research needs to be done into e-cigarettes, their potential benefits and harms.
- E-cigarettes are now included in the Juneau Clean Air Ordinance which means that there is protection from second-hand aerosols inside public places in Juneau.

Thank You

HB 40 – Relating to the use of electronic cigarettes

Representative Bob Herron, Sponsor

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30341-3724

TESTIMONY ON THE SCIENTIFIC EVIDENCE ON THE PUBLIC HEALTH EFFECTS OF SECONDHAND SMOKE AND ELECTRONIC NICOTINE DELIVERY SYSTEMS AEROSOL

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NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION
U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

ALASKA STATE LEGISLATURE
JUNEAU, ALASKA

February 12, 2015

Thank you for the opportunity to submit testimony today about the health impact of secondhand smoke exposure and aerosol from electronic nicotine delivery systems, including e-cigarettes. I am Dr. Brian King with the Office on Smoking and Health, Centers for Disease Control and Prevention (CDC), the lead Federal agency for comprehensive tobacco prevention and control. I am the author of over 50 peer-reviewed scientific articles on tobacco prevention and control. I am also a contributing author to the 50th anniversary Surgeon General's report, *The Health Consequences of Smoking—50 Years of Progress*, as well as the lead author of CDC's 2014 evidence-based state guide, *Best Practices for Comprehensive Tobacco Control Programs*. I am an international subject matter expert on the issue of secondhand smoke, and have worked for nearly a decade to provide sound scientific evidence to inform tobacco control policy and practice, as well as to effectively communicate this information to key stakeholders at the national, state, and local levels. I am also an international subject matter expert on electronic nicotine delivery systems and have authored multiple peer-reviewed publications on the issues of electronic nicotine delivery system use among adults and youth, susceptibility among youth, and public health policy related to these products.

For the record, I am submitting expert written testimony today at the request of Alison Kulas, Program Manager of the state of Alaska's Tobacco Prevention and Control Program, to discuss the scientific evidence for eliminating exposure to secondhand smoke, as well as the public health effects of electronic nicotine delivery systems, including exposure to the aerosol emitted from these products.

Also for the record, this testimony is not for or against any specific legislative proposal.

The Health Effects of Secondhand Smoke Exposure

I will begin by discussing the harms of secondhand smoke exposure, which has a robust scientific evidence base reflecting decades of research.

Secondhand smoke from burning tobacco products is deadly. In adults, secondhand smoke exposure causes stroke, lung cancer, and coronary heart disease, as well as nasal irritation and reproductive effects in women, such as low birth weight.[1] Children who are exposed to secondhand smoke are at an increased risk for sudden infant death syndrome (SIDS), acute respiratory infections such as pneumonia and bronchitis, middle ear disease, more severe asthma, respiratory symptoms, and slowed lung growth.[1]

The scientific evidence on the harmful effects of secondhand smoke exposure is well-documented. The Surgeon General first concluded that secondhand smoke causes lung cancer in 1986.[2] In 2006, the Surgeon General's Report on *The Health Consequences of Involuntary Exposure to Tobacco Smoke* concluded that there is no risk-free level of secondhand smoke exposure.[3] Separating smokers and nonsmokers, using designated smoking areas, cleaning or filtering the air, and using separately ventilated areas do not work.[3]

In 2010, the Surgeon General's Report on *How Tobacco Smoke Causes Disease* reaffirmed the conclusion that there is no risk-free level of exposure to tobacco smoke.[4] The report and subsequent findings also documented how the complex mix of chemicals in tobacco smoke causes disease, including finding that cigarette smoke contains 7,000 chemicals, 250 of which are toxic and nearly 70 of which cause cancer.[1,4]

In 2014, the 50th Anniversary Surgeon General's Report on *The Health Consequences of Smoking* further affirmed these findings.[1] The report estimates that secondhand smoke exposure increases the risk of stroke by 20 to 30%.[1]

The effects of secondhand smoke exposure on the body are immediate.[3] A 2011 study reported that secondhand smoke exposure can produce adverse inflammatory and respiratory effects within 60 minutes of exposure and that these effects persist for at least three hours after the exposure.[5] These findings are significant; the concern is not just secondhand smoke exposure for guests during a meal at a restaurant, but also the compounded health effects for an employee working an eight-hour shift in a smoke-filled restaurant or bar.[3]

The Burden of Secondhand Smoke Exposure

Secondhand smoke exposure costs nonsmokers—especially vulnerable populations, such as children—their health and wellbeing. These costs are born not just by individuals, but by society: exposure to secondhand smoke costs the United States billions of dollars in lost productivity and medical expenses every year.[1]

As a result of the considerable body of evidence documenting the adverse effects of secondhand smoke, substantial progress has been made toward eliminating nonsmokers' exposure to this preventable health hazard over the last 50 years.[1] Recent assessments of cotinine, a metabolite of nicotine and biomarker of recent secondhand smoke exposure, indicates that about 1 in 4 Americans continue to be exposed to secondhand smoke.[6]

In the past 50 years, secondhand smoke exposure is estimated to have caused nearly 2.5 million deaths in nonsmoking Americans.[1] Each year, an estimated 7,330 lung cancer deaths and 33,950 coronary heart disease deaths are attributable to secondhand smoke exposure.[1] The smoking-attributable economic costs in the United States also include about $5.6 billion in lost productivity every year due to secondhand smoke exposure.[1] Many of these deaths and this lost productivity could be prevented if comprehensive smokefree laws prohibiting smoking in all indoor areas of worksites, restaurants, and bars were implemented nationwide.[1]

Preventing Secondhand Smoke Exposure

We know what works to prevent these harms. In 2006, the Surgeon General concluded that eliminating smoking in indoor spaces is the only way to fully protect nonsmokers from secondhand smoke exposure.[3] In 2009, the World Health Organization's International Agency for Research on Cancer reiterated these findings, concluding that smokefree policies lead to substantial declines in secondhand smoke exposure, citing air quality improvements of up to 90% in high-risk settings, such as bars.[7]

The latest Surgeon General's report delved deeper into the science behind the success of smokefree laws in protecting people's health. Specifically, the report concluded that smokefree laws directly cause reductions in coronary events (especially heart attacks), making comprehensive smokefree laws one of the most effective and cost-effective approaches for reducing heart disease—the leading cause of death—in the country.[1]

Finally, beyond reducing exposure to secondhand smoke, smokefree laws also lower smoking rates as a whole, especially among vulnerable youth and young adults.[1] Both the Surgeon General and the U.S. Guide to Community Preventive Services conclude that smokefree laws in workplaces and communities help smokers quit and reduce tobacco use.[1,8] In addition, smokefree workplaces and communities make youth and young adults less likely to start smoking due to a number of factors, including lower visibility of people who smoke, fewer opportunities to smoke alone or with others, and reduced social acceptability for smoking.[1] The implementation of smokefree laws also increase the adoption of voluntary smokefree rules in homes, which can further protect nonsmokers—especially the most vulnerable that are exposed to secondhand smoke in the home, such as children.[1]

CDC defines a comprehensive smokefree law as one that prohibits smoking at all times, in all indoor areas of all workplaces and public places, including restaurants and bars. If a law allows exemptions for designated or ventilated smoking areas in workplaces, restaurants or bars, the state or community is not considered to have a comprehensive smokefree law. As of January 2015, CDC has determined that 26 states, Puerto Rico, the District of Columbia, and over 697 other communities in the United States have comprehensive smokefree laws in effect.[9,10]

Smokefree policies in hospitality venues such as restaurants, bars, and casinos protect employees and patrons from the health effects of secondhand smoke. These policies are associated with improved indoor air quality and with reduced secondhand smoke exposure, reduced sensory and respiratory symptoms, and improved lung function in nonsmoking employees, which translates into improved productivity.[2] Comprehensive smokefree laws

are also associated with rapid reductions in hospitalizations due to heart attacks and strokes.[11] These improvements occur within months after implementation.[12,13] For instance, in Colorado, following the implementation of a comprehensive smokefree law in 2006, the state saw a 23 percent drop in ambulance calls from these venues.[14] However, there was no change in ambulance calls from casinos until the law was expanded in 2008 to include casinos—after which, ambulance calls from casinos dropped nearly 20 percent.[14] Again, this illustrates that these health improvements are lifesaving and nearly immediate.

The Business Case for Smokefree Laws

The evidence concerning the economic impact of smokefree laws is also well-documented. In 2006, the Surgeon General concluded that "evidence from peer-reviewed studies shows that smokefree policies and regulations do not have an adverse economic impact on the hospitality industry."[3]

These findings have been replicated numerous times at the international, state, and local levels.[1,3,7] In 2009, the International Agency for Research on Cancer conducted a comprehensive review of 97 studies from eight countries on the economic impact of smokefree policies and found that studies consistently conclude that smokefree policies do not harm business.[7]

At the state and local level, studies consistently reiterate these conclusions. The largest analysis of the impact of local smokefree ordinances, which examined nine states (Alabama, Indiana, Kentucky, Mississippi, Missouri, South Carolina, Texas, and West Virginia), found that smokefree laws do not have a negative impact on either employment or sales in restaurants and bars.[15] A study of El Paso, Texas's smokefree policy found that the law had no effect on restaurant and bar revenue.[16] Furthermore, a 2007 study on the economic impact of a smokefree law in Lexingon-Fayette County, Kentucky found that "no important economic harm stemmed from the smoke-free legislation…despite the fact that Lexington is located in a tobacco-producing state with higher-than-average smoking rates."[17]

Further reviews of the literature have also found that, in some cases, a smokefree policy produces positive effects for local businesses.[18,19,20] A number of cities and localities have experienced these positive effects. For instance, an in-depth analysis of tax revenue data in California after the state implemented their smokefree restaurant law (in 1995) and bar law (in 1998) found that the smokefree restaurant law was associated with an increase in restaurant revenues, and the smokefree bar law was associated with an increase in bar revenues.[21] Additionally, just one year after implementation of the New York City smokefree law, an evaluation found that restaurant and bar revenues in New York City increased by 8.7% from April 2003 through January 2004.[22]

These economic impact studies highlight one of the key benefits to implementing a comprehensive smokefree law, rather than relying on voluntary policies: an equal playing field for businesses. Businesses can compete fully on their merits, while protecting the health of their workers and patrons and promoting healthy communities.

Electronic Nicotine Delivery Systems

I will now summarize the current market and regulation of electronic nicotine delivery systems, or ENDS, as well as the current scientific literature on these products, including the effect of ENDS aerosol on nonusers.

The Current Regulation of Electronic Nicotine Delivery Systems

E-cigarettes are part of a class of products often referred to as electronic nicotine delivery systems (ENDS), which are battery-powered devices that provide doses of nicotine and other additives to the user in an aerosol.[23] There are currently multiple types of ENDS on the U.S. market, including e-cigarettes, e-hookahs, hookah pens, vape pens, e-cigars, and others. Some of these products are disposable varieties, while others can be refilled or recharged for repeated use.

ENDS, including e-cigarettes, are currently not regulated by the U.S. Food and Drug Administration (FDA) under the Family Smoking Prevention and Tobacco Control Act (FSPTCA), although FDA issued a proposed rule in April 2014 to regulate them under its tobacco product authorities.[24] FDA's authority, however, does not extend to certain key policy interventions related to ENDS, such as use in public places.[24]

Absent federal regulation, the current landscape of ENDS—including product design and availability, sales, marketing, use, and related legislation—is one of rapid change and high variability. Furthermore, given that ENDS have only recently entered the U.S. market, significant questions remain regarding ENDS' safety.

Scientific Evidence of the Health Effects of Electronic Nicotine Delivery Systems

We have very little information about the ingredients of ENDS liquids, or the exposure to harmful and potentially harmful constituents when using electronic cigarettes over the short-term or long-term. To date, manufacturers are not required to publish what chemicals are in the ENDS solution, or to perform or reveal results from systematic testing. Studies have demonstrated wide variability in design, operation, and contents and emissions of carcinogens, other toxicants, and nicotine from ENDS.[1] Depending on the brand, ENDS cartridges typically contain nicotine, a component to produce the aerosol (e.g., propylene glycol or glycerol), and flavorings (e.g., fruit, mint, or chocolate).[25] Harmful or potentially harmful constituents have also been documented in some ENDS, including tobacco-specific nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, and tobacco alkaloids, but at lower levels than in conventional cigarettes.[26] However, because there are hundreds of manufacturers and no manufacturing standards, there is no way to ensure that all ENDS have acceptably low levels of toxicants.

Smokefree Laws and ENDS

ENDS aerosol is not "water vapor." It contains nicotine and can contain additional toxins, and thus, it is not as safe as clean air.[27]

Although nicotine exposure in the absence of combustion is less hazardous than exposure to combusted conventional tobacco products, nicotine itself is not without risk.[1,28] Nicotine is addictive.[1] Pregnant women can transfer nicotine to their developing fetus, which can be toxic.[1] The evidence is also suggestive that nicotine exposure during adolescence may have lasting adverse consequences for brain development.[1] And for non-smokers, nicotine is an acute irritant, potentially causing headache, nausea, and discomfort; for former smokers, nicotine exposure can trigger cravings jeopardizing their abstinence.[29,30]

Furthermore, beyond the concerns of nonuser exposure to nicotine, there are also reports in the news media about the potential for e-cigarettes to be altered to deliver other psychoactive substances such THC, the active ingredient in marijuana.[31,32] Like nicotine, in an aerosolized form, THC is largely odorless, making it very difficult for the public to discern if they have been exposed.

Air containing ENDS aerosol is less safe than clean air, and ENDS use has the potential to involuntarily expose children and adolescents, pregnant women, and non-users to aerosolized nicotine and, if the products are altered, to other psychoactive substances. In fact, research has documented the presence of secondhand nicotine exposure using environmental monitoring and the measurement of biomarkers among exposed nonusers.[33] Therefore, clean air—free of both smoke and ENDS aerosol—remains the standard to protect health.

As of November 2014, three states and over 200 localities nationwide have incorporated ENDS into their smokefree laws.[34] In fact, North Dakota, the most recent state to pass a comprehensive statewide smokefree law, included the prohibition of ENDS use in indoor public places, including restaurants and bars.[34]

Conclusion

ENDS have a range of potential impacts on individual and population health, and significant questions remain regarding their safety However, given that these products emit nicotine—a psychoactive drug that can harm those involuntarily exposed—and other toxins, ENDS use should be prohibited in all places where smoking is prohibited in order to: protect children and adolescents, pregnant women, and non-smokers from involuntary exposure to aerosolized nicotine and potentially to other psychoactive substances, support enforcement of clean indoor air policies, and prevent renormalization of tobacco use.[1,34]

While we continue to learn more about the specific health effects of ENDS, the evidence shows that secondhand smoke causes considerable death and disease, costing the United States billions every year in direct health care costs and lost productivity. And unlike many other health hazards, these harms are completely preventable.

Thank you.

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[1] U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
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Electronic Smoking Devices and Secondhand Aerosol

Electronic smoking devices (or ESDs), which are often called **e-cigarettes**, heat and vaporize a solution that typically contains nicotine. The devices are metal or plastic tubes that contain a cartridge filled with a liquid that is vaporized by a battery-powered heating element. The aerosol is inhaled by the user when they draw on the device, as they would a regular tobacco cigarette, and the user exhales the aerosol into the environment.

"If you are around somebody who is using e-cigarettes, you are breathing an aerosol of exhaled nicotine, ultra-fine particles, volatile organic compounds, and other toxins." Dr. Stanton Glantz, Director for the Center for Tobacco Control Research and Education at the University of California, San Francisco.

Current Legislative Landscape

- As of October 1, 2014, **225 municipalities and three states include electronic smoking devices** as products that are prohibited from use in smokefree environments.

Constituents of Secondhand Aerosol

Electronic smoking devices (ESDs) do not just emit "harmless water vapor." **Secondhand aerosol (incorrectly called vapor by the industry) from ESDs contains nicotine, ultrafine particles and low levels of toxins** that are known to cause cancer.

- ESD aerosol is made up of a high concentration of ultrafine particles, and the particle concentration is higher than in conventional tobacco cigarette smoke.[1]

- Exposure to fine and ultrafine particles may exacerbate respiratory ailments like asthma, and constrict arteries which could trigger a heart attack.[2]

- At least 10 chemicals identified in ESD aerosol are on California's Proposition 65 list of carcinogens and reproductive toxins, also known as the Safe Drinking Water and Toxic Enforcement Act of 1986. The compounds that have already been identified in mainstream (MS) or secondhand (SS) ESD aerosol include: **Acetaldehyde (MS), Benzene (SS), Cadmium (MS), Formaldehyde (MS,SS), Isoprene (SS), Lead (MS), Nickel (MS), Nicotine (MS, SS), N-Nitrosonornicotine (MS, SS), Toluene (MS, SS).**[3,4]

- **ESDs contain and emit propylene glycol**, a chemical that is used as a base in ESD solution and is one of the primary components in the aerosol emitted by ESDs.
    - Short term exposure causes eye, throat, and airway irritation.[5]
    - Long term inhalation exposure can result in children developing asthma.[6]

- Even though propylene glycol is FDA approved for use in some products, the inhalation of vaporized nicotine in propylene glycol is not. Some studies show that heating propylene glycol changes its chemical composition, producing small amounts of propylene oxide, a known carcinogen.[7]

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- There are **metals in ESD aerosol, including chromium, nickel, and tin nanoparticles.**[8]

- FDA scientists found detectable levels of carcinogenic tobacco-specific nitrosamines in ESD aerosol.[9]

- People exposed to ESD aerosol absorb nicotine (measured as cotinine), with one study showing levels comparable to passive smokers.[10]

- **Diethylene Glycol**, a poisonous organic compound, was also detected in ESD aerosol.[11]

- **Exhaled ESD aerosol contained propylene glycol, glycerol, flavorings, and nicotine, along with acetone, formaldehyde, acetaldehyde, propanal, diacetin, and triacitine.**[12]

- Many of the elements identified in the aerosol are known to **cause respiratory distress and disease.** The aerosol contained particles >1 μm comprised of tin, silver, iron, nickel, aluminum, and silicate and nanoparticles (<100 nm) of tin, chromium and nickel. The concentrations of nine of eleven elements in ESD aerosol were higher than or equal to the corresponding concentrations in conventional cigarette smoke.[13]

- ESDs cause exposure to different chemicals than found in conventional cigarettes and there is a need for risk evaluation for both primary and passive exposure to the aerosol in smokers and nonsmokers.[14]

- Short term use of ESD has been shown to increase respiratory resistance and impair lung function, which may result in difficulty breathing.[15]

- The first study to look at exposure to aerosol from ESDs in real-use conditions found that non-smokers who were exposed to conventional cigarette smoke and ESD aerosol absorbed similar levels of nicotine.[16]

- The "E-cigarettes do not produce a vapor (gas), but rather a dense visible aerosol of liquid sub-micron droplets consisting of glycols, nicotine, and other chemicals, some of which are carcinogenic (e.g., formaldehyde, metals like cadmium, lead, & nickel, and nitrosamines)." ASHRAE concluded that ESDs emit harmful chemicals into the air and need to be regulated in the same manner as tobacco smoking.[17]

- Some chemicals used as flavorings in ESD liquid, which are approved by the FDA for food use (ingestion), are not approved for inhalation and are associated with respiratory disease when inhaled.[18]

- There is a risk of thirdhand exposure to nicotine released from ESD aerosol that deposits on indoor surfaces.[19]

- Overall, ESDs are a new source of **Volatile Organic Compounds (VOCs) and ultrafine/fine particles in the indoor environment,** thus resulting in "passive vaping."[20]

- The World Health Organization (WHO) recommends that ESDs not be used indoors, especially in smokefree environments, in order to minimize the risk to bystanders of breathing in the aerosol emitted by the devices and to avoid undermining the enforcement of smokefree laws.[21]

- The American Industrial Hygiene Association (AIHA) also recommends that ESDs be included in smokefree laws: "***Because e-cigarettes are a potential source of pollutants (such as airborne nicotine, flavorings, and thermal degradation products), their use in the indoor***

environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants."[22]

ESD aerosol is a new source of pollution and toxins being emitted into the environment. We do not know the long-term health effects of ESD use and although the industry marketing of the product implies that these products are harmless, the aerosol that ESD emit is not purely water vapor.

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March 3, 2015

To Whom it May Concern:

I am writing in support of House Bill 40 (HB40), as introduced by Representative Bob Herron.

We strongly support prohibiting the use of Electronic Nicotine Delivery Systems (ENDS or E-Cigs) in places open to the public and places of employment. We support inclusion of E-Cigs in the definition of "tobacco product" and "smoke or smoking" in the smoke-free workplace law, and to prohibit the use of E-cigs in the places where smoking is prohibited. Including electronic smoking devices will protect the public from involuntary exposure to psychoactive substances and health effects thereof, both known and unknown.

HB40 is the first step to protecting employees and the public from inadvertent exposure to nicotine and other chemicals and poisons. E-Cigs are not FDA approved smoking cessation devices and do not emit harmless water vapor. Studies have found formaldehyde, benzene and tobacco-specific nitrosamines (a carcinogen) coming from the secondhand emissions from e-cigarettes. Nicotine levels due to secondhand aerosol exposure have been found to be equivalent to those exposed to secondhand smoke.

The standard must be clean air, free of both smoke and aerosol.

Sincerely,

Marge Stoneking
Executive Director

March 4, 2015

Representative Bob Herron
Alaska State Capitol
Juneau, AK

Dear Representative Herron:

On behalf of the American Cancer Society Cancer Action Network (ACS CAN), I am writing in support of House Bill 40. Thank you for bringing the potential hazards of secondhand electronic cigarette aerosol to the public's attention through this legislation.

A growing number of studies have examined the contents of e-cigarette aerosol. Unlike a vapor, an aerosol contains fine particles of liquid, solid, or both. Propylene glycol, nicotine, and flavorings were most commonly found in e-cigarette aerosol. Other studies have found the aerosol to contain heavy metals, volatile organic compounds and tobacco-specific nitrosamines, among other potentially harmful chemicals.

While the health effects of e-cigarettes are currently under study, there are serious questions about the safety of inhaling the substances in e-cigarette aerosol. Studies have shown that the use of e-cigarettes can cause short-term lung changes and irritations, while the long-term health effects are unknown. Both exposure to and health effects of secondhand aerosol from e-cigarettes require further research, but preliminary studies indicate nonusers can be exposed to the same potentially harmful chemicals as users, including nicotine, ultrafine particles and volatile organic compounds.

ACS CAN advocates for comprehensive smoke-free laws in all workplaces to protect workers and the public from the harmful effects of secondhand exposure and to create communities that support tobacco-free living. Electronic cigarettes, or e-cigarettes, including supposed non-nicotine e-cigarettes, should also be prohibited in all workplaces, restaurants, and bars to protect against secondhand exposure to nicotine and other potentially harmful chemicals, to ensure the enforcement of existing smoke-free laws are not compromised, and that the public health benefits of a smoke-free laws are not undermined.

Thank you again for bringing this important issue forward for public discourse, and for your work to protect the health of all Alaskans.

Sincerely,

Emily E. Nenon
Alaska Government Relations Director
3851 Piper Street, Suite U240 • Anchorage, AK • 99508
Phone 907.277.8696 • Fax 907.273.2073

THE STATE of ALASKA
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Electronic Cigarette and Aerosol Emissions Product Update and Position

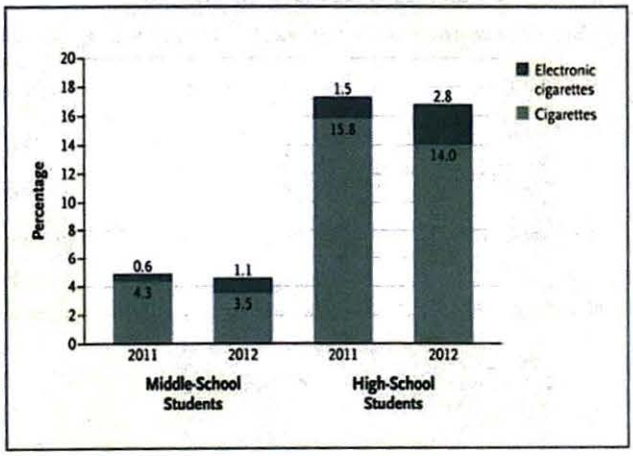
Electronic cigarettes (e-cigarettes, e-cigs, e-hookah or vape pens) are marketed by the Tobacco Industry and other manufacturers as a new nicotine delivery system. These battery-powered devices heat nicotine, flavor additives and other chemicals, to produce an aerosol inhaled by the user. Their production is unregulated and varies widely - recent research and consumer experience reflect questionable product quality, content and safety.[1] With only limited research to date, the presence of toxins and cancer-causing agents as well as the health effects of their use are not yet fully known.

Chemical and Toxin Emissions in E-Cigarette Aerosol

- E-cigarettes do not just emit "harmless water vapor." Secondhand e-cigarette aerosol (incorrectly called vapor by the industry) contains nicotine, ultrafine particles and low levels of toxins that are known to cause cancer.[2] The FDA's initial investigation into the content of e-cigarettes found the aerosol potentially hazardous to the public's health due to tobacco-specific nitrosamines and other volatile organic compounds.[3]
- Studies have shown the presence of heavy metals and carcinogens in e-cigarette aerosol.[4,5,6]
- Propylene glycol, a chemical that is used as a base in e-cigarette solution, is one of the primary components in the aerosol emitted by e-cigarettes.
    - Short term exposure causes eye, throat and airway irritation.[7]
    - Long term inhalation exposure can result in children developing asthma.[8]
- Because they look like traditional cigarettes and emit the aerosol, e-cigarettes have the potential to negatively impact social norms and make smokefree workplace policies harder to enforce. In some states and communities, the public is being protected from potential health harms through local ordinances and regulations prohibiting e-cigarette use in indoor environments.

Industry Marketing and the Rise in Youth E-Cigarette Use

- The U.S. Food and Drug Administration (FDA) does not currently regulate these products.
- Marketers use child-friendly flavors such as "Gumi Bearz" or "Mount N' Do"[9], themes of rebellion, and celebrity endorsements - strategies long used to market traditional cigarettes to children.
- Sales of e-cigarettes in the U.S. have doubled since 2011 to $1.7 billion in 2013.[3]
- Although youth smoking rates have decreased, e-cigarette use has risen across the U.S. and, alarmingly, doubled among middle and high school students between 2011 and 2012.[10]



Use of Cigarettes and Electronic Cigarettes by U.S. Students in 2011 and 2012. Data are from the Centers for Disease Control and Prevention[7]

Lack of Reliability, Safety Require Regulation and Extensive Research

E-cigarettes contain varying levels of nicotine - a tobacco-derived product – which can initiate and/or prolong nicotine addiction. [1]

- These unregulated products may provide uncontrolled doses of nicotine and other harmful chemicals - users have no way of being certain how much is being inhaled or exhaled. [11]
- Ingestion or skin contact with nicotine solution from a cartridge can lead to nicotine poisoning and can be deadly, especially to children and animals. Accidental nicotine poisonings and lethal doses are a serious concern because the refill "juice" is not sold in child-resistant containers.
- Dozens of Alaskan youth are treated for nicotine poisoning every year. [12]
- Nicotine affects the nervous system and heart, and can negatively affect the developing brain. It should not be made available to minors.

E-Cigarettes are Not an FDA-approved Cessation Device

- The FDA has not approved e-cigarettes as an effective method to help smokers quit.
- FDA-approved tobacco cessation products provide controlled doses of nicotine and have been tested and regulated as cessation products.
- Alaska's Tobacco Quit Line is a free service for all Alaskans ready to quit tobacco. Counseling and FDA-approved Nicotine Replacement Therapies, when used in combination, have been shown to be a safe and effective way to quit. Call 1-800 QUIT NOW or visit www.alaskaquitline.com to enroll today.

Alaska has seen tremendous progress in reducing smoking but we must remain ever vigilant to protect our young people. Because they are unregulated, the e-cigarette industry has grown markedly over the last few years using old tactics like celebrities to promote and glamorize their use, addicting those most impressionable. More research is needed on the long-term health effects, but we can take steps today to protect our young people.

Ward B. Hurlburt, M.D., MPH
Chief Medical Officer, Alaska Department of Health and Social Services

May 21, 2014

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E-Cigarettes & Smoke-free Laws

ACS CAN's Current Views

E-cigarette use should be prohibited in all workplaces, restaurants, and bars.

ACS CAN advocates for comprehensive smoke-free laws in all workplaces to protect workers and the public from the harmful effects of secondhand exposure and to create communities that support tobacco-free living. Electronic cigarettes, or e-cigarettes, including supposed non-nicotine e-cigarettes, should also be prohibited in all workplaces, restaurants, and bars to protect against secondhand exposure to nicotine and other potentially harmful chemicals, to ensure the enforcement of existing smoke-free laws are not compromised, and that the public health benefits of a smoke-free laws are not undermined.

E-cigarette aerosol can contain nicotine and other potentially harmful chemicals.

E -cigarettes are typically battery-operated products designed to deliver a heated solution, or aerosol of nicotine and other chemicals, to the user. E-cigarettes can be disposable or consist of a rechargeable, battery-operated heating element; a replaceable or refillable cartridge that may contain nicotine, flavoring agents, and other chemicals (sometimes called "e-juices"); and an atomizer that uses heat to convert the contents of the cartridge into an aerosol that is inhaled by the user.[1]

A growing number of studies have examined the contents of e-cigarette aerosol. Unlike a vapor, an aerosol contains fine particles of liquid, solid, or both. Propylene glycol, nicotine, and flavorings were most commonly found in e-cigarette aerosol. Other studies have found the aerosol to contain heavy metals, volatile organic compounds and tobacco-specific nitrosamines, among other potentially harmful chemicals.[2,3] A 2009 study done by the FDA found cancer-causing substances in several of the e-cigarette samples tested.[4] Additionally, Food and Drug Administration (FDA) tests found nicotine in some e-cigarettes that claimed to contain no nicotine.

Chemicals identified in some e-cigarette aerosol include:

- Propylene glycol
- Nicotine
- Tobacco-specific nitrosamines
- Metals
- Volatile organic compounds
- Polycyclic aromatic hydrocarbons
- Flavorings

Firsthand exposure to the aerosol comes from personal use of an e-cigarette. Secondhand exposure occurs when the user exhales the aerosol, at which time, a nonuser can be exposed. The level of secondhand exposure to a nonuser will depend on a number of factors including the type of e-cigarette used, particle sizes in the aerosol, how the e-cigarette is used, and other environmental factors such as air flow and room size.

While the health effects of e-cigarettes are currently under study, there are still serious questions about the safety of inhaling the substances in e-cigarette aerosol. Studies have shown that the use of e-cigarettes can cause short-term lung changes and irritations, while the long-term health effects are unknown.[5] Both exposure to and health effects of secondhand aerosol from e-cigarettes require further research, but preliminary studies indicate nonusers can be exposed to the same potentially harmful chemicals as users, including nicotine, ultrafine particles and volatile organic compounds.[67] This exposure could be especially problematic for vulnerable populations such as children, pregnant women, and people with heart disease depending on the level of exposure.

Finally, it is important to establish the potential exposure and associated risks of e-cigarette aerosol to users and nonusers, in addition to comparing those risks to exposure to cigarette smoke, as several studies have done.

October 2014

E-cigarette use in workplaces, restaurants, and bars can undermine the public health benefits of smoke-free laws and compromise enforcement.

Tobacco users are not the only ones who breathe its deadly smoke—all the people around them are forced to inhale it too. Recognizing that there is no safe level of secondhand smoke exposure, 24 states and more than 673 localities have comprehensive smoke-free laws.[8] These laws not only protect nonusers from exposure to secondhand smoke, they also reduce the acceptability of smoking which reduces the number of people, especially youth, who start smoking and increases quit attempts by smokers. The increased protection and reduced acceptability have led to lower smoking rates and improved health status, including fewer heart attacks and cancers.[9]

The use of e-cigarettes in workplaces, restaurants, and bars can undermine the public health benefits that have been and continue to be achieved by smoke-free laws. E-cigarette users who continue to use cigarettes will not experience the health benefits of quitting, and nonusers can be exposed to their secondhand aerosol. Because some e-cigarettes are designed to look like cigarettes and cigars, the unacceptability of smoking in these places could be compromised which could lead to new users or a reduction in current users who quit. Additionally, from a practical standpoint, business owners can face difficulty when enforcing smoke-free laws if e-cigarette use is permitted because of their designs. These risks do not prevent some e-cigarette manufacturers from specifically marketing their products for use in places where smoking is prohibited.

E-cigarette use is on the rise and requires federal, state, and local action.

Since the introduction of e-cigarettes to the U.S. market approximately 7 years ago, the marketing and use of these products have increased.

- Youth: A study from the Centers for Disease Control and Prevention (CDC) found that e-cigarette use increased from 3.3 to 6.8 percent among middle and high school students between 2011 and 2012, resulting in an estimated 1.78 million youth who have tried e-cigarettes.[10]
- Adults: A study looking at data from 2010-2013 found an increase in the number of adults who have ever used e-cigarettes, from 3.3 to 8.5 percent. In 2013, 36.5 percent of current smokers had ever tried e-cigarettes, as compared to 79.8 percent of former smokers and 1.2 percent of never smokers.[11]

While e-cigarette manufacturers may claim the ingredients are just "water vapor" or "safe," without federal regulation there is no sure way for e-cigarette users to know what they are consuming. Nor is there any way of knowing what nonusers are exposed to and the extent of the risk to their health. Additionally, there are hundreds of types of e-cigarettes on the market today and the products vary considerably by ingredients, and quality control and assurance. Prohibiting the use of e-cigarettes in workplaces, restaurants, and bars can protect the public health by preventing nonusers from being exposed nicotine and other potentially harmful chemicals in these products.

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Electronic Smoking Devices and Secondhand Aerosol

Electronic smoking devices (or ESDs), which are often called **e-cigarettes**, heat and vaporize a solution that typically contains nicotine. The devices are metal or plastic tubes that contain a cartridge filled with a liquid that is vaporized by a battery-powered heating element. The aerosol is inhaled by the user when they draw on the device, as they would a regular tobacco cigarette, and the user exhales the aerosol into the environment.

"If you are around somebody who is using e-cigarettes, you are breathing an aerosol of exhaled nicotine, ultra-fine particles, volatile organic compounds, and other toxins." Dr. Stanton Glantz, Director for the Center for Tobacco Control Research and Education at the University of California, San Francisco.

Current Legislative Landscape

- As of October 1, 2014, **225 municipalities and three states include electronic smoking devices** as products that are prohibited from use in smokefree environments.

Constituents of Secondhand Aerosol

Electronic smoking devices (ESDs) do not just emit "harmless water vapor." **Secondhand aerosol (incorrectly called vapor by the industry) from ESDs contains nicotine, ultrafine particles and low levels of toxins** that are known to cause cancer.

- ESD aerosol is made up of a high concentration of ultrafine particles, and the particle concentration is higher than in conventional tobacco cigarette smoke.[1]

- Exposure to fine and ultrafine particles may exacerbate respiratory ailments like asthma, and constrict arteries which could trigger a heart attack.[2]

- At least 10 chemicals identified in ESD aerosol are on California's Proposition 65 list of carcinogens and reproductive toxins, also known as the Safe Drinking Water and Toxic Enforcement Act of 1986. The compounds that have already been identified in mainstream (MS) or secondhand (SS) ESD aerosol include: **Acetaldehyde (MS), Benzene (SS), Cadmium (MS), Formaldehyde (MS,SS), Isoprene (SS), Lead (MS), Nickel (MS), Nicotine (MS, SS), N-Nitrosonornicotine (MS, SS), Toluene (MS, SS).**[3,4]

- **ESDs contain and emit propylene glycol**, a chemical that is used as a base in ESD solution and is one of the primary components in the aerosol emitted by ESDs.
    - Short term exposure causes eye, throat, and airway irritation.[5]
    - Long term inhalation exposure can result in children developing asthma.[6]

- Even though propylene glycol is FDA approved for use in some products, the inhalation of vaporized nicotine in propylene glycol is not. Some studies show that heating propylene glycol changes its chemical composition, producing small amounts of propylene oxide, a known carcinogen.[7]

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- There are **metals in ESD aerosol, including chromium, nickel, and tin nanoparticles.**[8]
- FDA scientists found detectable levels of carcinogenic tobacco-specific nitrosamines in ESD aerosol.[9]
- People exposed to ESD aerosol absorb nicotine (measured as cotinine), with one study showing levels comparable to passive smokers.[10]
- **Diethylene Glycol**, a poisonous organic compound, was also detected in ESD aerosol.[11]
- **Exhaled ESD aerosol contained propylene glycol, glycerol, flavorings, and nicotine, along with acetone, formaldehyde, acetaldehyde, propanal, diacetin, and triacitine.**[12]
- Many of the elements identified in the aerosol are known to **cause respiratory distress and disease.** The aerosol contained particles >1 μm comprised of tin, silver, iron, nickel, aluminum, and silicate and nanoparticles (<100 nm) of tin, chromium and nickel. The concentrations of nine of eleven elements in ESD aerosol were higher than or equal to the corresponding concentrations in conventional cigarette smoke.[13]
- ESDs cause exposure to different chemicals than found in conventional cigarettes and there is a need for risk evaluation for both primary and passive exposure to the aerosol in smokers and nonsmokers.[14]
- Short term use of ESD has been shown to increase respiratory resistance and impair lung function, which may result in difficulty breathing.[15]
- The first study to look at exposure to aerosol from ESDs in real-use conditions found that non-smokers who were exposed to conventional cigarette smoke and ESD aerosol absorbed similar levels of nicotine.[16]
- The "E-cigarettes do not produce a vapor (gas), but rather a dense visible aerosol of liquid sub-micron droplets consisting of glycols, nicotine, and other chemicals, some of which are carcinogenic (e.g., formaldehyde, metals like cadmium, lead, & nickel, and nitrosamines)." ASHRAE concluded that ESDs emit harmful chemicals into the air and need to be regulated in the same manner as tobacco smoking.[17]
- Some chemicals used as flavorings in ESD liquid, which are approved by the FDA for food use (ingestion), are not approved for inhalation and are associated with respiratory disease when inhaled.[18]
- There is a risk of thirdhand exposure to nicotine released from ESD aerosol that deposits on indoor surfaces.[19]
- Overall, ESDs are a new source of **Volatile Organic Compounds (VOCs) and ultrafine/fine particles in the indoor environment,** thus resulting in "passive vaping."[20]
- The World Health Organization (WHO) recommends that ESDs not be used indoors, especially in smokefree environments, in order to minimize the risk to bystanders of breathing in the aerosol emitted by the devices and to avoid undermining the enforcement of smokefree laws.[21]
- The American Industrial Hygiene Association (AIHA) also recommends that ESDs be included in smokefree laws: "***Because e-cigarettes are a potential source of pollutants (such as airborne nicotine, flavorings, and thermal degradation products), their use in the indoor***

environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants."[22]

ESD aerosol is a new source of pollution and toxins being emitted into the environment. We do not know the long-term health effects of ESD use and although the industry marketing of the product implies that these products are harmless, the aerosol that ESD emit is not purely water vapor.

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TESTIMONY ON THE SCIENTIFIC EVIDENCE ON THE PUBLIC HEALTH EFFECTS OF SECONDHAND SMOKE AND ELECTRONIC NICOTINE DELIVERY SYSTEMS AEROSOL

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ALASKA STATE LEGISLATURE
JUNEAU, ALASKA

February 12, 2015

Thank you for the opportunity to submit testimony today about the health impact of secondhand smoke exposure and aerosol from electronic nicotine delivery systems, including e-cigarettes. I am Dr. Brian King with the Office on Smoking and Health, Centers for Disease Control and Prevention (CDC), the lead Federal agency for comprehensive tobacco prevention and control. I am the author of over 50 peer-reviewed scientific articles on tobacco prevention and control. I am also a contributing author to the 50th anniversary Surgeon General's report, *The Health Consequences of Smoking—50 Years of Progress*, as well as the lead author of CDC's 2014 evidence-based state guide, *Best Practices for Comprehensive Tobacco Control Programs*. I am an international subject matter expert on the issue of secondhand smoke, and have worked for nearly a decade to provide sound scientific evidence to inform tobacco control policy and practice, as well as to effectively communicate this information to key stakeholders at the national, state, and local levels. I am also an international subject matter expert on electronic nicotine delivery systems and have authored multiple peer-reviewed publications on the issues of electronic nicotine delivery system use among adults and youth, susceptibility among youth, and public health policy related to these products.

For the record, I am submitting expert written testimony today at the request of Alison Kulas, Program Manager of the state of Alaska's Tobacco Prevention and Control Program, to discuss the scientific evidence for eliminating exposure to secondhand smoke, as well as the public health effects of electronic nicotine delivery systems, including exposure to the aerosol emitted from these products.

Also for the record, this testimony is not for or against any specific legislative proposal.

The Health Effects of Secondhand Smoke Exposure

I will begin by discussing the harms of secondhand smoke exposure, which has a robust scientific evidence base reflecting decades of research.

Secondhand smoke from burning tobacco products is deadly. In adults, secondhand smoke exposure causes stroke, lung cancer, and coronary heart disease, as well as nasal irritation and reproductive effects in women, such as low birth weight.[1] Children who are exposed to secondhand smoke are at an increased risk for sudden infant death syndrome (SIDS), acute respiratory infections such as pneumonia and bronchitis, middle ear disease, more severe asthma, respiratory symptoms, and slowed lung growth.[1]

The scientific evidence on the harmful effects of secondhand smoke exposure is well-documented. The Surgeon General first concluded that secondhand smoke causes lung cancer in 1986.[2] In 2006, the Surgeon General's Report on *The Health Consequences of Involuntary Exposure to Tobacco Smoke* concluded that there is no risk-free level of secondhand smoke exposure.[3] Separating smokers and nonsmokers, using designated smoking areas, cleaning or filtering the air, and using separately ventilated areas do not work.[3]

In 2010, the Surgeon General's Report on *How Tobacco Smoke Causes Disease* reaffirmed the conclusion that there is no risk-free level of exposure to tobacco smoke.[4] The report and subsequent findings also documented how the complex mix of chemicals in tobacco smoke causes disease, including finding that cigarette smoke contains 7,000 chemicals, 250 of which are toxic and nearly 70 of which cause cancer.[1,4]

In 2014, the 50th Anniversary Surgeon General's Report on *The Health Consequences of Smoking* further affirmed these findings.[1] The report estimates that secondhand smoke exposure increases the risk of stroke by 20 to 30%.[1]

The effects of secondhand smoke exposure on the body are immediate.[3] A 2011 study reported that secondhand smoke exposure can produce adverse inflammatory and respiratory effects within 60 minutes of exposure and that these effects persist for at least three hours after the exposure.[5] These findings are significant; the concern is not just secondhand smoke exposure for guests during a meal at a restaurant, but also the compounded health effects for an employee working an eight-hour shift in a smoke-filled restaurant or bar.[3]

The Burden of Secondhand Smoke Exposure

Secondhand smoke exposure costs nonsmokers—especially vulnerable populations, such as children—their health and wellbeing. These costs are born not just by individuals, but by society: exposure to secondhand smoke costs the United States billions of dollars in lost productivity and medical expenses every year.[1]

As a result of the considerable body of evidence documenting the adverse effects of secondhand smoke, substantial progress has been made toward eliminating nonsmokers' exposure to this preventable health hazard over the last 50 years.[1] Recent assessments of cotinine, a metabolite of nicotine and biomarker of recent secondhand smoke exposure, indicates that about 1 in 4 Americans continue to be exposed to secondhand smoke.[6]

In the past 50 years, secondhand smoke exposure is estimated to have caused nearly 2.5 million deaths in nonsmoking Americans.[1] Each year, an estimated 7,330 lung cancer deaths and 33,950 coronary heart disease deaths are attributable to secondhand smoke exposure.[1] The smoking-attributable economic costs in the United States also include about $5.6 billion in lost productivity every year due to secondhand smoke exposure.[1] Many of these deaths and this lost productivity could be prevented if comprehensive smokefree laws prohibiting smoking in all indoor areas of worksites, restaurants, and bars were implemented nationwide.[1]

Preventing Secondhand Smoke Exposure

We know what works to prevent these harms. In 2006, the Surgeon General concluded that eliminating smoking in indoor spaces is the only way to fully protect nonsmokers from secondhand smoke exposure.[3] In 2009, the World Health Organization's International Agency for Research on Cancer reiterated these findings, concluding that smokefree policies lead to substantial declines in secondhand smoke exposure, citing air quality improvements of up to 90% in high-risk settings, such as bars.[7]

The latest Surgeon General's report delved deeper into the science behind the success of smokefree laws in protecting people's health. Specifically, the report concluded that smokefree laws directly cause reductions in coronary events (especially heart attacks), making comprehensive smokefree laws one of the most effective and cost-effective approaches for reducing heart disease—the leading cause of death—in the country.[1]

Finally, beyond reducing exposure to secondhand smoke, smokefree laws also lower smoking rates as a whole, especially among vulnerable youth and young adults.[1] Both the Surgeon General and the U.S. Guide to Community Preventive Services conclude that smokefree laws in workplaces and communities help smokers quit and reduce tobacco use.[1,8] In addition, smokefree workplaces and communities make youth and young adults less likely to start smoking due to a number of factors, including lower visibility of people who smoke, fewer opportunities to smoke alone or with others, and reduced social acceptability for smoking.[1] The implementation of smokefree laws also increase the adoption of voluntary smokefree rules in homes, which can further protect nonsmokers—especially the most vulnerable that are exposed to secondhand smoke in the home, such as children.[1]

CDC defines a comprehensive smokefree law as one that prohibits smoking at all times, in all indoor areas of all workplaces and public places, including restaurants and bars. If a law allows exemptions for designated or ventilated smoking areas in workplaces, restaurants or bars, the state or community is not considered to have a comprehensive smokefree law. As of January 2015, CDC has determined that 26 states, Puerto Rico, the District of Columbia, and over 697 other communities in the United States have comprehensive smokefree laws in effect.[9,10]

Smokefree policies in hospitality venues such as restaurants, bars, and casinos protect employees and patrons from the health effects of secondhand smoke. These policies are associated with improved indoor air quality and with reduced secondhand smoke exposure, reduced sensory and respiratory symptoms, and improved lung function in nonsmoking employees, which translates into improved productivity.[2] Comprehensive smokefree laws

are also associated with rapid reductions in hospitalizations due to heart attacks and strokes.[11] These improvements occur within months after implementation.[12,13] For instance, in Colorado, following the implementation of a comprehensive smokefree law in 2006, the state saw a 23 percent drop in ambulance calls from these venues.[14] However, there was no change in ambulance calls from casinos until the law was expanded in 2008 to include casinos—after which, ambulance calls from casinos dropped nearly 20 percent.[14] Again, this illustrates that these health improvements are lifesaving and nearly immediate.

The Business Case for Smokefree Laws

The evidence concerning the economic impact of smokefree laws is also well-documented. In 2006, the Surgeon General concluded that "evidence from peer-reviewed studies shows that smokefree policies and regulations do not have an adverse economic impact on the hospitality industry."[3]

These findings have been replicated numerous times at the international, state, and local levels.[1,3,7] In 2009, the International Agency for Research on Cancer conducted a comprehensive review of 97 studies from eight countries on the economic impact of smokefree policies and found that studies consistently conclude that smokefree policies do not harm business.[7]

At the state and local level, studies consistently reiterate these conclusions. The largest analysis of the impact of local smokefree ordinances, which examined nine states (Alabama, Indiana, Kentucky, Mississippi, Missouri, South Carolina, Texas, and West Virginia), found that smokefree laws do not have a negative impact on either employment or sales in restaurants and bars.[15] A study of El Paso, Texas's smokefree policy found that the law had no effect on restaurant and bar revenue.[16] Furthermore, a 2007 study on the economic impact of a smokefree law in Lexingon-Fayette County, Kentucky found that "no important economic harm stemmed from the smoke-free legislation…despite the fact that Lexington is located in a tobacco-producing state with higher-than-average smoking rates."[17]

Further reviews of the literature have also found that, in some cases, a smokefree policy produces positive effects for local businesses.[18,19,20] A number of cities and localities have experienced these positive effects. For instance, an in-depth analysis of tax revenue data in California after the state implemented their smokefree restaurant law (in 1995) and bar law (in 1998) found that the smokefree restaurant law was associated with an increase in restaurant revenues, and the smokefree bar law was associated with an increase in bar revenues.[21] Additionally, just one year after implementation of the New York City smokefree law, an evaluation found that restaurant and bar revenues in New York City increased by 8.7% from April 2003 through January 2004.[22]

These economic impact studies highlight one of the key benefits to implementing a comprehensive smokefree law, rather than relying on voluntary policies: an equal playing field for businesses. Businesses can compete fully on their merits, while protecting the health of their workers and patrons and promoting healthy communities.

Electronic Nicotine Delivery Systems

I will now summarize the current market and regulation of electronic nicotine delivery systems, or ENDS, as well as the current scientific literature on these products, including the effect of ENDS aerosol on nonusers.

The Current Regulation of Electronic Nicotine Delivery Systems

E-cigarettes are part of a class of products often referred to as electronic nicotine delivery systems (ENDS), which are battery-powered devices that provide doses of nicotine and other additives to the user in an aerosol.[23] There are currently multiple types of ENDS on the U.S. market, including e-cigarettes, e-hookahs, hookah pens, vape pens, e-cigars, and others. Some of these products are disposable varieties, while others can be refilled or recharged for repeated use.

ENDS, including e-cigarettes, are currently not regulated by the U.S. Food and Drug Administration (FDA) under the Family Smoking Prevention and Tobacco Control Act (FSPTCA), although FDA issued a proposed rule in April 2014 to regulate them under its tobacco product authorities.[24] FDA's authority, however, does not extend to certain key policy interventions related to ENDS, such as use in public places.[24]

Absent federal regulation, the current landscape of ENDS—including product design and availability, sales, marketing, use, and related legislation—is one of rapid change and high variability. Furthermore, given that ENDS have only recently entered the U.S. market, significant questions remain regarding ENDS' safety.

Scientific Evidence of the Health Effects of Electronic Nicotine Delivery Systems

We have very little information about the ingredients of ENDS liquids, or the exposure to harmful and potentially harmful constituents when using electronic cigarettes over the short-term or long-term. To date, manufacturers are not required to publish what chemicals are in the ENDS solution, or to perform or reveal results from systematic testing. Studies have demonstrated wide variability in design, operation, and contents and emissions of carcinogens, other toxicants, and nicotine from ENDS.[1] Depending on the brand, ENDS cartridges typically contain nicotine, a component to produce the aerosol (e.g., propylene glycol or glycerol), and flavorings (e.g., fruit, mint, or chocolate).[25] Harmful or potentially harmful constituents have also been documented in some ENDS, including tobacco-specific nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, and tobacco alkaloids, but at lower levels than in conventional cigarettes.[26] However, because there are hundreds of manufacturers and no manufacturing standards, there is no way to ensure that all ENDS have acceptably low levels of toxicants.

Smokefree Laws and ENDS

ENDS aerosol is not "water vapor." It contains nicotine and can contain additional toxins, and thus, it is not as safe as clean air.[27]

Although nicotine exposure in the absence of combustion is less hazardous than exposure to combusted conventional tobacco products, nicotine itself is not without risk.[1,28] Nicotine is addictive.[1] Pregnant women can transfer nicotine to their developing fetus, which can be toxic.[1] The evidence is also suggestive that nicotine exposure during adolescence may have lasting adverse consequences for brain development.[1] And for non-smokers, nicotine is an acute irritant, potentially causing headache, nausea, and discomfort; for former smokers, nicotine exposure can trigger cravings jeopardizing their abstinence.[29,30]

Furthermore, beyond the concerns of nonuser exposure to nicotine, there are also reports in the news media about the potential for e-cigarettes to be altered to deliver other psychoactive substances such THC, the active ingredient in marijuana.[31,32] Like nicotine, in an aerosolized form, THC is largely odorless, making it very difficult for the public to discern if they have been exposed.

Air containing ENDS aerosol is less safe than clean air, and ENDS use has the potential to involuntarily expose children and adolescents, pregnant women, and non-users to aerosolized nicotine and, if the products are altered, to other psychoactive substances. In fact, research has documented the presence of secondhand nicotine exposure using environmental monitoring and the measurement of biomarkers among exposed nonusers.[33] Therefore, clean air—free of both smoke and ENDS aerosol—remains the standard to protect health.

As of November 2014, three states and over 200 localities nationwide have incorporated ENDS into their smokefree laws.[34] In fact, North Dakota, the most recent state to pass a comprehensive statewide smokefree law, included the prohibition of ENDS use in indoor public places, including restaurants and bars.[34]

Conclusion

ENDS have a range of potential impacts on individual and population health, and significant questions remain regarding their safety However, given that these products emit nicotine—a psychoactive drug that can harm those involuntarily exposed—and other toxins, ENDS use should be prohibited in all places where smoking is prohibited in order to: protect children and adolescents, pregnant women, and non-smokers from involuntary exposure to aerosolized nicotine and potentially to other psychoactive substances, support enforcement of clean indoor air policies, and prevent renormalization of tobacco use.[1,34]

While we continue to learn more about the specific health effects of ENDS, the evidence shows that secondhand smoke causes considerable death and disease, costing the United States billions every year in direct health care costs and lost productivity. And unlike many other health hazards, these harms are completely preventable.

Thank you.

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Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks?

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Abstract

The aim of this paper is to review available data on chemistry of aerosols and liquids of electronic cigarettes and to make predictions about compliance with occupational exposure limits of personal exposures of vapers (e-cigarette users) to compounds found in the aerosol. Both peer-reviewed and "grey" literatures were accessed and more than 9000 observations of highly variable quality were extracted. Comparisons to the most universally recognized workplace exposure standards, Threshold Limit Values (TLVs), were conducted under "worst case" assumptions about both chemical content of aerosol and liquids as well as behavior of vapers. The calculations reveal that there was no evidence of potential for exposures of e-cigarette users to contaminants that are associated with risk to health at a level that would warrant attention if it were an involuntary workplace exposures by approaching half of TLV. The vast majority of predicted exposures are <<1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was plausible. Only exposures to the declared major ingredients -- propylene glycol and glycerin -- warrant attention because of precautionary nature of TLVs for exposures to hydrocarbons with no established toxicity. Comparing the exposure to nicotine to existing occupational exposure standards is not valid so long as nicotine-containing liquid is not mislabeled as nicotine-free. It must be noted that the quality of much of the data that was available for these assessment was poor, and so much can be done to improve certainty in this risk assessment. However, the existing research is of the quality that is comparable with most workplace assessments for novel technologies. In summary, an analysis of current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to *contaminants* of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (contaminants *plus declared ingredients*), if it were an emission from industrial process, creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.

Keywords: vaping, e-cigarettes, tobacco harm reduction, risk assessment, aerosol, occupational exposure limit

Introduction

Electronic cigarettes (also known as e-cigarettes) are generally recognized as a safer alternative to combusted tobacco products (reviewed in [1]), but there are conflicting claims about the degree to which these products warrant concern for the health of the vapers (e-cigarette users). A vaper inhales aerosol generated during heating of liquid contained in the e-cigarette. The technology and patterns of use are summarized by Etter [1], though there is doubt about how current, complete and accurate this information is. Rather conclusive evidence has been amassed to date on comparison of the chemistry of aerosol generated by electronic cigarettes to cigarette smoke [2-8]. However, it is meaningful to consider the question of whether aerosol generated by electronic cigarettes would warrant health concerns on its own, in part because vapers will include persons who would not have been smokers and for whom the question of harm reduction from smoking is therefore not relevant, and perhaps more importantly, simply because there is value in minimizing the harm of those practicing harm reduction.

One way of approaching risk evaluation in this setting is to rely on the practice, common in occupational hygiene, of relating the chemistry of industrial processes and the emissions they generate to the potential worst case of personal exposure and then drawing conclusions about whether there would be interventions in an occupational setting based on comparison to occupational exposure limits, which are designed to ensure safety of unintentionally exposed individuals. In that context, exposed individuals are assumed to be adults, and this assumption appears to be suitable for the intended consumers of electronic cigarettes. "Worst case" refers to the maximum personal exposure that can be achieved given what is known about the process that generates contaminated atmosphere (in the context of airborne exposure considered here) and the pattern of interaction with the contaminated atmosphere. It must be noted that harm reduction notions are embedded in this approach since it recognizes that while elimination of the exposure may be both impossible and undesirable, there nonetheless exists a level of exposure that is associated with negligible risks. To date, a comprehensive review of the chemistry of electronic cigarettes and the aerosols they generate has not been conducted, depriving the public of the important element of a risk-assessment process that is mandatory for environmental and occupational health policy making.

The present work considers both the contaminants present in liquids and aerosols as well as the declared ingredients in the liquids. The distinction between exposure to declared ingredients and contaminants of a consumer product is important in the context of comparison to occupational or environmental exposure standards. Occupational exposure limits are developed for unintentional exposures that a person does not elect to experience. For example, being a bread baker is a choice that does not involve election to be exposed to substances that cause asthma that are part of the flour dust (most commonly, wheat antigens and fungal enzymes). Therefore, suitable occupational exposure limits are created to attempt to protect individuals from such risk on the job, with no presumption of "assumed risk" inherent in the occupation. Likewise, special regulations are in effect to protect persons from unintentional exposure to nicotine in workplaces (http://www.cdc.gov/niosh/docs/81-123/pdfs/0446.pdf; accessed July 12, 2013), because in environments where such exposures are possible, it is reasonable to protect individuals who do not wish to experience its effects. In other words, occupational exposure limits are based on protecting people from involuntary and unwanted exposures, and thus can be seen as appropriately more stringent than the standards that might be used for hazards that people intentionally choose to accept.

By contrast, a person who elects to lawfully consume a substance is subject to different risk tolerance, as is demonstrated in the case of nicotine by the fact that legally sold cigarettes deliver doses of nicotine that exceed occupational exposure limits[9]: daily intake of 20 mg of nicotine, assuming nearly 100% absorption in the lungs and

inhalation of 4 m^3 of air, corresponds to roughly 10 times the occupational exposure limit of 0.5 mg/m^3 atmosphere over 8 hours[10]. Thus, whereas there is a clear case for applicability of occupational exposure limits to contaminants in a consumer product (e.g. aerosol of electronic cigarettes), there is no corresponding case for applying occupational exposure limits to declared ingredients desired by the consumer in a lawful product (e.g. nicotine in the aerosol of an electronic cigarette). Clearly, some limits must be set for voluntary exposure to compounds that are known to be a danger at plausible doses (e.g. limits on blood alcohol level while driving), but the regulatory framework should reflect whether the dosage is intentionally determined and whether the risk is assumed by the consumer. In the case of nicotine in electronic cigarettes, if the main reason the products are consumed is as an alternative source of nicotine compared to smoking, then the only relevant question is whether undesirable exposures that accompany nicotine present health risks, and the analogy with occupational exposures holds. In such cases it appears permissible to allow at least as much exposure to nicotine as from smoking before admitting to existence of new risk. It is expected that nicotine dosage will not increase in switching from smoking to electronic cigarettes because there is good evidence that consumers adjust consumption to obtain their desired or usual dose of nicotine[11]. The situation is different for the vapers who want to use electronic cigarettes without nicotine and who would otherwise not have consumed nicotine. For these individuals, it is defensible to consider total exposure, including that from any nicotine contamination, in comparison to occupational exposure limits. In consideration of vapers who would never have smoked or would have quit entirely, it must be remembered that the exposure is still voluntary and intentional, and comparison to occupational exposure limits is legitimate only for those compounds that the consumer does not elect to inhale.

The specific aims of this review were to:

1. Synthesize evidence on the chemistry of liquids and aerosols of electronic cigarettes, with particular emphasis on the contaminants.
2. Evaluate the quality of research on the chemistry of liquids and aerosols produced by electronic cigarettes.
3. Estimate potential exposures from aerosols produced by electronic cigarettes and compare those potential exposures to occupational exposure standards.

Methods

Literature search

Articles published in peer-reviewed journals were retrieved from *PubMed* (http://www.ncbi.nlm.nih.gov/pubmed/) using combinations of the following keywords: "electronic cigarettes", "e-cigarettes", "smoking alternatives", "chemicals", "risks", "electronic cigarette vapor", "aerosol", "ingredients", "e-cigarette liquid", "e-cig composition", "e-cig chemicals", "e-cig chemical composition", "e-juice electronic cigarette", "electronic cigarette gas", "electronic cigars". In addition, references of the retrieved articles were examined to identify further relevant articles, with particular attention paid to non-peer reviewed reports and conference presentations. Unpublished results obtained through personal communications were also reviewed. The Consumer Advocates for Smoke-free Alternatives Association (CASAA) was asked to review the retrieved bibliography to identify any reports or articles that were missed. The papers and reports were retained for analysis if they reported on the chemistry of e-cigarette liquids or aerosols. No explicit quality control criteria were applied in selection of literature for examination, except that secondary reporting of analytical results was not used. Where substantial methodological problems that precluded interpretation of analytical results were noted, these are described below. For each article that contained relevant analytical results, the compounds quantified, limits of detection, and analytical results were summarized in a spreadsheet. Wherever possible, individual analytical results (rather than averages) were recorded (see electronic **Appendix A**:

https://dl.dropboxusercontent.com/u/4285761/CASAA/eAppendixA.xlsx). Data contained in **Appendix A** is not fully summarized in the current report but can be used to investigate a variety of specific questions that may interest the reader. Each entry in **Appendix A is** identified by a *Reference Manage ID* that is linked to source materials in a list in **Appendix B** (linked via *RefID*: https://dl.dropboxusercontent.com/u/4285761/CASAA/AppendixB.rtf) and attached electronic copies of all original materials (**Biobliography.zip**: https://dl.dropboxusercontent.com/u/4285761/CASAA/bibliography.zip).

Comparison of observed concentrations in aerosol to occupational exposure limits

For articles that reported mass or concentration of specific compounds in the aerosol (generated by smoking machines or from volunteer vapers), measurements of compounds were converted to concentrations in the "personal breathing zone",[a] which can be compared to occupational exposure limits (OELs). The 2013 Threshold Limit Values (TLVs)[10] were used as OELs because they are the most up to date and are most widely recognized internationally when local jurisdictions do not establish their own regulations (see http://www.ilo.org/oshenc/part-iv/occupational-hygiene/item/575; accessed July 3, 2013). Whenever there was an uncertainty in how to perform the calculation, a "worst case" scenario was used, as is the standard practice in occupational hygiene, where the initial aim is to recognize potential for hazardous exposures and to err on the side of caution. The following assumptions were made to enable the calculations that approximate the worst-case personal exposure of a vaper (Equation 1):

1. Air the vaper breathes consists of a small volume of aerosol generated by e-cigarettes that contains a specific chemical plus pristine air;
2. The volume of aerosols inhaled from e-cigarettes is negligible compared to total volume of air inhaled;
3. The period of exposure to the aerosol considered was normalized to 8 hours, for comparability to the standard working shift for which TLVs were developed (this does not mean only 8 hours worth of vaping was considered (see point 4) but rather that amount of breathing used to dilute the day's worth of vaping exposure was 8 hours);
4. Consumption of 150 puffs in 8 hours (an upper estimate based on a rough estimate of 150 puffs by a typical vaper in a day[1]) was assumed to be conservative;
5. Breathing rate is 8 liters per minute [12,13];
6. Each puff contains the same quantity of compounds studied.

$$[mg/m^3] = mg/puff \times puffs/(8\ hr\ day) \times 1/(m^3\ air\ inhaled\ in\ 8\ hr) \qquad Eq.\ 1$$

The only exception to this methodology was when assessing a study of aerosol emitted by 5 vapers in a 60 m^3 room over 5 hours that seemed to be a sufficient approximation of worst-case "bystander" exposure[6]. All calculated concentrations were expressed as the most stringent (lowest) TLV for a specific compound (i.e. assuming the most toxic form if analytical report is ambiguous) and expressed as "percent of TLV". Considering that all the above calculations are approximate and reflecting that exposures in occupational and general environment can easily vary by a factor of 10 around the mean, we added a 10-fold safety factor to the "percent of TLV" calculation. Details of all calculations are provided in an Excel spreadsheet (see electronic **Appendix C**: https://dl.dropboxusercontent.com/u/4285761/CASAA/eAppendixC.xlsx).

No systematic attempt was made to convert the content of the studied liquids into potential exposures because sufficient information was available on the chemistry of aerosols to use those studies rather than making the necessary

[a] Atmosphere that contains air inhaled by a person

simplifying assumptions to do the conversion. However, where such calculations were performed in the original research, the following approach as used: under the (probably false – see the literature on formation of carbonyl compounds below) assumption of no chemical reaction to generate novel ingredients, composition of liquids can be used to estimate potential for exposure if it can be established how much volume of liquid is consumed in given 8 hours, following an algorithm analogous to the one described above for the aerosols (Equation 2):

$$[mg/m^3] = mg/(mL\ liquid) \times (mL\ liquid)/puff \times puffs/(8\ hr\ day) \times 1/(m^3\ air\ inhaled\ in\ 8\ hr) \qquad Eq.\ 2$$

Comparison to cigarette smoke was not performed here because the fact that e-cigarette aerosol is at least orders of magnitude less contaminated by toxic compounds is uncontroversial [2-8].

Results and discussion

General comments on methods

In excess of 9,000 determinations of single chemicals (and rarely, mixtures) were reported in reviewed articles and reports, typically with multiple compounds per electronic cigarette tested [2-8,14-42]. Although the quality of reports is highly variable, if one assumes that each report contains some information, this asserts that quite a bit is known about composition of e-cigarette liquids and aerosols. The only report that was excluded from consideration was work of McAuley et al.[23] because of clear evidence of cross-contamination – admitted to by the authors – with cigarette smoke and, possibly, reagents. The results pertaining to non-detection of tobacco-specific nitrosamines (TSNAs) are potentially trustworthy, but those related to PAH are not since it is incredible that cigarette smoke would contain fewer polycyclic aromatic hydrocarbons (PAH; arising in incomplete combustion of organic matter) than aerosol of e-cigarettes that do not burn organic matter [23]. In fairness to the authors of that study, similar problems may have occurred in other studies but were simply not reported, but it is impossible to include a paper in a review once it is known for certain that its quantitative results are not trustworthy. When in doubt, we erred on the side of trusting that proper quality controls were in place, a practice that is likely to increase appearance of atypical or erroneous results in this review. From this perspective, assessment of concordance among independent reports gains higher importance than usual since it is unlikely that two experiments would be flawed in the same exact manner (though of course this cannot be assured).

It was judged that the simplest form of publication bias – disappearance of an entire formal study from the available literature – was unlikely given the exhaustive search strategy and the contested nature of the research question. It is clearly the case that only a portion of all industry technical reports were available for public access, so it is possible that those with more problematic results were systematically suppressed, though there is no evidence to support this speculation. No formal attempt was made to ascertain publication bias *in situ* though it is apparent that anomalous results do gain prominence in typical reviews of the literature: diethylene glycol[43,44] detected at non-dangerous levels (see details below) in one test of 18 of early-technology products by FDA[22] and one outlier in measurement of formaldehyde content of exhaled air [4] and aldehydes in aerosol generated from one e-cigarette in Japan [37]. It must be emphasized that the alarmist report of aldehydes in experiments presented in [37] is based on the concentration in generated aerosol rather than air inhaled by the vaper over prolonged period of time (since vapers do not inhale only aerosol). Thus, results reported in [37] cannot be the basis of any claims about health risk, a fallacy committed both by the authors themselves and commentators on this work [44].

It was also unclear from [37] what the volume of aerosol sampled was – a critical item for extrapolating to personal exposure and a common point of ambiguity in the published reports. However, in a personal exchange with the authors of [37][July 11, 2013], it was clarified that the sampling pump drew air at 500 mL/min through e-cigarette for 10 min, allowing more appropriate calculations for estimation of health risk that are presented below. Such misleading reporting is common in the field that confuses concentration in the aerosol (typically measured directly) with concentration in the air inhaled by the vaper (never determined directly and currently requiring additional assumptions and modeling). This is important because the volume of aerosol inhaled (maximum ~8 L/day) is negligible compared to the volume of air inhaled daily (8L/min); this point is illustrated in the **Figure**.

A similar but more extreme consideration applies to the exposure of bystanders which is almost certainly several orders of magnitude lower than the exposure of vapers. In part this is due to the absorption, rather than exhalation, of a portion of the aerosol by the vapers: there is no equivalent to the "side-stream" component of exposure to conventional cigarettes, so all of the exposure to bystanders results from exhalation. Furthermore, any environmental contamination that results from exhalation of aerosol by vaper will be diluted into the air prior to entering a bystander's personal breathing zone. Lastly, the number of puffs that affects exposure to bystander is likely to be much smaller than that of a vaper unless we are to assume that vaper and bystander are inseparable.

It is unhelpful to report results in cigarette-equivalents, as in [42], because this does not enable one to estimate exposures of vapers . Moreover, there is no value in comparison of the content of e-cigarette aerosol to cigarette smoke when the two products produce emissions that are orders of magnitude apart. To be useful for risk assessment, the results on the chemistry of the aerosols and liquids must be reported in a form that enables the calculations in Equations 1 and 2. It must be also be noted that typical investigations consisted of qualitative and quantitative phases such that quantitative data is available mostly on compounds that passed the qualitative screen. This biased all reports on concentration of compounds towards both higher levels and chemicals which a particular lab was most adept at analyzing.

Declared Ingredients: comparison to occupational exposure limits

Propylene glycol and glycerin have default or precautionary TLV of 10 mg/m^3 over 8 hours set for all organic mists with no specific exposure limits or identified toxicity (http://www.osha.gov/dts/chemicalsampling/data/CH_243600.html; accessed July 5, 2013). These interim TLVs tend to err on the side of being too high and are typically lowered if evidence of harm to health accumulates. For example, in a study that related exposure of theatrical fogs (containing propylene glycol) to respiratory symptoms [45], "mean personal inhalable aerosol concentrations were 0.70 mg/m^3 (range 0.02 to 4.1)" [46]. The only available estimate of propylene concentration of propylene glycol in the aerosol indicates personal exposure on the order of 3-4 mg/m^3 in the personal breathing zone over 8 hours (under the assumptions we made for all other comparisons to TLVs) [2]. The latest (2006) review of risks of occupational exposure to propylene glycol performed by the Health Council of the Netherlands (known for OELs that are the most protective that evidence supports and based exclusively on scientific considerations rather than also accounting for feasibility as is the case for the TLVs) recommended exposure limit of 50 mg/m^3 over 8 hours; concern over short-term respiratory effects was noted [http://www.gezondheidsraad.nl/sites/default/files/200702OSH.pdf; accessed July 29, 2013]. Assuming extreme consumption of the liquid per day via vaping (5 to 25 ml/day and 50-95% propylene glycol in the liquid)[b], levels of propylene glycol in inhaled air can reach 1-6 mg/m^3. It has been suggested that propylene glycol is

[b] This estimate of consumption was derived from informal reports from vaping community; 5 ml/day was identified as a high but not rare quantity of consumption and 25 ml/day was the high end of claimed use, though some skepticism was expressed about

very rapidly absorbed during inhalation [4,6] making the calculation under worst case scenario of all propylene glycol becoming available for inhalation credible. It must also be noted that when consuming low-nicotine or nicotine-free liquids, the chance to consume larger volumes of liquid increases (large volumes are needed to reach the target dose or there is no nicotine feedback), leading to the upper end of propylene glycol and glycerin exposure. Thus, estimated levels of exposure to propylene glycol and glycerin are close enough to TLV to warrant concern.

Nicotine is present in most liquids and has TLV of 0.5 mg/m^3 for average exposure intensity over 8 hours. If approximately 4 m^3 of air is inhaled in 8 hours, the consumption of 2 mg nicotine from e-cigarettes in 8 hours would place the vaper at the occupational exposure limit. For a liquid that contains 18 mg nicotine/ml, TLV would be reached upon vaping ~0.1-0.2 ml of liquid in a day, and so is achieved for most anyone vaping nicotine-containing e-cigarettes[1]. Results presented in [24] on 16 e-cigarettes also argue in favor of exceedance of TLV from most any nicotine-containing e-cigarette, as they predict >2mg of nicotine released to aerosol in 150 puffs (daily consumption figure adopted in this report). But as noted above, since delivery of nicotine is the purpose of nicotine-containing e-cigarettes, the comparison to limits on unintended, unwanted exposures does not suggest a problem and serves merely to offer complete context. If nicotine is present but the liquid is labeled as zero-nicotine [24,43], it could be treated as a contaminant, with the vaper not intending to consume nicotine and the TLV, which would be most likely exceeded, is relevant. However, when nicotine content is disclosed, even if inaccurately, then comparison to TLV is not valid. Accuracy in nicotine content is a concern with respect to truth in advertising rather than unintentional exposure, due to self-regulation of consumption by persons who use e-cigarettes as a source of nicotine.

Overall, the declared ingredients in the liquid would warrant a concern by standards used in occupational hygiene, provided that comparison to occupational exposure limits is valid, as discussed in the introduction. However, this is not to say that the exposure is affirmatively believed to be harmful; as noted, the TLVs for propylene glycol and glycerin mists is based on uncertainty rather than knowledge. These TLVs are not derived from knowledge of toxicity of propylene glycol and glycerin mists, but merely apply to any compound of no known toxicity present in workplace atmosphere. This aspect of the exposure from e-cigarettes simply has little precedent (but see study of theatrical fogs below). Therefore, the exposure will provide the first substantial collection evidence about the effects, which calls for monitoring of both exposure levels and outcomes, even though there are currently no grounds to be concerned about the immediate or chronic health effects of the exposure. The argument about nicotine is presented here for the sake of completeness and consistency of comparison to TLVs, but in itself does not affect the conclusions of this analysis because it should not be modeled as if it were a contaminant when declared as an ingredient in the liquid.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) were quantified in several reports in aerosols [5,6,42] and liquids [7,18,41]. These compounds include well-known carcinogens, the levels of which are not subject to TLV but are instead to be kept "as low as reasonably achievable" (the so called ALARA principle)[10]. For PAH, only non-carcinogenic pyrene that is abundant in the general environment was detected at 36 ng/cartridge in 5 samples of liquid [7]; PAHs were not detected in most of the analyses of aerosols, except for chrysene in the analysis of the aerosol of one e-cigarette[42].

Tobacco-Specific Nitrosamines

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whether the latter quantity was truly possible. High-quality formal studies to verify these figures do not yet exist but they are consistent with report of Etter (2012).

The same risk assessment considerations that exist for PAH also hold for carcinogenic tobacco-specific nitrosamines (TSNAs)[47] for which no occupational exposure limits exist because (a) these exposures do not appear to occur in occupational settings often enough to warrant development of TLVs, and (b) it is currently accepted in establishing TLVs that carcinogens do not have minimal thresholds of toxicity. As expected because the TSNAs are contaminants of nicotine from tobacco leaf, there is also evidence of association between nicotine content of the liquid and TSNA concentrations, with reported concentrations <5 ng/cartridge tested [7]. Smaller studies of TSNA content in liquids are variable, with some not reporting any detectable levels [17,32,34] and others clearly identifying these compounds in the liquids when controlling for background contamination (n=9)[22]. Analyses of aerosols indicate that TSNAs are present in amounts that can results in doses of <ng/day[5,32] to µg/day [8] (assuming 150 puffs/day) (see also [42]). The most comprehensive survey of TSNA content of 105 samples of liquids from 11 manufactures indicates that almost all tested liquids (>90%) contained TSNAs in µg/L quantities [35]. This is roughly equivalent to 1/1000 of the concentration of TSNAs in modern smokeless tobacco products (like snus), which are in the ppm range [47]. The TSNA concentration of the liquids is orders of magnitude less than smokeless tobacco products, though the actual dosage from e-cigarettes vs. smokeless tobacco remains to be clearly understood. For example, 10 µg/L (0.01 ppm) of total TSNA in liquid[35] can translate to a daily dose of 0.000025-0.00005 µg from vaping (worst case assumption of 5 ml/day); if 15 g of snus is consumed a day [48] with 1 ppm of TSNAs [47] and half of it were absorbed, then the daily dose is estimated to be 0.008 µg, which is 160-320 times that due to the worst case of exposure from vaping. Various assumptions about absorption of TSNAs alter the result of this calculation by a factor that is dwarfed in magnitude compared to that arising from differences considered above. This is reassuring because smokeless tobacco products, such as snus, pose negligible cancer risk[49], certainly orders of magnitude smaller than smoking (if one considers the chemistry of the products alone). In general, it appears that the cautious approach in face of variability and paucity of data is to seek better understanding of predictors of presence of TSNA in liquids and aerosols so that measures for minimizing exposure to TSNAs from aerosols can be devised. This can include considering better control by manufactures of the nicotine.

Volatile Organic Compounds

Total volatile organic compounds (VOC) were determined in aerosol to be non-detectable[3] except in one sample that appeared to barely exceed the background concentration of 1 mg/m^3 by 0.73 mg/m^3[6]. These results are corroborated by analyses of liquids[18] and most likely testify to insensitivity of employed analytic methods for total VOC for characterizing aerosol generated by e-cigarettes, because there is ample evidence that specific VOC are present in the liquids and aerosols.[c] Information on specific commonly detected VOC in the aerosol is given in **Table 1a**. It must be observed that these reported concentrations are for analyses that first observed qualitative evidence of the presence of a given VOC and thus represent worst case scenarios of exposure when VOC is present (i.e. zero exposures are missing from the overall summary of worst case exposures presented here). For most VOC and aldehydes, one can predict the concentration in air inhaled by a vaper to be <<1% of TLV. The only exceptions to this generalization are:

(a) acrolein: ~1% of TLV (average of 12 measurements) and measurements at a mean of 2% of TLV (average of 150 measurements)[39,40] and

(b) formaldehyde: between 0 and 3% of TLV based on 18 tests (average of 12 measurements at 2% of TLV, the most reliable test) and an average of 150 results at 4% of TLV [39,40].

[c] The term "VOC" loosely groups together all organic compounds present in aerosol and because the declared ingredients of aerosol are organic compounds, it follows that "VOC are present"

Levels of acrolein in exhaled aerosol reported in [6] were below 0.0016 mg/m^3 and correspond to predicted exposure of <1% of TLV (**Table 2**). It must re-emphasized that all calculations based on one electronic cigarette analyzed in [37] are best treated as qualitative in nature (i.e. indicating presence of a compound without any particular meaning attached to the reported level with respect to typical levels) due to great uncertainty about whether the manner in which the e-cigarette was operated could have resulted in overheating that led to generation of acrolein in the aerosol. In fact, a presentation made by the author of [37] clearly stated that the "atomizer, generating high concentration carbonyls, had been burned black" [39,40]. In unpublished work,[39] there are individual values of formaldehyde, acrolein and glyoxal that approach TLV, but it is uncertain how typical these are because there is reason to believe the liquid was overheated; considerable variability among brands of electronic cigarettes was also noted. Formaldehyde and other aldehydes, but not acrolein, were detected in the analysis one e-cigarette [42]. The overwhelming majority of the exposure to specific VOC that are predicted to result from inhalation of the aerosols lie far below action level of 50% of TLV at which exposure has to be mitigated according to current code of best practice in occupational hygiene[50].

Finding of an unusually high level of formaldehyde by Schripp *et al.*[4] – 0.5 ppm predicted vs. 15-minute TLV of 0.3 ppm (not given in **Table 2**) – is clearly attributable to endogenous production of formaldehyde by the volunteer smoker who was consuming e-cigarettes in the experimental chamber, since there was evidence of build-up of formaldehyde prior to vaping and liquids used in the experiments did not generate aerosol with detectable formaldehyde. This places generalizability of other findings from [4] in doubt, especially given that the only other study of exhaled air by vapers who were not current smokers reports much lower concentrations for the same compounds [6] (**Table 2**). It should be noted that the report by Romagna *et al.*[6] employed more robust methodology, using 5 volunteer vapers (no smokers) over an extended period of time. Except for benzene, acetic acid and isoprene, all calculated concentrations for detected VOC were much below 1% of TLV in exhaled air [6]. In summary, these results do not indicate that VOC generated by vaping are of concern by standards used in occupational hygiene.

Diethylene glycol and ethylene glycol became a concern following the report of their detection by FDA[43], but these compounds are not detected in the majority of tests performed to date [3,14,16,18,22]. Ten batches of the liquid tested by their manufacture did not report any diethylene glycol above 0.05% of the liquid [41]. Methods used to detect diethylene glycol appear to be adequate to be informative and capable of detecting the compound in quantities <<1% of TLV[14,16,22]. Comparison to TLV is based on a worst case calculation analogous to the one performed for propylene glycol. For diethylene glycol, TLV of 10 mg/m^3 is applicable (as in the case of all aerosols with no know toxicity by inhalation), and there is a recent review of regulations of this compound conducted for the Dutch government by the Health Council of the Netherlands (jurisdiction with some of the most strict occupational exposure limits) that recommended OEL of 70 mg/m^3 and noted lack of evidence for toxicity following inhalation [http://www.gezondheidsraad.nl/sites/default/files/200703OSH.pdf; accessed July 29; 2013]. In conclusion, even the quantities detected in the single FDA result were of little concern, amounting to less than 1% of TLV.

Inorganic compounds

Special attention has to be paid to the chemical form of compounds when there is detection of metals and other elements by inductively coupled plasma mass spectrometry (ICP-MS)[8,25]. Because the parent molecule that occurs in the aerosol is destroyed in such analysis, the results can be alarmist and not interpretable for risk assessment. For example, the presence of sodium (4.18 µg/10 puffs)[25] does not mean that highly reactive and toxic sodium metal is in the aerosol, which would be impossible given its reactivity, but most likely means the presence of the ubiquitous compound that contains sodium, dissolved table salt (NaCl). If so, the corresponding daily dose of NaCl that arises from

these concentrations from 150 puffs is about 10,000 times lower than allowable daily intake according to CDC (http://www.cdc.gov/features/dssodium/; accessed July 4, 2013). Likewise, a result for presence of silica is meaningless for health assessment unless the crystalline form of SiO_2 is known to be present. When such ambiguity exists, a TLV equivalence calculation was not performed. We compared concentrations to TLVs when it was even remotely plausible that parent molecules were present in the aqueous solution. However, even these are to be given credence only in an extremely pessimistic analyst, and further investigation by more appropriate analytical methods could clarify exactly what compounds are present, but is not a priority for risk assessment. It should also be noted that one study that attempted to quantify metals in the liquid found none above 0.1-0.2 ppm levels [7] or above unspecified threshold [18]. **Table 1b** indicates that most metals that were detected were present at <1% of TLV even if we assume that the analytical results imply the presence of the most hazardous molecules containing these elements that can occur in aqueous solution. For example, when elemental chromium was measured, it is compared to TLV for insoluble chromium IV that has the lowest TLV of all chromium compounds. Analyses of metals given in [42] are not summarized here because of difficulty with translating reported units into meaningful terms for comparison with the TLV, but only mercury (again with no information on parent organic compound) was detected in trace quantities, but arsenic, beryllium, chromium, cadmium, lead and nickel were not. Taken as the whole, it can be inferred that there is no evidence of contamination of the aerosol with metals that warrants a health concern.

Consideration of exposure to a mixture of contaminants

All calculations conducted so far assumed only one contaminant present in clean air at a time. What are the implications of small quantities of various compounds with different toxicities entering the personal breathing zone at the same time? For evaluation of compliance with exposure limits for mixtures, Equation 3 is used:

$$OEL_{mixture} = \sum_{i=1}^{n} (C_i / TLV_i), \qquad \text{Eq. 3}$$

where C_i is the concentration of the i^{th} compound (i=1,...,n, where n>1 is the number of ingredients present in a mixture) in the contaminated air and TLV_i is the TLV for the i^{th} compound in the contaminated air; if $OEL_{mixture} > 1$, then there is evidence of the mixture exceeding TLV.

The examined reports detected no more than 5-10 compounds in the aerosol, and the above calculation does not place any of them out of compliance with TLV for mixture. Let us imagine that 50 compounds with TLVs were detected. Given that the aerosol tends to contain various compounds at levels, on average, of no more than 0.5% of TLV (**Table 1**), such a mixture with 50 ingredients would be at 25% of TLV, a level that is below that which warrants a concern, since the "action level" for implementation of controls is traditionally set at 50% of TLV to ensure that the majority of persons exposed have personal exposure below mandated limit [50]. Pellerino et al.[2] reached conclusions similar to this review based on their single experiment: contaminants in the liquids that warrant health concerns were present in concentrations that were less than 0.1% of that allowed by law in the European Union. Of course, if the levels of the declared ingredients (propylene glycol, glycerin, and nicotine) are considered, the action level would be met, since those ingredients are present in the concentrations that are near the action level. There are no known synergistic actions of the examined mixtures, so Equation 3 is therefore applicable. Moreover, there is currently no reason to suspect that the trace amounts of the contaminants will react to create compounds that would be of concern.

Conclusions

By the standards of occupational hygiene, current data do not indicate that exposures to vapers from contaminants in electronic cigarettes warrant a concern. There are no known toxicological synergies among compounds in the aerosol, and mixture of the contaminants does not pose a risk to health. However, exposure of vapers to propylene glycol and glycerin reaches the levels at which, if one were considering the exposure in connection with a workplace setting, it would be prudent to scrutinize the health of exposed individuals and examine how exposures could be reduced. This is the basis for the recommendation to monitor levels and effects of prolonged exposure to propylene glycol and glycerin that comprise the bulk of emissions from electronic cigarettes other than nicotine and water vapor. From this perspective, and taking the analogy of work on theatrical fogs [45,46], it can be speculated that respiratory functions and symptoms (but not cancer of respiratory tract or non-malignant respiratory disease) of the vaper is of primary interest. Monitoring upper airway irritation of vapers and experiences of unpleasant smell would also provide early warning of exposure to compounds like acrolein because of known immediate effects of elevated exposures (http://www.atsdr.cdc.gov/toxprofiles/tp124-c3.pdf; accessed July 11, 2013). However, it is questionable how much concern should be associated with observed concentrations of acrolein and formaldehyde in the aerosol. Given highly variable assessments, closer scrutiny is probably warranted to understand sources of this variability, although there is no need at present to be alarmed about exceeding even the occupational exposure limits, since occurrence of occasional high values is accounted for in established TLVs. An important clue towards a productive direction for such work is the results reported in [39,40] that convincingly demonstrate how heating the liquid to high temperatures generates compounds like acrolein and formaldehyde in the aerosol. A better understanding about the sources of TSNA in the aerosol may be of some interest as well, but all results to date consistently indicate quantities that are of no more concern than TSNA in smokeless tobacco products. Exposures to nicotine from electronic cigarettes is not expected to exceed that from smoking due to self-titration[11]; it is only a concern when a vaper does not intend to consume nicotine, a situation that can arise from incorrect labeling of liquids[24,43].

The cautions about propylene glycol and glycerin apply only to the exposure experienced by the vapers themselves. Exposure of bystanders to the listed ingredients, let alone the contaminants, does not warrant a concern as the exposure is likely to be orders of magnitude lower than exposure experienced by vapers. Further research employing realistic conditions could help quantify the quantity of exhaled aerosol and its behavior in the environment under realistic worst-case scenarios (i.e., not small sealed chambers), but this is not a priority since the exposure experienced by bystanders is clearly very low compared to the exposure of vapers, and thus there is no reason to expect it would have any health effects.

The key to making the best possible effort to ensure that hazardous exposures from contaminants do not occur is ongoing monitoring of actual exposures and estimation of potential ones. Direct measurement of personal exposures is not possible in vaping due to the fact the aerosol is inhaled directly, unless, of course, suitable biomarkers of exposure can be developed. The current review did not identify any suitable biomarkers, though cotinine is a useful proxy for exposure to nicotine-containing liquids. Monitoring of potential composition of exposures is perhaps best achieved though analysis of aerosol generated in a manner that approximates vaping, for which better insights are needed on how to modify "smoking machines" to mimic vaping given that there are documented differences in inhalation patterns[51]. These smoking machines would have to be operated under a realistic mode of operation of the atomizer to ensure that the process for generation of contaminants is studied under realistic temperatures. To estimate dosage (or exposure in personal breathing zone), information on the chemistry of aerosol has to be combined with models of the inhalation pattern of vapers, mode of operation of e-cigarettes and quantities of liquid consumed. Assessment of

exhaled aerosol appears to be of little use in evaluating risk to vapers due to evidence of qualitative differences in the chemistry of exhaled and inhaled aerosol.

Monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. This can be done systematically as a routine quality control measure by the manufacturers to ensure uniform quality of all production batches. However, we do not know how this relates to aerosol chemistry because previous researchers have failed to appropriately pair analyses of chemistry of liquids and aerosols. It is standard practice in occupational hygiene to analyze the chemistry of materials generating an exposure, and it is advisable that future studies of the aerosols explicitly pair these analyses with examination of composition of the liquids used to generate the aerosols. Such an approach can lead to the development of predictive models that relate the composition of the aerosol to the chemistry of liquids, the e-cigarette hardware, and the behavior of the vaper, as these, if accurate, can anticipate hazardous exposures before they occur. The current attempt to use available data to develop such relationships was not successful due to studies failing to collect appropriate data. Systematic monitoring of quality of the liquids would also help reassure consumers and is best done by independent laboratories rather than manufactures to remove concerns about impartiality (real or perceived).

Future work in this area would greatly benefit from standardizing laboratory protocols (e.g. methods of extraction of compounds from aerosols and liquids, establishment of "core" compounds that have to be quantified in each analysis (as is done for PAH and metals), development of minimally informative detection limits that are needed for risk assessment, standardization of operation of "vaping machine", etc.), quality control experiments (e.g. suitable positive and negative controls without comparison to conventional cigarettes, internal standards, estimation of %recovery, etc.), and reporting practices (e.g. in units that can be used to estimate personal exposure, use of uniform definitions of limits of detection and quantification, etc.), all of which would improve on the currently disjointed literature. Detailed recommendations on standardization of such protocols lie outside of scope of this report.

All calculations conducted in this analysis are based on information about patterns of vaping and the content of aerosols and liquids that are highly uncertain in their applicability to "typical" vaping as it is currently practiced and says even less about future exposures due to vaping. However, this is similar to assessments that are routinely performed in occupational hygiene for novel technology as it relied on "worst case" calculations and safety margins that attempt to account for exposure variability. The approach adopted here and informed by some data is certainly superior to some currently accepted practices in the regulatory framework in occupational health that rely purely on description of emission processes to make claims about potential for exposure (e.g.[52]). Clearly, routine monitoring of potential and actual exposure is required if we were to apply the principles of occupational hygiene to vaping. Detailed suggestions on how to design such exposure surveillance are available in [53].

In summary, analysis of the current state of knowledge about the chemistry of *contaminants* in liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to these contaminants at a level that would prompt measures to reduce exposure by the standards that are used to ensure safety of workplaces. Indeed, there is sufficient evidence to be reassured that there are no such risks from the broad range of the studied products, though the lack of quality control standards means that this cannot be assured for all products on the market. However, aerosol generated during vaping on the whole, when considering the declared ingredients themselves, if it were treated in the same manner as an emission from industrial process, creates personal exposures that would justify surveillance of exposures and health among exposed persons. Due to the uncertainty about the effects of these quantities of propylene glycol and glycerin, this conclusion holds after setting aside concerns about health effects of nicotine. This conclusion holds notwithstanding the benefits of tobacco harm reduction, since

there is value in understanding and possibly mitigating risks even when they are known to be far lower than smoking. It must be noted that the proposal for such scrutiny of "total aerosol" is not based on specific health concerns suggested by compounds that resulted in exceedance of occupational exposure limits, but is instead a conservative posture in the face of unknown consequences of inhalation of appreciable quantities of organic compounds that may or may not be harmful at doses that occur during vaping.

Key Conclusions:

- Even when compared to workplace standards for involuntary exposures, and using several conservative (erring on the side of caution) assumptions, the exposures from using e-cigarettes fall well below the threshold for concern for compounds with known toxicity. That is, even ignoring the benefits of e-cigarette use and the fact that the exposure is actively chosen, and even comparing to the levels that are considered unacceptable to people who are not benefiting from the exposure and do not want it, the exposures would not generate concern or call for remedial action.
- Expressed concerns about nicotine only apply to vapers who do not wish to consume it; a voluntary (indeed, intentional) exposure is very different from a contaminant.
- There is no serious concern about the contaminants such as volatile organic compounds (formaldehyde, acrolein, etc.) in the liquid or produced by heating. While these contaminants are present, they have been detected at problematic levels only in a few studies that apparently were based on unrealistic levels of heating.
- The frequently stated concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains based on a single sample of an early technology product (and even this did not rise to the level of health concern) and has not been replicated.
- Tobacco-specific nitrosamines (TSNA) are present in trace quantities and pose no more (likely much less) threat to health than TSNAs from modern smokeless tobacco products, which cause no measurable risk for cancer.
- Contamination by metals is shown to be at similarly trivial levels that pose no health risk, and the alarmist claims about such contamination are based on unrealistic assumptions about the molecular form of these elements.
- The existing literature tends to overestimate the exposures and exaggerate their implications. This is partially due to rhetoric, but also results from technical features. The most important is confusion of the concentration in aerosol, which on its own tells us little about risk to heath, with the relevant and much smaller total exposure to compounds in the aerosol averaged across all air inhaled in the course of a day. There is also clear bias in previous reports in favor of isolated instances of highest level of chemical detected across multiple studies, such that average exposure that can be calculated are higher than true value because they are "missing" all true zeros.
- Routine monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. Combined with an understanding of how the chemistry of the liquid affects the chemistry of the aerosol and insights into behavior of vapers, this can serve as a useful tool to ensure the safety of e-cigarettes.
- The only unintentional exposures (i.e., not the nicotine) that seem to rise to the level that they are worth further research are the carrier chemicals themselves, propylene glycol and glycerin. This exposure is not known to cause health problems, but the magnitude of the exposure is novel and thus is at the levels for concern based on the lack of reassuring data.

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Figure: Illustrating the difference between concentrations in the aerosol generated by vaping and inhaled air in a day. *Panel A* shows black square that represents aerosol contaminated by some compound as it would be measured by a "smoking machine" and extrapolated to dosage from vaping in one day. This black square is located inside the white square that represents total uncontaminated air that is inhaled in a day by a vaper. The relative sizes of the two squares are exaggerated as the volume of aerosol generated in vaping relative to inhaled air is much smaller in the figure. *Panel B* shows how exposure from contaminated air (black dots) is diluted over a day for appropriate comparison to occupational exposure limits that are expressed in terms of "time-weighted average" or average contamination over time rather than as instantaneous exposures (with the exception of "ceiling limits" that do not affect the vast majority of comparisons in this report). Exposure during vaping occurs in a dynamic process where the atmosphere inhaled by the vaper alternates between the smaller black and larger white squares in *Panel A*. Thus, the concentration of contaminants that a vaper is exposed to over a day is much smaller than that which is measured in the aerosol (and routinely improperly cited as reason for concern about "high" exposures).

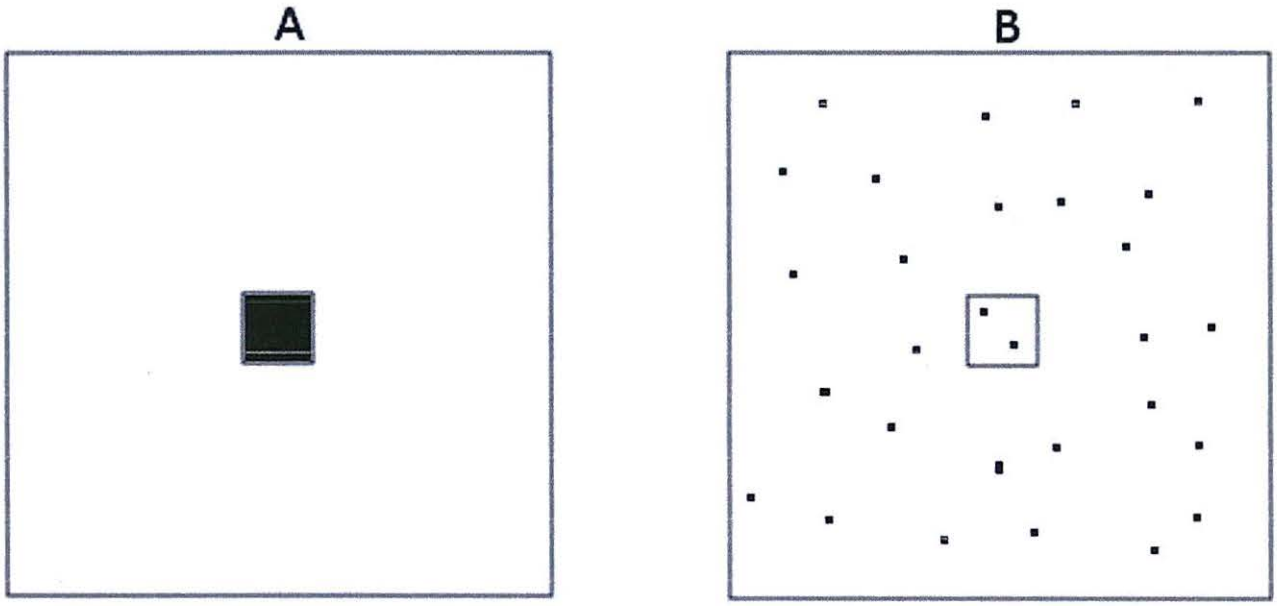

Table 1a: Exposure predictions based on analysis of aerosols generated by smoking machines: Volatile Organic Compounds

Compound	N#	Estimated concentration in personal breathing zone		Ratio of most stringent TLV (%)		Reference
		PPM	mg/m^3	Calculated directly	Safety factor 10	
Acetaldehyde	1	0.005		**0.02**	**0.2**	[5]
	3	0.003		**0.01**	**0.1**	[4]
	12	0.001		**0.004**	**0.04**	[8]
	1	0.00004		**0.0001**	**0.001**	[3]
	1	0.0002		**0.001**	**0.008**	[3]
	150	0.001		**0.004**	**0.04**	[39,40]
	1	0.008		**0.03**	**3**	[37]
Acetone	1	0.002		**0.0003**	**0.003**	[37]
	150	0.0004		**0.0001**	**0.001**	[39,40]
Acrolein	12	0.001		**1**	**13**	[8]
	150	0.002		**2**	**20**	[39,40]
	1	0.006		**6**	**60**	[37]
Butanal	150	0.0002		**0.001**	**0.01**	[39,40]
Crotonaldehyde	150		0.0004	**0.01**	**0.1**	[39,40]
Formaldehyde	1	0.002		**0.6**	**6**	[5]
	3	0.008		**3**	**30**	[4]
	12	0.006		**2**	**20**	[8]
	1	<0.0003		**<0.1**	**<1**	[3]
	1	0.0003		**0.1**	**1**	[3]
	150	0.01		**4**	**40**	[39,40]
	1	0.009		**3**	**30**	[37]
Glyoxal	1		0.002	**2**	**20**	[37]
	150		0.006	**6**	**60**	[39,40]
o-Methylbenzaldehyde	12		0.001	**0.05**	**0.5**	[8]
p,m-Xylene	12		0.00003	**0.001**	**0.01**	[8]
Propanal	3	0.002		**0.01**	**0.1**	[4]
	150	0.0006		**0.002**	**0.02**	[39,40]
	1	0.005		**0.02**	**0.2**	[37]
Toluene	12	0.0001		**0.003**	**0.03**	[8]
Valeraldehyde	150		0.0001	**0.0001**	**0.001**	[39,40]

average is presented when N>1

Table 1b: Exposure predictions based on analysis of aerosols generated by smoking machines: Inorganic Compounds[#]

Element quantified	Assumed compound containing the element for comparison with TLV	N[##]	Estimated concentration in personal breathing zone (mg/m^3)	Ratio of most stringent TLV (%)		Reference
				Calculated directly	Safety factor 10	
Aluminum	Respirable Al metal & insoluble compounds	1	0.002	**0.2**	**1.5**	[25]
Barium	Ba & insoluble compounds	1	0.00005	**0.01**	**0.1**	[25]
Boron	Boron oxide	1	0.02	**0.1**	**1.5**	[25]
Cadmium	Respirable Cd & compounds	12	0.00002	**1**	**10**	[8]
Chromium	Insoluble Cr (IV) compounds	1	3E-05	**0.3**	**3**	[25]
Copper	Cu fume	1	0.0008	**0.4**	**4.0**	[25]
Iron	Soluble iron salts, as Fe	1	0.002	**0.02**	**0.2**	[25]
Lead	Inorganic compounds as Pb	1	7E-05	**0.1**	**1**	[25]
		12	0.000025	**0.05**	**0.5**	[8]
Magnesium	Inhalable magnesium oxide	1	0.00026	**0.003**	**0.03**	[25]
Manganese	Inorganic compounds, as Mn	1	8E-06	**0.04**	**0.4**	[25]
Nickel	Inhalable soluble inorganic compounds, as Ni	1	2E-05	**0.02**	**0.2**	[25]
		12	0.00005	**0.05**	**0.5**	[8]
Potassium	KOH	1	0.001	**0.1**	**1**	[25]
Tin	Organic compounds, as Sn	1	0.0001	**0.1**	**1**	[25]
Zinc	Zinc chloride fume	1	0.0004	**0.04**	**0.4**	[25]
Zirconium	Zr and compounds	1	3E-05	**0.001**	**0.01**	[25]
Sulfur	SO_2	1	0.002	**0.3**	**3**	[25]

The actual molecular form in the aerosol unknown and so worst case assumption was made if it was physically possible (e.g. it is not possible for elemental lithium & sodium to be present in the aerosol); there is no evidence from the research that suggests the metals were in the particular highest risk form, and in most cases a general knowledge of chemistry strongly suggests that this is unlikely. Thus, the TLV ratios reported here probably do not represent the (much lower) levels that would result if we knew the molecular forms.

average is presented when N>1

Table 2: Exposure predictions for volatile organic compounds based on analysis of aerosols generated by volunteer vapers

Compound	N#	Estimated concentration in personal breathing zone (ppm)	Ratio of most stringent TLV (%)		Reference
			Calculated directly	Safety factor 10	
2-butanone (MEK)	3	0.04	**0.02**	0.2	[4]
	1	0.002	**0.0007**	0.007	[6]
2-furaldehyde	3	0.01	**0.7**	7	[4]
Acetaldehyde	3	0.07	**0.3**	3	[4]
Acetic acid	3	0.3	**3**	30	[4]
Acetone	3	0.4	**0.2**	2	[4]
Acrolein	1	<0.001	**<0.7**	<7	[6]
Benzene	3	0.02	**3**	33	[4]
Butyl hydroxyl toluene	1	4E-05	**0.0002**	0.002	[6]
Isoprene	3	0.1	**7**	70	[4]
Limonene	3	0.009	**0.03**	0.3	[4]
	1	2E-05	**0.000001**	0.00001	[6]
m,p-Xyelen	3	0.01	**0.01**	0.1	[4]
Phenol	3	0.01	**0.3**	3	[4]
Propanal	3	0.004	**0.01**	0.1	[4]
Toluene	3	0.01	**0.07**	0.7	[4]

average is presented when N>1

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Study Confirms That E-Cigarettes Generate Virtually No Toxins

Levels are about the same as those found in air.

Jacob Sullum | Mar. 4, 2015 6:32 pm

FIN Ecig ad

Anti-smoking activists and public health officials who question the usefulness of electronic cigarettes in reducing tobacco-related disease often talk as if the content of the aerosol generated by these newfangled contraptions is utterly mysterious. While it may be plausible that the absence of combustion makes e-cigarettes safer than the conventional kind, they say, we can't know for sure without more information about exactly what vapers are sucking into their lungs. That stance is misleading and disingenuous, since we already have a pretty good idea.

A 2013 study reported in *Tobacco Control*, for example, looked at a dozen e-cigarette brands available in Poland and found that "the levels of potentially toxic compounds in e-cigarette vapour are 9–450-fold lower than those in the smoke from conventional cigarettes, and in many cases comparable with the trace amounts present in pharmaceutical preparations [of nicotine]." A new study of leading American and British brands, reported in *Regulatory Toxicology and Pharmacology*, confirms this point, finding that the levels of potentially problematic substances in e-cigarette aerosol are about the same as those detected in ambient air.

For their analysis the researchers picked three flavors of Blu eCigs, which account for about 50 percent of the U.S. market, and two flavors of SKYCIGS, which represent around 30 percent of the e-cigarettes sold in the U.K. They compared the output of these products with air samples and with the smoke generated by Marlboro Golds and two varieties of Lambert & Butler cigarettes. Here is what they found:

> Analysis of the smoke from conventional cigarettes showed that the mainstream

> cigarette smoke delivered approximately 1500 times more harmful and potentially harmful constituents (HPHCs) tested when compared to e-cigarette aerosol or to puffing room air. The deliveries of HPHCs tested for these e-cigarette products were similar to the study air blanks rather than to deliveries from conventional cigarettes; no significant contribution of cigarette smoke HPHCs from any of the compound classes tested was found for the e-cigarettes. Thus, the results of this study support previous researchers' discussion of e-cigarette products' potential for reduced exposure compared to cigarette smoke.

The e-cigarette aerosols consisted mainly of glycerin or propylene glycol (70 percent to 85 percent), water (10 percent to 19 percent), flavoring (3 percent to 11 percent) and nicotine (1 percent to 2 percent). The researchers measured eight kinds of HPHCs: carbon monoxide, carbonyls, phenolics, volatiles, metals, tobacco-specific nitrosamines, polyaromatic amines, and polyaromatic hydrocarbons. The combined weight of all these in 99 puffs from a Blu Classic Tobacco Disposable (which proved to be typical) was less than 0.17 milligram. That's almost the same as the total amount of HPHCs (0.16 milligram) found in 99 puffs of air. By contrast, a single Marlboro Gold generated 30.6 milligrams of HPHCs—180 times as much as the Blu eCig. Per puff, the Marlboro Gold generated 3,357 nanograms of HPHCs—about 2,000 times as much as the Blu eCig.

You can find the specific breakdown by substance class and sample in Tables 4 and 5. But any way you cut it, the difference is enormous.

Does this mean e-cigarette vapor is about as safe as air? Not quite, since we don't know the long-term respiratory effects of inhaling the glycerin or propylene glycol that delivers nicotine into vapers' lungs. But whatever those effects are, it is safe to say they will not compare to the effects of smoking.

In light of data like these, anyone who implies that e-cigarette vapor is about as dangerous as tobacco smoke cannot be taken seriously. That includes Mark Leno, the California legislator who predicts that "we're going to see hundreds of thousands of family members and friends die from e-cigarette use, just like we did from traditional tobacco use." It also includes Ron Chapman, director of California's Department of Public Health, who recently declared e-cigarettes "a community heallth threat" in a report that includes panic-promoting pronouncements like these:

> E-cigarettes do not emit water vapor, but a concoction of chemicals toxic to human cells in the form of an aerosol. The chemicals in the aerosol travel through the circulatory system to the brain and all organs.

> Mainstream and secondhand e-cigarette aerosol has been found to contain at least ten chemicals that are on California's Proposition 65 list of chemicals known to cause cancer, birth defects, or other reproductive harm.

You would never guess from such dire warnings that the toxic chemicals Chapman cites are present in e-cigarette aerosol at levels nearly indistinguishable from those in the air he is breathing right now. But since that appears to be the case, there is no justification for this sort of scaremongering.

[via Michael Siegel]

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Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air

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ABSTRACT

Leading commercial electronic cigarettes were tested to determine bulk composition. The e-cigarettes and conventional cigarettes were evaluated using machine-puffing to compare nicotine delivery and relative yields of chemical constituents. The e-liquids tested were found to contain humectants, glycerin and/or propylene glycol, (⩾75% content); water (<20%); nicotine (approximately 2%); and flavor (<10%). The aerosol collected mass (ACM) of the e-cigarette samples was similar in composition to the e-liquids. Aerosol nicotine for the e-cigarette samples was 85% lower than nicotine yield for the conventional cigarettes. Analysis of the smoke from conventional cigarettes showed that the mainstream cigarette smoke delivered approximately 1500 times more harmful and potentially harmful constituents (HPHCs) tested when compared to e-cigarette aerosol or to puffing room air. The deliveries of HPHCs tested for these e-cigarette products were similar to the study air blanks rather than to deliveries from conventional cigarettes; no significant contribution of cigarette smoke HPHCs from any of the compound classes tested was found for the e-cigarettes. Thus, the results of this study support previous researchers' discussion of e-cigarette products' potential for reduced exposure compared to cigarette smoke.

1. Introduction

Electronic cigarettes (e-cigarettes) are a relatively new consumer product. Unlike conventional cigarettes, e-cigarettes do not burn tobacco to deliver flavor. Instead, they contain a liquid-based flavorant (typically referred to as e-liquid or e-juice) that is thermally vaporized by an electric element. This liquid typically consists of a mixture of water, glycerin, and/or propylene glycol. The liquid also contains nicotine and flavor, although nicotine-free products are available.

While there are decades of characterization studies and numerous standardized analytical procedures for conventional cigarettes, relatively little published analytical data exists for commercial e-cigarette products. Furthermore, no standardized test methods or reference products exist for e-cigarettes.

Electronic cigarettes are generally purported to provide reduced exposure to conventional cigarettes' chemical constituents because they deliver flavors and nicotine through vaporization rather than by burning tobacco. Goniewicz et al. (2014) reported low levels of select chemical constituents in select e-cigarette brands commercially available in Poland. A recent review of analyses from diverse e-cigarettes shows comparatively simple chemical composition relative to conventional cigarette smoke (Burstyn, 2014). However, limited published results exist for commercial products that represent a significant presence in the marketplace (Cheng, 2014).

The purpose of this study was to evaluate e-cigarette products with a significant presence in the marketplace for bulk composition, including nicotine, and for select constituents for comparison with conventional cigarette products. Three blu eCigs products (approximately 50% of the US market) and two SKYCIG products (approximately 30% of the UK market) were chosen for evaluation. Marlboro Gold Box (US), and Lambert & Butler Original and Menthol products (UK), with significant market share in their respective geographical areas, were included in the study for conventional cigarette comparisons.

Abbreviations: ACM, aerosol collected mass; HPHC, harmful and potentially harmful constituents; CO, carbon monoxide; TSNA, tobacco-specific nitrosamines; PAA, polyaromatic amines; PAH, polyaromatic hydrocarbons; LOQ, limit of quantitation; LOD, limit of detection; CAN, Health Canada Test Method T-115; blu CTD, Classic Tobacco Disposable; blu MMD, Magnificent Menthol Disposable; blu CCH, Cherry Crush, Premium, High Strength; SKYCIG CTB, Classic Tobacco Bold; SKYCIG CMB, Crown Menthol Bold; MGB, Marlboro Gold Box; L&B O, Lambert & Butler Original; L&B M, Lambert & Butler Menthol; TPM, total particulate matter; PG, propylene glycol.

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The products used in the study were evaluated for content and delivery of major ingredients (glycerin, propylene glycol, water, and nicotine) and for select constituents (carbon monoxide (CO), carbonyls, phenolics, volatile organic compounds (volatiles), metals, tobacco-specific nitrosamines (TSNAs), polyaromatic amines (PAAs), and polyaromatic hydrocarbons (PAHs)). Many of these constituents are included in cigarette industry guidance issued by the FDA that includes reporting obligations for harmful and potentially harmful constituents (HPHCs) in cigarette filler and smoke under section 904(a)(3) of the 2009 Family Smoking Prevention and Tobacco Control Act (FDA, 2012). For delivery studies, the conventional cigarettes were smoked under an intense puffing regime published by Health Canada (1999). The e-cigarettes were tested using minimal modifications to this smoking regime. Ninety-nine puffs were used to collect approximately the same aerosol mass as obtained from conventional cigarette testing. Ambient 'air' samples, empty port collections, were included as a negative control of aerosol testing for cigarette constituents (i.e. HPHC).

2. Materials and methods

2.1. Test products

Two disposable e-cigarette products and three rechargeable e-cigarette products were obtained from the manufacturers. Three conventional cigarette products were purchased through wholesale or retail sources for testing. Information for each of the products is listed in Table 1.

2.2. Methods overview

ISO 17025 accredited analytical methods were used to evaluate the cigarette samples for select HPHCs in mainstream smoke. Official methods are cited and other, internally validated, methods are briefly described for general understanding. Furthermore, because no standardized methods exist for e-cigarette analysis, the methods used to evaluate the conventional cigarettes were adapted to evaluate the e-cigarette products and the study blanks (room air). In an effort to maximize signal and lower methods' limits of quantitation, aerosol collection amounts were maximized (but maintained below breakthrough) and extraction solvent volumes were minimized. In some cases, alternative instrumentation was employed to improve detection. For example, mainstream smoke TSNAs were analyzed by GC–TEA while aerosol and air blank samples were analyzed by LC–MS/MS. Accuracy, precision, and method limits of quantitation and detection (LOQ and LOD) were verified for each method. On average, accuracy and method variability for the analytes tested were determined to be 98% and 3%, respectively. Analyte LOD and LOQ information is listed in Supplemental Appendix A Tables 1 and 2. Method resolution for low levels of analytes was influenced by background levels of select analytes in air control samples. These background levels are attributed to instrument or smoking machine carry-over as evidenced in solvent or air blanks. In addition, the high concentration of glycerin and water in e-cigarette aerosol present challenges for volatile-based measurement systems (i.e. GC). Additional method refinements and dedicated e-cigarette puffing machines are two areas for consideration to improve e-cigarette aerosol method sensitivities. Method development and verification details for e-cigarette liquids and aerosols are the subject of a future publication.

2.3. Smoke and aerosol collection

Cigarette preparation and machine smoking for conventional cigarettes are described in Health Canada Test Method T-115 (CAN) (1999). Two to three cigarettes were smoked per replicate for conventional cigarettes and 99 puffs were taken from single e-cigarettes for no more than approximately 200 mg of particulates collected per pad. Three to five replicates were tested for each measurement. Prior to analysis, filter pads from cigarette smoke collection were visually inspected for overloading of particulates, as evidenced by brown spotting on the back of the filter pad. To ensure no overloading of particulates for aerosol collection, e-cigarette units were weighed before and after collection to verify that product weight change and filter pad weight change were comparable. Air blanks were prepared by puffing room air (99 puffs) through an empty smoking machine port to the indicated trapping media for an analysis method. These air blank samples were prepared and analyzed in the same manner and at the same time as the e-cigarette aerosol samples. Smoke and aerosol collection sections were conducted separately. Smoke and aerosol particulate was collected onto 44 mm glass fiber filter pads with >99% particulate trapping efficiency for each replicate analysis. For carbonyls, smoke/aerosol was collected directly by two impingers, in series. For smoke metals analysis, electrostatic precipitation was used. For volatiles and PAH determinations, single chilled impingers were placed in-line with the filter pads. e-Liquid glycerin and nicotine were quantitated using GC–FID and/or GC–MS using a method equivalent to ISO 10315 (ISO, 2000a). e-Liquid water was quantitated using Karl Fischer analysis. A reference e-liquid was developed and used as a testing monitor for ingredient determinations in the e-liquid samples. The reference e-liquid is composed primarily of glycerin, propylene glycol, and water with low levels of nicotine, menthol, and Tween 80. The Tween 80 is added to improve solubility of menthol in the solution. The reference is not meant to directly mimic an e-liquid used for consumption but merely used for analytical control charts. Three replicates were tested for each sample and the reference.

2.4. Analytical assays

Carbon monoxide was determined concurrently with aerosol and smoke collection for nicotine and water and analyzed by NDIR using ISO method 8454:2007 (ISO, 2007). Carbonyls were trapped using 2,4-dinitrophenylhydrazine as a derivatizing agent with

Table 1
List of cigarette and e-cigarette products tested.

Product	Manufacturer	Product type	Nicotine information provided on packaging
Classic Tobacco Disposable (blu CTD)	blu eCigs	Disposable e-cigarette	Content: 24 mg/unit
Magnificent Menthol Disposable (blu MMD)	blu eCigs	Disposable e-cigarette	Content: 24 mg/unit
Cherry Crush, Premium, High Strength (blu CCH)	blu eCigs	Rechargeable e-cigarette	Content: 16 mg/unit
Classic Tobacco Bold (SKYCIG CTB)	SKYCIG	Rechargeable e-cigarette	Content: 18 mg/unit
Crown Menthol Bold (SKYCIG CMB)	SKYCIG	Rechargeable e-cigarette	Content: 18 mg/unit
Marlboro Gold Box (MGB)	Philip Morris USA	Conventional cigarette	–
Lambert & Butler Original (L&B O)	Imperial Tobacco	Conventional cigarette	Yield: 0.9 mg/cig (ISO)
Lambert & Butler Menthol (L&B M)	Imperial Tobacco	Conventional cigarette	Yield: 0.5 mg/cig (ISO)

subsequent analysis by UPLC–UV using CORESTA method 74 (CORESTA, 2013). For phenolics determination, filter pads were extracted with 20 mL of 1% acetic acid/2.5% methanol (MEOH) in water using 30 min of agitation. Extracts were analyzed by UPLC-fluorescence detection using a C18 column for separation. For volatiles analysis, filter pads and impinger solutions (20 mL MEOH) were combined. Extracts were analyzed by GC–MS in SIM mode using a WAX capillary column. For metals analysis, cigarette smoke was collected using an electrostatic precipitator while e-cigarette aerosol was collected on glass fiber filter pads. After smoking, the cigarette smoke condensate was rinsed from the electrostatic precipitation tube using methanol. The dried condensates were digested using hydrochloric (10% v/v), nitric acids (80% v/v), and heat and were diluted prior to analysis by ICP-MS. For aerosol samples, filter pads were extracted using 20 mL of a mixture of nitric (2% v/v) and hydrochloric acids (0.5% v/v) using wrist action shaker (20 min). Resultant extracts were analyzed by ICP-MS equipped with an octapole reaction cell.

For TSNA analysis of smoke, samples were extracted in nonpolar solvent, treated to an SPE clean-up, concentrated and analyzed by GC–TEA following CORESTA method 63 (CORESTA, 2005). For TSNA analysis of aerosol samples, filter pads were extracted with 20 mL of 5 mM aqueous ammonium with 15 min of shaking. Extracts were analyzed by LC–MS/MS with a C18 column. For PAA determinations, filter pads were extracted using 25 mL of 5% HCl (aq) and shaking (30 min) followed by solvent exchange and derivatization with pentafluoropropionic acid anhydride and trimethylamine. After an SPE clean-up step (Florisil® SEP-PAK), samples were analyzed by GC–MS in SIM mode using negative chemical ionization. PAH analysis was conducted by extraction in MEOH followed by SPE clean-up and analysis by GC–MS in SIM mode (Tarrant et al., 2009).

The results obtained from these analyses were tabulated as mean ± one standard deviation for levels of selected compounds in Supplementary Appendix A. In cases where quantifiable amounts of analyte were present in an e-cigarette aerosol sample above that of the associated air blanks, an Analysis of Variance (ANOVA) was used to compare the means for the cigarette smoke data with respective aerosol data. Statistical analyses were performed using JMP 10.0.0 (SAS Institute, Inc. Cary, NC, USA). The significance level was established as $p < 0.05$ for all comparisons.

3. Results and discussion

3.1. Collection of aerosol

Machine smoking of cigarettes under standardized regimes is for comparative purposes and is not intended to represent the range of consumer smoking behaviors. Thus, standardized equipment, cigarette reference products, and methodology have been established to allow comparison of different products under a common set of controlled conditions. ISO 3308:2000E and Health Canada (CAN) methods are frequently used for standardized smoking of conventional cigarettes for the purposes of laboratory comparisons among products (ISO, 2000b; Health Canada, 1999). Following each of these methods, conventional cigarettes are smoked to a specified butt length using a fixed and specified puffing volume, duration, and interval.

Regarding e-cigarette experimentation, there is no generally accepted standard e-cigarette puffing regime at this time. Topography studies are limited but anecdotal information indicates e-cigarette usage depends greatly on the individual consumer and product design and capabilities. For the purposes of this study, our objective was to collect sufficient aerosol to be able to detect, if present, select HPHCs. A wide range of parameters would be adequate to accomplish this. Given the objectives of this study, use of collection parameters which are compatible with conventional and electronic cigarettes was essential for facilitating comparisons between cigarette smoke and e-cigarette aerosol. The more intense of the standard regimes used with cigarettes, CAN, which requires 55 mL puffs taken twice a minute, was adapted for this investigation. The key difference required for testing e-cigarettes with the CAN method is that a fixed puff count (rather than 'butt length') is necessary for aerosol collection. A standard of 99 puffs was adopted for all e-cigarette and air blank analyses. This puff count provides similar total particulate collection per pad between the e-cigarette samples and the conventional cigarette testing. This also represents approximately 11 times more puffs than are typically observed for a conventional cigarette. Marlboro Gold Box, L&B O, and L&B M averaged 9.1, 8.2, and 7.2 puffs per cigarette, respectively, when machine-smoked to the standard butt length. If more aggressive puffing parameters had been chosen for the study, the puff count specification would have been lowered to maintain the target level of ACM collected. Note that the range of puffs collected in-use may vary widely depending on product design, battery strength, and user puffing preferences. Thus, the 99 puffs collection in this study is not intended to represent a life time use yield for any of the analytes tested.

3.2. Aerosol and smoke characterization – reference information

Traditional cigarette testing incorporates the use of monitor or reference cigarettes that serve as positive controls and provide quality metrics for standardized analytical methods. Key examples are Kentucky Reference cigarettes and CORESTA monitor cigarettes (CORESTA, 2009; ISO, 2003; University of Kentucky, 2014). Each of

Table 2
Percent composition of e-liquid and aerosol.

	Glycerin (%)	Propylene glycol (%)	Water (%)	Nicotine (%)	Flavor[a] (%)
e-Liquid composition					
blu Classic Tobacco Disposable	82	–	9	2	7
blu Magnificent Menthol Disposable	75	–	18	2	5
blu Cherry Crush High Premium	77	–	14	2	7
SKYCIG Classic Tobacco Bold	24	67	6	2	1
SKYCIG Crown Menthol Bold	21	66	7	2	4
e-Cigarette aerosol composition[b]					
blu Classic Tobacco Disposable	73	–	15	1	11
blu Magnificent Menthol Disposable	80	–	18	2	–
blu Cherry Crush High Premium	70	–	19	1	10
SKYCIG Classic Tobacco Bold	24	61	10.4	1.4	3
SKYCIG Crown Menthol Bold	21	59	12	2	6

[a] Flavor content is estimated by difference.
[b] Aerosol % composition calculated based on the ACM delivery as analyte yield (mg)/ACM (mg) × 100.

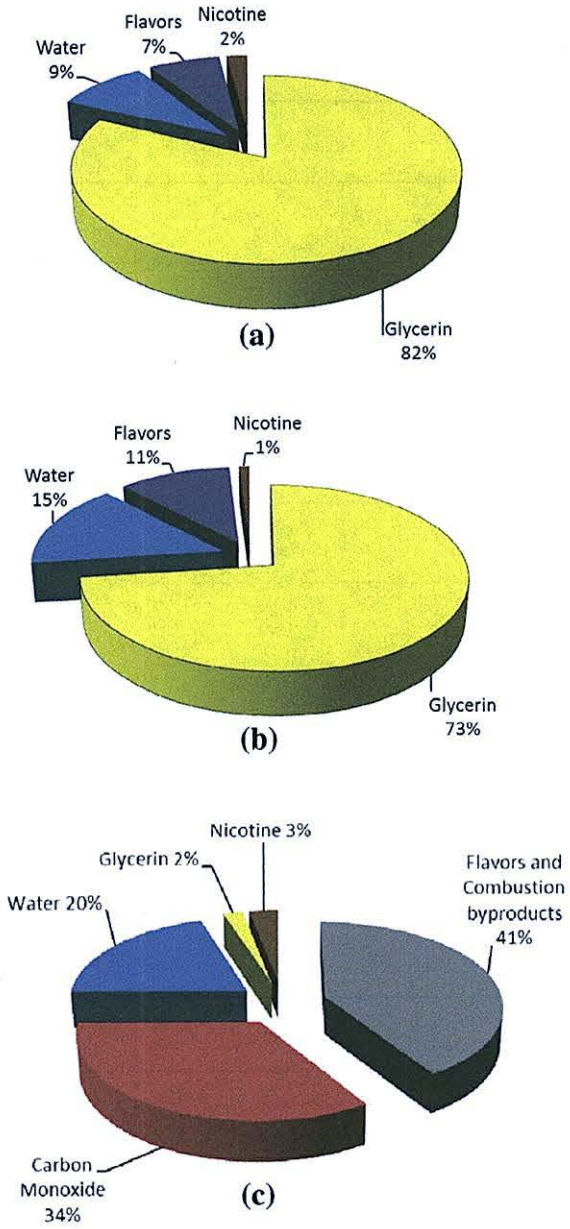

Fig. 1. Percent composition comparison for e-liquid, e-cigarette aerosol, and cigarette smoke: (a) Classic Tobacco Disposable e-liquid Composition. (b) Classic Tobacco Disposable Aerosol Composition (99 puffs, CAN). (c) Marlboro Gold Box Smoke Composition (9 puffs, CAN).

these reference cigarettes can serve as a single positive control and an indicator of method variability within and among laboratories for all analytes of interest. The manufacture, design, and function of these reference products are similar to those of commercial cigarettes. Currently reference products are not available for e-cigarette testing. Given the range of e-cigarette designs, development of a consensus strategy to produce positive controls or monitors for e-cigarette testing is needed.

In the absence of standardized e-cigarette references, measures were taken to ensure experimental robustness. For example, aerosol collected mass (ACM) results for the e-cigarette samples were compared across methods as an indicator of puffing consistency for a given product among the machine-puffing sessions required to conduct the battery of tests. Thus, if a sample set yielded ACM outside of a specified ranged deemed typical for a given product, the sample set was repeated. This range was determined for each product based on collection of 20 or more replicates across the product lot using CAN parameters.

Also, because results from initial analyses indicated low or no measurable levels of many of the analytes, blank samples were included to verify any contribution of analyte from the laboratory environment, sample preparation, and/or analyses for each HPHC test method. The air blank results are listed with the samples' results in Tables 4 and 5. There were instances for which solvent blank and air blank samples had measurable levels of an analyte. This is due to the ubiquitous nature of some of the analytes, such as formaldehyde, or to carry-over. Laugesen reported similar findings (2009). These observations serve as a cautionary note regarding the measurement of extremely low levels of constituents with highly sensitive instrumentation.

3.3. Main ingredients

e-Liquid expressed from the individual products was tested for reported e-cigarette ingredients to compare the percent compositions of the e-liquids and the aerosols. Percent composition calculations of the ingredients are shown in Table 2 for each sample and in Fig. 1 for blu CTD, as this product's comparative results were exemplary of the samples. The primary ingredients in the e-cigarette samples were glycerin and/or propylene glycol ($\geqslant$75%). Water ($\leqslant$18%) and nicotine ($\sim$2%) were also present. Based on a mass balance, other ingredients, presumed to be flavorants, were present at less than 7%. Note that this calculation would also include method uncertainty and any possible HPHCs, if present. The composition of the aerosol was calculated based on the ACM delivery as analyte yield (mg)/ACM (mg) $\times$ 100. The bulk composition of the delivered aerosol was similar to the bulk composition of the e-liquid.

By comparison, the total particulate matter (TPM) of the conventional cigarettes tested is 30% water and <5% nicotine. The essential difference between the ACM composition of the e-cigarettes tested and the TPM of the conventional cigarettes is that the remaining 65% of the TPM of the conventional cigarette is predominantly combustion byproducts. There was no detectable carbon monoxide in the emitted aerosol of the e-cigarette samples. The conventional cigarettes, on the other hand, delivered more than 20 mg/cig of CO. Smoke composition for Marlboro Gold Box, exemplary of the conventional cigarettes tested, is shown in Fig. 1 in contrast to the e-liquid and aerosol results for blu CTD.

While the percent composition of the nicotine in the ACM and TPM are relatively similar, it should be noted that the actual deliveries of nicotine are markedly lower for the e-cigarettes tested than the conventional cigarettes. The nicotine yields ranged from 8 μg/puff to 33 μg/puff for the e-cigarette samples which was 85% lower than the 194–232 μg/puff for the conventional cigarettes. These results are presented in Table 3.

3.4. Aerosol and smoke HPHC testing

For cigarette smoke analysis, the conventional cigarettes were machine smoked by established cigarette smoking procedures. Approximately 7–9 puffs per cigarette were collected. For the e-cigarette samples and air blanks, 99 puffs were collected. Results were compared on an 'as tested' basis; i.e. yields for a single cigarette of 7–9 puffs compared to yields from 99 puffs of an e-cigarette as displayed in Table 4. Additionally, in order to simplify making comparisons between the cigarette and e-cigarette samples, all values were converted to yield per puff. These results are summarized by class in Table 5. Results for individual analytes are tabulated as mean ± one standard deviation in Supplemental Appendix A Tables 1 and 2.

Table 3
Nicotine content and yield comparison between e-cigarettes and conventional cigarettes (mean ± standard deviation).

	Nicotine content (μg/unit)	Nicotine yield (μg/puff)
blu Classic Tobacco Disposable	20,600 ± 1500	33 ± 12
blu Magnificent Menthol Disposable	20,000 ± 300	25 ± 4
blu Cherry Crush High Premium	11,700 ± 300	8 ± 3
SKYCIG Classic Tobacco Bold	12,750 ± 295	29 ± 4
SKYCIG Crown Menthol Bold	13,027 ± 280	33 ± 6
Marlboro Gold Box	11,431 ± 80	226 ± 2
L&B Original	12,941 ± 26	232 ± 5
L&B Menthol	12,131 ± 24	194 ± 10

Number of replicates = 3–5.

Table 4
Analytical characterization of commercial e-cigarettes and conventional cigarettes collected using CAN parameters – select cigarette HPHC methodology (mg/total puffs collected) summary by analyte classes.

	CO	Carbonyls[a]	Phenolics[b]	Volatiles[c]	Metals[d]	TSNAs[e]	PAA[f]	PAH[g]	Sum
Marlboro Gold Box (mg/cig)	27	1.92	0.204	1.430	<0.00020	0.000550	0.000024	0.00222	<30.6 mg
L&B Original (mg/cig)	22	1.89	0.26	1.02	<0.0002	0.000238	0.000019	0.00219	<25.2
L&B Menthol (mg/cig)	20	1.81	0.17	0.94	<0.0003	0.000185	0.000017	0.00153	<22.9
blu CTD (mg/99 puffs)	<0.1	<0.07	<0.001	<0.001	<0.00004	<0.00002	<0.000004	<0.00016	<0.17
blu MMD (mg/99 puffs)	<0.1	<0.08	<0.001	<0.001	<0.00004	<0.00002	<0.000004	<0.00016	<0.18
blu CCHP (mg/99 puffs)	<0.1	<0.05	<0.003	<0.0004	<0.00004	<0.00002	<0.000004	<0.00014	<0.15
SKYCIG CTB (mg/99 puffs)	<0.1	<0.06	<0.0010	<0.008	<0.00006	<0.000013	<0.000014	<0.00004	<0.17
SKYCIG CMB (mg/99 puffs)	<0.1	<0.09	<0.0014	<0.008	<0.00006	<0.000030	<0.000014	<0.00004	<0.20
Air Blank (blu Set) (mg/99 puffs)	<0.1	<0.06	<0.001	<0.0004	<0.00004	<0.00002	<0.000004	<0.00015	<0.16
Air Blank (SKYCIG Set) (mg/99 puffs)	<0.1	<0.05	<0.0009	<0.008	<0.00006	<0.000013	<0.000014	<0.00006	<0.16

< Indicates some or all values were below method limits of quantitation or detection, number of replicates = 3–5.
[a] Formaldehyde, acetaldehyde, acrolein propionaldehyde, crotonaldehyde, MEK, butyraldehyde.
[b] Hydroquinone, resorcinol, catechol, phenol, m-+p-cresol, o-cresol.
[c] 1,3-Butadiene, isoprene, acrylonitrile, benzene, toluene, styrene.
[d] Beryllium, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, selenium, tin.
[e] NNN, NAT, NAB, NNK.
[f] 1-Aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl.
[g] Naphthalene, acenaphthylene, acenaphthene, fluorine, phenanthrene, anthracene, fluoranthene, pyrene, benzanthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, B(a)P, indeno[1,2,3-cd]pyrene, benzo(g,h,i)perylene.

Table 5
Analytical characterization of commercial e-cigarettes and conventional cigarettes collected using CAN parameters – select cigarette HPHC methodology (μg/puff) summary by analyte classes.

	CO	Carbonyls[a]	Phenolics[b]	Volatiles[c]	Metals[d]	TSNAs[e]	PAA[f]	PAH[g]	Sum
Marlboro Gold Box	2967	211	22	157	<0.026	0.0604	0.00264	0.244	<3357 μg
L&B Original	2683	230	32	124	<0.024	0.0290	0.00232	0.267	<3069
L&B Menthol	2778	251	24	130	<0.042	0.0257	0.00236	0.213	<3183
blu Classic Tobacco Disposable	<1.0	<0.7	<0.01	<0.01	<0.0004	<0.0002	<0.00004	<0.002	<1.7
blu Magnificent Menthol Disposable	<1.0	<0.8	<0.01	<0.01	<0.0004	<0.0002	<0.00004	<0.002	<1.8
blu Cherry Crush High Premium	<1.0	<0.5	<0.03	<0.004	<0.0004	<0.0002	<0.00004	<0.001	<1.5
SKYCIG Classic Tobacco Bold	<1.0	<0.6	<0.01	<0.08	<0.0006	<0.0001	<0.00014	<0.0004	<1.7
SKYCIG Crown Menthol Bold	<1.0	<0.9	<0.01	<0.08	<0.0006	<0.0003	<0.00014	<0.0004	<2.0
Air Blank (blu Set)	<1.0	<0.6	<0.01	<0.004	<0.0004	<0.0002	<0.00004	<0.002	<1.6
Air Blank (SKYCIG Set)	<1.0	<0.5	<0.01	<0.08	<0.0006	<0.0001	<0.00014	<0.001	<1.6

< Indicates some or all values were below method limits of quantitation or detection, number of replicates = 3–5.
[a] Formaldehyde, acetaldehyde, acrolein propionaldehyde, crotonaldehyde, MEK, butyraldehyde.
[b] Hydroquinone, resorcinol, catechol, phenol, m-+p-cresol, o-cresol.
[c] 1,3-Butadiene, isoprene, acrylonitrile, benzene, toluene, styrene.
[d] Beryllium, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, selenium, tin.
[e] NNN, NAT, NAB, NNK.
[f] 1-Aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl.
[g] Naphthalene, acenaphthylene, acenaphthene, fluorine, phenanthrene, anthracene, fluoranthene, pyrene, benzanthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, B(a)P, indeno[1,2,3-cd]pyrene, benzo(g,h,i)perylene.

Table 6
Per puff comparisons of quantifiable analytes for blu eCigs products from CAN puffing – yields and ratios to conventional product yields.

	Marlboro Gold Box µg/puff	blu MMD µg/puff	MGB/blu MMD
Acrolein	16.4 ± 0.2	0.19 ± 0.06	86
Phenol	1.53 ± 0.16	0.0017[a]	900

[a] Fewer than three replicates were quantifiable; no standard deviation is listed.

Table 7
Per puff comparisons of quantifiable analytes for SKYCIG products from CAN puffing – yields and ratios to conventional product yields.

	L&B average µg/puff	SKYCIG CTB µg/puff	SKYCIG CMB µg/puff	L&B average/SKYCIG CTB	L&B average/SKYCIG CMB
Acetaldehyde	174	–	0.32[a]	–	544
Acrolein	17	0.15 ± 0.02	–	113	–
Propionaldehyde	12	–	0.11 ± 0.05	–	109
N-Nitrosoanatabine	0.010	–	0.0002 ± 0.0001	–	50

[a] Fewer than three replicates were quantifiable; no standard deviation is listed.

All analytes tested were present in the cigarette smoke at quantifiable levels except for select metals. These results are consistent with internal historical results for commercial cigarettes tested under the CAN smoking regime. For the cigarette samples, the total yield range was 3069–3350 µg/puff of HPHCs tested.

Of the 55 HPHCs tested in aerosol, 5 were quantifiable in an e-cigarette sample but not the associated air blank. The quantifiable results for aerosol are listed in Tables 6 and 7 in contrast with the conventional cigarettes from the same geographical region. The five analytes which were quantifiable were statistically different ($p < 0.05$) at levels 50–900 times lower than the cigarette smoke samples. Phenol was quantified in one e-cigarette product at 900 times lower than cigarette smoke. N-Nitrosoanatabine was quantified in one product at 50 times lower than cigarette smoke. Three carbonyls (acrolein, acetaldehyde, and propionaldehyde) were quantified at 86–544 times lower than cigarette smoke.

All other analytes were not quantifiable above the air blanks in aerosol samples. The e-cigarettes and air blanks total yields for analytes were <2 µg/puff which is 99% less than the approximately 3000 µg/puff quantified for the cigarette smoke samples. Thus, the results support the premise of potentially reduced exposure to HPHCs for the e-cigarette products compared to conventional cigarette smoke.

4. Conclusions

The purpose of this study was to determine content and delivery of e-cigarette ingredients and to compare e-cigarette aerosol to conventional cigarettes with respect to select HPHCs for which conventional cigarette smoke is routinely tested. Routine analytical methods were adapted and verified for e-cigarette testing. Aerosol collection was conducted using conventional smoking machines and an intense puffing regime. As machine puffing cannot, and is not intended to, mimic human puffing, results of this study are limited to the scope of the comparisons made between the e-cigarette and conventional cigarette products tested.

The main ingredients for the e-cigarettes tested were consistent with disclosed ingredients: glycerin and/or propylene glycol (⩾75%), water (⩽18%), and nicotine (~2%). Machine-puffing of these products under a standardized intense regime indicated a direct transfer of these ingredients to the aerosol while maintaining an aerosol composition similar to the e-liquid. Nicotine yields to the aerosol were approximately 30 µg/puff or less for the e-cigarette samples and were 85% lower than the approximately 200 µg/puff from the conventional cigarettes tested.

Testing of the e-cigarette aerosol indicates little or no detectable levels of the HPHC constituents tested. Overall the cigarettes yielded approximately 3000 µg/puff of the HPHCs tested while the e-cigarettes and the air blanks yielded <2 µg. Small but measurable quantities of 5 of the 55 HPHCs tested were found in three of the e-cigarette aerosol samples at 50–900 times lower levels than measurable in the cigarette smoke samples. Overall, the deliveries of HPHCs tested for the e-cigarette products tested were more like the study air blanks than the deliveries for the conventional cigarettes tested. Though products tested, collection parameters, and analytical methods are not in common between this study and others, the results are very consistent. Researchers have reported that most or all of the HPHCs tested were not detected or were at trace levels. Burstyn (2014) used data from approximately 50 studies to estimate e-cigarette exposures compared to workplace threshold limit values (TLV) based on 150 puffs taken over 8 h. The vast majority of the analytes were estimated as ≪1% of TLV and select carbonyls were estimated as <5% of TLV. Cheng (2014) reviewed 29 publications reporting no to very low levels of select HPHCs relative to combustible cigarettes, while noting that some of the tested products exhibited considerable variability in their composition and yield. Goniewicz et al. (2014) tested a range of commercial products and reported quantifiable levels for select HPHCs in e-cigarette aerosols at 9- to 450-fold lower levels than those in cigarette smoke that in some instances were on the order of levels determined for the study reference (a medicinal nicotine inhaler). Laugesen (2009) and Theophilus et al. (2014) have presented results for commercial e-cigarette product liquids and aerosols having no quantifiable levels of tested HPHCs, or extremely low levels of measurable constituents relative to cigarette smoke. Additionally, findings from several recent studies indicate that short-term use of e-cigarettes by adult smokers is generally well-tolerated, with significant adverse events reported relatively rarely (Etter, 2010; Polosa et al., 2011, 2014; Caponnetto et al., 2013; Dawkins and Corcoran, 2014; Hajek et al., 2014). Thus, the results obtained in the aforementioned studies and in the present work broadly support the potential for e-cigarette products to provide markedly reduced exposures to hazardous and potentially hazardous smoke constituents in smokers who use such products as an alternative to cigarettes.

Additional research related to e-cigarette aerosol characterization is warranted. For example, continued characterization of

major components and flavors is needed. Establishment of standardized puffing regimes and reference products would greatly aid sharing of knowledge between researchers. Continued methods' refinement may be necessary for improved accuracy for quantitation of analytes at the low levels determined in this study. To that end, it is critical that negative controls and steps to avoid sample contamination be included when characterizing e-cigarette aerosol since analytes are on the order of what has been measured in the background levels of a laboratory setting. Though researchers have reported quantification of select analytes, great care must be taken when interpreting results at such trace levels.

Conflicts of interest

The company for which the study authors work and the companies that manufacture the e-cigarettes tested for this study are owned by the same parent company.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2014.10.010.

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Electronic Smoking Devices and Secondhand Aerosol

Electronic smoking devices (or ESDs), which are often called **e-cigarettes**, heat and vaporize a solution that typically contains nicotine. The devices are metal or plastic tubes that contain a cartridge filled with a liquid that is vaporized by a battery-powered heating element. The aerosol is inhaled by the user when they draw on the device, as they would a regular tobacco cigarette, and the user exhales the aerosol into the environment.

"If you are around somebody who is using e-cigarettes, you are breathing an aerosol of exhaled nicotine, ultra-fine particles, volatile organic compounds, and other toxins." Dr. Stanton Glantz, Director for the Center for Tobacco Control Research and Education at the University of California, San Francisco.

Current Legislative Landscape

- As of October 1, 2014, **225 municipalities and three states include electronic smoking devices** as products that are prohibited from use in smokefree environments.

Constituents of Secondhand Aerosol

Electronic smoking devices (ESDs) do not just emit "harmless water vapor." **Secondhand aerosol (incorrectly called vapor by the industry) from ESDs contains nicotine, ultrafine particles and low levels of toxins** that are known to cause cancer.

- ESD aerosol is made up of a high concentration of ultrafine particles, and the particle concentration is higher than in conventional tobacco cigarette smoke.[1]

- Exposure to fine and ultrafine particles may exacerbate respiratory ailments like asthma, and constrict arteries which could trigger a heart attack.[2]

- At least 10 chemicals identified in ESD aerosol are on California's Proposition 65 list of carcinogens and reproductive toxins, also known as the Safe Drinking Water and Toxic Enforcement Act of 1986. The compounds that have already been identified in mainstream (MS) or secondhand (SS) ESD aerosol include: **Acetaldehyde (MS), Benzene (SS), Cadmium (MS), Formaldehyde (MS,SS), Isoprene (SS), Lead (MS), Nickel (MS), Nicotine (MS, SS), N-Nitrosonornicotine (MS, SS), Toluene (MS, SS).**[3,4]

- **ESDs contain and emit propylene glycol**, a chemical that is used as a base in ESD solution and is one of the primary components in the aerosol emitted by ESDs.
    - Short term exposure causes eye, throat, and airway irritation.[5]
    - Long term inhalation exposure can result in children developing asthma.[6]

- Even though propylene glycol is FDA approved for use in some products, the inhalation of vaporized nicotine in propylene glycol is not. Some studies show that heating propylene glycol changes its chemical composition, producing small amounts of propylene oxide, a known carcinogen.[7]

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- There are **metals in ESD aerosol, including chromium, nickel, and tin nanoparticles.**[8]
- FDA scientists found detectable levels of carcinogenic tobacco-specific nitrosamines in ESD aerosol.[9]
- People exposed to ESD aerosol absorb nicotine (measured as cotinine), with one study showing levels comparable to passive smokers.[10]
- **Diethylene Glycol**, a poisonous organic compound, was also detected in ESD aerosol.[11]
- **Exhaled ESD aerosol contained propylene glycol, glycerol, flavorings, and nicotine, along with acetone, formaldehyde, acetaldehyde, propanal, diacetin, and triacitine.**[12]
- Many of the elements identified in the aerosol are known to **cause respiratory distress and disease.** The aerosol contained particles >1 μm comprised of tin, silver, iron, nickel, aluminum, and silicate and nanoparticles (<100 nm) of tin, chromium and nickel. The concentrations of nine of eleven elements in ESD aerosol were higher than or equal to the corresponding concentrations in conventional cigarette smoke.[13]
- ESDs cause exposure to different chemicals than found in conventional cigarettes and there is a need for risk evaluation for both primary and passive exposure to the aerosol in smokers and nonsmokers.[14]
- Short term use of ESD has been shown to increase respiratory resistance and impair lung function, which may result in difficulty breathing.[15]
- The first study to look at exposure to aerosol from ESDs in real-use conditions found that non-smokers who were exposed to conventional cigarette smoke and ESD aerosol absorbed similar levels of nicotine.[16]
- The "E-cigarettes do not produce a vapor (gas), but rather a dense visible aerosol of liquid sub-micron droplets consisting of glycols, nicotine, and other chemicals, some of which are carcinogenic (e.g., formaldehyde, metals like cadmium, lead, & nickel, and nitrosamines)." ASHRAE concluded that ESDs emit harmful chemicals into the air and need to be regulated in the same manner as tobacco smoking.[17]
- Some chemicals used as flavorings in ESD liquid, which are approved by the FDA for food use (ingestion), are not approved for inhalation and are associated with respiratory disease when inhaled.[18]
- There is a risk of thirdhand exposure to nicotine released from ESD aerosol that deposits on indoor surfaces.[19]
- Overall, ESDs are a new source of **Volatile Organic Compounds (VOCs) and ultrafine/fine particles in the indoor environment,** thus resulting in "passive vaping."[20]
- The World Health Organization (WHO) recommends that ESDs not be used indoors, especially in smokefree environments, in order to minimize the risk to bystanders of breathing in the aerosol emitted by the devices and to avoid undermining the enforcement of smokefree laws.[21]
- The American Industrial Hygiene Association (AIHA) also recommends that ESDs be included in smokefree laws: "***Because e-cigarettes are a potential source of pollutants (such as airborne nicotine, flavorings, and thermal degradation products), their use in the indoor***

environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants."[22]

ESD aerosol is a new source of pollution and toxins being emitted into the environment. We do not know the long-term health effects of ESD use and although the industry marketing of the product implies that these products are harmless, the aerosol that ESD emit is not purely water vapor.

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United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7510P)

EPA-739-R-06-002
September 2006

EPA

Reregistration Eligibility Decision For Propylene Glycol and Dipropylene Glycol

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

CERTIFIED MAIL

Dear Registrant:

This is to inform you that the Environmental Protection Agency (hereafter referred to as EPA or the Agency) has completed its review of the available data for the antimicrobials propylene glycol and dipropylene glycol. The Reregistration Eligibility Decision (RED) was approved in the form of a decision memorandum which summarized the regulatory decision for propylene glycol and dipropylene glycol on September 30, 2004.

Based on its review, EPA is now publishing its Reregistration Eligibility Decision (RED) for propylene glycol and dipropylene glycol and its associated human health and environmental risks. A Notice of Availability will be published in the *Federal Register* announcing the publication of the RED.

The RED and supporting documents for propylene glycol and dipropylene glycol will be available to the public in EPA's Pesticide Docket EPA-HQ-OPP-2006-0831 at: www.regulations.gov.

Please note that the attached RED document pertains only to propylene glycol and dipropylene glycol. This RED presents the Agency's conclusions on the dietary, drinking water, occupational and ecological risks posed by exposure to propylene glycol or dipropylene glycol alone. This document also contains product-specific data that the Agency intends to require in Data Call-Ins (DCIs). Note that DCIs, with all pertinent instructions, will be sent to registrants at a later date. Currently, there are no generic data requirements. Additionally, for product-specific DCIs, the first set of required responses will be due 90 days from the receipt of the DCI letter. The second set of required responses will be due eight months from the receipt of the DCI letter.

As part of the RED, the Agency has determined that propylene glycol and dipropylene glycol are eligible for reregistration. Sections IV and V of this RED document describe product-specific data requirements.

If you have questions on this document or the label changes relevant to this reregistration decision, please contact the Chemical Review Manager, Michelle Centra, at (703) 308-2476. For questions about product reregistration and/or the Product DCI that accompanies this document, please contact Marshall Swindell at (703) 308-6341.

Sincerely,

Betty Shackleford for

Frank T. Sanders
Director, Antimicrobials Division

REREGISTRATION ELIGIBILITY
DECISION
for
Propylene Glycol and Dipropylene Glycol
List C
CASE 3126

Approved By:

Betty Shackleford for

Frank T. Sanders
Director, Antimicrobials Division
September 29, 2006

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GLOSSARY OF TERMS AND ABBREVIATIONS

a.i.	Active Ingredient
aPAD	Acute Population Adjusted Dose
APHIS	Animal and Plant Health Inspection Service
ARTF	Agricultural Re-entry Task Force
BCF	Bioconcentration Factor
CDC	Centers for Disease Control
CDPR	California Department of Pesticide Regulation
CFR	Code of Federal Regulations
ChEI	Cholinesterase Inhibition
CMBS	Carbamate Market Basket Survey
cPAD	Chronic Population Adjusted Dose
CSFII	USDA Continuing Surveys for Food Intake by Individuals
CWS	Community Water System
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DL	Double layer clothing (i.e., coveralls over SL)
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDSP	Endocrine Disruptor Screening Program
EDSTAC	Endocrine Disruptor Screening and Testing Advisory Committee
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
EXAMS	Tier II Surface Water Computer Model
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOB	Functional Observation Battery
FQPA	Food Quality Protection Act
FR	Federal Register
GL	With gloves
GPS	Global Positioning System
HIARC	Hazard Identification Assessment Review Committee
IDFS	Incident Data System
IGR	Insect Growth Regulator
IPM	Integrated Pest Management
RED	Reregistration Eligibility Decision
LADD	Lifetime Average Daily Dose
LC50	Median Lethal Concentration. Statistically derived concentration of a substance expected to cause death in 50% of test animals, usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LCO	Lawn Care Operator
LD50	Median Lethal Dose. Statistically derived single dose causing death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation), expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOC	Level of Concern
LOEC	Lowest Observed Effect Concentration
mg/kg/day	Milligram Per Kilogram Per Day
MOE	Margin of Exposure

MP	Manufacturing-Use Product
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted.
MRL	Maximum Residue Level
N/A	Not Applicable
NASS	National Agricultural Statistical Service
NAWQA	USGS National Water Quality Assessment
NG	No Gloves
NMFS	National Marine Fisheries Service
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NPIC	National Pesticide Information Center
NR	No respirator
OP	Organophosphorus
OPP	EPA Office of Pesticide Programs
ORETF	Outdoor Residential Exposure Task Force
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDCI	Product Specific Data Call-In
PDP	USDA Pesticide Data Program
PF10	Protection factor 10 respirator
PF5	Protection factor 5 respirator
PHED	Pesticide Handler's Exposure Data
PHI	Pre-harvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
PRZM	Pesticide Root Zone Model
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RPA	Reasonable and Prudent Alternatives
RPM	Reasonable and Prudent Measures
RQ	Risk Quotient
RTU	(Ready-to-use)
RUP	Restricted Use Pesticide
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
SL	Single layer clothing
SLN	Special Local Need (Registrations Under Section 24C of FIFRA)
STORET	Storage and Retrieval
TEP	Typical End-Use Product
TGAI	Technical Grade Active Ingredient
TRAC	Tolerance Reassessment Advisory Committee
TTRS	Transferable Turf Residues
UF	Uncertainty Factor
USDA	United States Department of Agriculture
USFWS	United States Fish and Wildlife Service
USGS	United States Geological Survey
WPS	Worker Protection Standard

ABSTRACT

The Environmental Protection Agency (EPA or the Agency) has completed the human health and environmental risk assessments for propylene glycol and dipropylene glycol and is issuing its risk management decision and tolerance reassessment. The risk assessments, which are summarized below, are based on the review of the required target database supporting the use patterns of currently registered products. As a result of this review, EPA has determined that products containing propylene glycol and dipropylene glycol alone are eligible for reregistration. Products containing propylene glycol and dipropylene glycol in combination with other active ingredients will be reregistered only when all of the active ingredients have been determined to be eligible for reregistration. That decision is discussed fully in this document.

I. INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984 and amended again by the Pesticide Registration Improvement Act of 2003 to set time frames for the issuance of Reregistration Eligibility Decisions. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all submitted data by the Agency. Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether the pesticide meets the "no unreasonable adverse effects" criteria of FIFRA.

On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law. This Act amends FIFRA to require a tolerance reassessment. The Agency has decided that, for those chemicals that have tolerances and are undergoing reregistration, the tolerance reassessment will be initiated through this reregistration process. The Act also required that by 2006, EPA must review all tolerances in effect on the day before the date of the enactment of the FQPA. FQPA also amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to require a safety finding in the tolerance reassessment based on factors including consideration of cumulative effects of chemicals with a common mechanism of toxicity. This document presents the Agency's human health and ecological review and the Reregistration Eligibility Decision for propylene and dipropylene glycol.

As active ingredients, propylene glycol and dipropylene glycol are formulated primarily as pressurized liquids and ready-to-use solutions. Propylene glycol is used in air sanitization and hard surface disinfection and dipropylene glycol is used in air sanitization. Pest (fleas, mites, red lice, and various bacteria and viruses) control for pets (cats, dogs, and birds) is also a major active use for propylene glycol. As an inert ingredient, propylene glycol is formulated into end-use agricultural and antimicrobial pesticide products whereas dipropylene glycol is formulated into pesticide products for use in agricultural settings. Products containing propylene glycol and dipropylene glycol in combination with other active ingredients will be reregistered only when all of the active ingredients have been determined to be eligible for reregistration. This document addresses the exposures and risks from the use of these pesticides as both active and inert ingredients in pesticide products.

The Agency has concluded that the FQPA Safety Factor for propylene glycol and dipropylene glycol should be removed (equivalent to 1X) because there is no pre- or post-natal evidence of increased susceptibility for infants and children following exposure to either propylene or dipropylene glycol.

The Food Quality Protection Act (FQPA) requires that the Agency consider available information concerning the cumulative effects of a particular pesticide's residues and other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that

cause a common toxic effect by a common toxic mechanism could lead to the same adverse health effect that would occur at a higher level of exposure to any of the substances individually. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for propylene or dipropylene glycol and any other substances. Neither propylene nor dipropylene glycol appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that propylene or dipropylene glycol have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by the EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative.

This document presents the Agency's decision regarding the reregistration eligibility of the registered uses of propylene and dipropylene glycol. In an effort to simplify the RED, the information presented herein is summarized from more detailed information which can be found in the technical supporting documents for these pesticides referenced in this RED. Related documents will be available in the Public Docket at www.regulations.gov.

This document consists of six sections. Section I is the introduction. Section II provides a chemical overview, a profile of the use and usage of propylene and dipropylene glycol, and their regulatory history. Section III gives an overview of the revised human health and environmental assessments based on the data available to the Agency. Section IV presents the reregistration eligibility and risk management decisions. Section V summarizes procedures for the product-specific data call-in (PDCI). Finally, the Appendices contain all use patterns eligible for reregistration, bibliographic information, generic data requirements and studies used to make the reregistration decision, related documents and how to access them, and Data Call-In (DCI) information.

II. CHEMICAL OVEVIEW

A. Regulatory History

Propylene glycol and dipropylene glycol were first registered in 1950 and 1959, respectively, by the FDA for use in hospitals as air disinfectants. At one point, there were approximately 190 pesticide chemical companies having active propylene or dipropylene glycol registrations. Many of these registrations were canceled over the years and more recently, the majority of the remaining producers of propylene and dipropylene glycol formulated pesticide products are being represented by a consortium called the CSPA (Consumer Specialty Products Association) Glycols Joint Venture. The member companies currently represented by this consortium are: Amrep, Inc., Beaumont Products, Inc., Chase Products, MEDO/SOPUS Products, Reckitt Benkiser, Inc., S.C. Johnson & Son, Inc., Wellmark International, and Waterbury Companies, Inc.

B. Chemical Identification

1. Propylene Glycol:

Common Name:	Propylene Glycol
Chemical Name:	1, 2-Propanediol or 1,2-hydroxypropane
Chemical family:	None
Case number:	3126
CAS registry number:	57-55-6
OPP chemical code:	068603
Empirical formula:	$C_3H_8O_2$
Molecular weight:	76.00 g/mol
Trade and other names:	Propylene glycol
Manufacturers:	CSPA Glycols Joint Venture (Amrep, Beaumont Products, Inc., Chase Products, MEDO/SOPUS Products, Reckitt Benkiser, Inc., S.C. Johnson & Son, Inc., and Waterbury Companies, Inc.
Specific Gravity:	1.038

Solubility:	Highly miscible in water
Boiling Point:	188 °C at 760 mm Hg
Melting Point:	N/A
Vapor Pressure:	0.04 – 0.08 mm Hg at 20 °C
Structure:	$OH\text{-}CH_2\text{-}CH(OH)\text{-}CH_3$

2. Dipropylene Glycol:

Common Name:	Dipropylene Glycol
Chemical Name:	Oxybispropanol
Chemical family:	None
Case number:	3126
CAS registry number:	25265-71-8
OPP chemical code:	068604
Empirical formula:	$C_6H_{14}O_3$
Molecular weight:	134.00 g/mol
Trade and other names:	Dipropylene glycol
Manufacturers:	CSPA Glycols Joint Venture (Waterbury Companies, Inc., and Beaumont Products, Inc.)
Specific Gravity:	1.038
Solubility:	Highly miscible in water
Boiling Point:	188 °C at 760 mm Hg
Melting Point:	N/A
Vapor Pressure:	0.04 – 0.08 mm Hg at 20 °C
Structure:	$OH\text{-}CH_2\text{-}CH(OH)\text{-}CH_3$

C. Use Profile

1. Propylene Glycol
The following is information on the currently registered uses of propylene glycol products and an overview of use sites and application methods. A detailed table of the uses of propylene glycol eligible for reregistration is contained in Appendix A.

Type of Pesticide: Bacteriostat, Fungistat

Summary of Use Sites:

Indoor Non-Food: Propylene glycol is used on the following use sites: air treatment (eating establishments, hospital, commercial, institutional, household, bathroom, transportational facilities); medical premises and equipment, commercial, institutional and industrial premises and equipment; laundry equipment; hard non-porous surface treatments (bathroom facilities); automobiles; air conditioning filters; pet treatment, including cats, dogs, and caged birds; environmental inanimate hard surfaces; garbage containers/storage.

Target Pests: Odor-causing bacteria, Fleas, Mites, Red lice, Animal pathogenic bacteria (G- and G+ vegetative), Shigella bacteria, Pasteurella bacteria, Listeria bacteria, Herpes Simplex I and II, Animal viruses, Influenza Virus A2, Aspergillus Niger Fungus, Mold/Mildew, Pseudomonas SPP., Shigella Flexneri, Shigella Sonnei.

Inert Uses: As an inert ingredient, propylene glycol facilitates delivery of formulated pesticide chemical products that are used as herbicides, fungicides, insecticides, growth regulators and attractants on various commodities. It is also used in the formulation and repackaging of wood preservatives.

Formulation Types: Pressurized liquid, ready-to-use

Method and Rates of Application

Pet Treatment
For dogs, puppies, cats, kittens; hold spray container 4-6 inches away from animal and direct spray into fur, starting from tail. Rub spray down into fur so that skin is treated. For birds, hold spray bottle three feet from bird and spray lightly - one burst every two or three seconds. Apply no more that two times per week.

Air Sanitizer
Read the directions included with the automatic dispenser for proper installation of unit and refill. Remove cap from aerosol can and place in a sequential aerosol dispenser which

automatically releases a metered amount every 15 minutes. One unit should treat 6000 ft^3 of closed air space. Dispenser should be located at a height of eight feet and at a point where wind flow will carry the particles throughout the area. Each spray dose is 100 mg and the median particle size is 30 microns. For regular, non-metered applications, spray room until a light fog forms. To sanitize the air, spray 6 to 8 seconds in an average size room (10' x10').

Hard, Non-Porous Surface Disinfectant
Spray surface until thoroughly wet and let stand 10 minutes, then wipe with a dry paper towel. On non-porous surfaces, rinse surface with water. To sanitize non-porous surfaces, spray until wet. Let stand one minute, then wipe. To prevent mold and mildew on pre-cleaned non-porous surfaces, spray surface until wet. Allow to air dry. Repeat application on pre-cleaned surface at weekly intervals.

Table 1 lists the registrant and the respective EPA registration numbers for products containing propylene glycol.

Table 1. EPA Registration Numbers for Propylene Glycol Products

Use Category	Formulation	Registrant	EPA Registration Numbers
Air Sanitizer/ Disinfectant	Pressurized Liquid	S. C. Johnson & Son, Inc.*	4822-491
Air Sanitizer	Pressurized Liquid	Amrep, Inc.*	10807-24, 10807-37, 10807-43
Air Sanitizer	Pressurized Liquid	MEDO/SOPUS Industries, Inc.*	51838-1, 51838-2
Mite, flea, and Lice Control	Pressurized Liquid	Wellmark International *,**	2724-514, 2724-618, 2724-763, 2724-764

* Member companies of the GSPA Glycols Joint Venture.
** The insecticidal products containing propylene glycol in addition to other active ingredients will be reregistered only when all of the active ingredients have been determined to be eligible for reregistration.

Use Classification: General use.

2. Dipropylene Glycol
The following is information on the currently registered uses of dipropylene glycol products and an overview of use sites and application methods. A detailed table of the uses of dipropylene glycol eligible for reregistration is contained in Appendix A.

Type of Pesticide: Bacteriostat, Fungistat

Summary of Use Sites:

Indoor Non-Food: Dipropylene glycol is used on the following use sites: air treatment (eating establishments, hospital, commercial, institutional, household, bathroom)

Target Pests: Odor-causing bacteria, Animal pathogenic bacteria (G- and G+ vegetative), Animal viruses

Inert Uses: As an inert ingredient, dipropylene glycol facilitates delivery of formulated pesticide chemical products that are used as herbicides, fungicides, insecticides, growth regulators and attractants on various commodities.

Formulation Types: Pressurized liquid, ready-to-use

Method and Rates of Application

Air Sanitizer
As an air sanitizer, remove cap from aerosol can and place in a sequential aerosol dispenser which automatically releases a metered amount every 15 minutes. One unit should treat 6000 ft^3 of closed air space. Dispenser should be located at a height of eight feet and at a point where wind flow will carry the particles throughout the area. Each spray dose is 100 mg and the median particle size is 30 microns. Table 2 lists the registrant and the respective EPA registration numbers for products containing dipropylene glycol.

Use Classification: General use.

Table 2 lists the registrant and the respective EPA registration numbers for products containing dipropylene glycol.

Table 2. EPA Registration Numbers for Dipropylene Glycol Products

Use Category	Formulation	Registrant	EPA Registration Numbers
Air Sanitizer	Pressurized Liquid	Waterbury Companies, Inc.*	9444-19, 9444-136

* Member companies of the GSPA Glycols Joint Venture.

III. SUMMARY OF PROPYLENE GLYCOL AND DIPROPYLENE GLYCOL ASSESSMENT

A. Human Health Assessment

The Agency's use of human studies in the propylene glycol and dipropylene glycol assessment is in accordance with the Agency's Final Rule promulgated on January 26, 2006, related to Protections for Subjects in Human Research, which is codified in 40 CFR Part 26.

1. Toxicity of Propylene Glycol and Dipropylene Glycol

A brief overview of the toxicity of propylene glycol and dipropylene glycol is presented below. Further details on the toxicity of propylene glycol and dipropylene glycol can be found in the supporting documentation for this RED. The Antimicrobials Division Toxicology Endpoint Selection Committee (ADTC) memorandum and the toxicology chapter for the are available in EPA's Pesticide Docket, EPA-HQ-OPP-2006-0831 at www.regulations.gov.

The toxicological database for propylene glycol and dipropylene glycol is currently comprised of published and unpublished studies either submitted to the Agency or obtained directly from the open literature. Although the available studies do not meet the requirements of the Agency's OPPTS harmonized test guidelines published in 1998, it was determined that these studies contain useful information that is adequate for hazard characterization of propylene glycol and dipropylene glycol. These acceptable non-guideline studies include acute, subchronic, chronic, developmental, and reproductive toxicity, carcinogenicity, mutagenicity, metabolism/pharmacokinetics and dermal absorption studies. Therefore, the Agency has determined that the toxicological database is complete and sufficient for reregistration.

Major features of the acute toxicology profile for propylene glycol and dipropylene glycol are presented below in Table 3. Propylene glycol and dipropylene glycol are shown to be of low acute toxicity (Toxicity Category IV).

Table 3. Acute Toxicity of Propylene Glycol and Dipropylene Glycol Technical

Table 3. Acute Toxicity Profile of Propylene/Dipropylene Glycol			
Guideline	**Study Type**	**Results**	**Toxicity Category**
Propylene Glycol			
870.1100	Acute Oral - Rat	LD_{50} range = 8000 - 46000 mg/kg	IV
870.1100	Acute Oral - Mouse	LD_{50} range = 23000 - 24900 mg/kg	IV
870.1100	Acute Oral - Rabbit, Guinea pig	LD_{50} range = 18000 - 20000 mg/kg	IV
870.2400	Acute Eye Irritation - Rabbit	non irritant	IV
870.2500	Acute Skin Irritation - Rabbit		IV

Table 3. Acute Toxicity Profile of Propylene/Dipropylene Glycol			
		non irritant	
870.2600	Skin Sensitization	non sensitizer	N/A
Dipropylene Glycol			
870.1100	Acute Oral - Rat	LD_{50} > 5010 mg/kg	IV
870.1100	Acute Oral - Rat	LD_{50} range > 5000 to >15000 mg/kg	IV
870.1200	Acute Dermal - Rabbit	LD_{50} > 5010 mg/kg	IV
870.1200	Acute Dermal - Rabbit	LD_{50} > 2000 mg/kg	IV
870.1300	Acute Inhalation - Rat	LC_{50} > 2.34 mg/L	IV
870.2400	Acute Eye Irritation - Rabbit	slight irritant	IV
870.2400	Acute Eye Irritation - Rabbit	slight irritant	IV
870.2500	Acute Skin Irritation - Rabbit	non irritant	IV
870.2600	Skin Sensitization - Guinea Pig	non sensitizer	N/A

N/A = not applicable

General Toxicity Observations

Upon reviewing the available toxicity information, the Agency has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to propylene glycol and dipropylene glycol. This conclusion is based on the results of toxicity testing of propylene glycol and dipropylene glycol in which 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 observed.

Carcinogenicity Classification

A review of the available data has shown propylene glycol and dipropylene glycol to be negative for carcinogenicity in studies conducted up to the testing limit doses established by the Agency; therefore, no further carcinogenic analysis is required.

Mutagenicity Potential

Propylene glycol and dipropylene glycol were tested for mutagenic or genotoxic potential and found to be negative in a battery of studies: a bacterial gene mutation assay using Salmonella

typhimurium, and in vitro Chinese hamster ovary (CHO) mutation assay, an in vitro Chinese hamster ovary (CHO) chromosomal aberration assay and an in vitro sister chromatid exchange assay.

2. FQPA Safety Factor

The FQPA Safety Factor (as required by the Food Quality Protection Act of 1996) is intended to provide an additional 10-fold safety factor (10X), to protect for special sensitivity in infants and children to specific pesticide residues in food, drinking water, or residential exposures, or to compensate for an incomplete database. The FQPA Safety Factor has been removed (i.e., reduced to 1X) for propylene glycol and dipropylene glycol because there is no pre- or post-natal evidence for increased susceptibility following exposure. Further, the Agency has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to propylene glycol and dipropylene glycol based on the low toxicity observed in studies conducted near or above testing limit doses as established in the OPPTS 870 series harmonized test guidelines. Therefore, a quantitative risk assessment was not conducted for propylene glycol and dipropylene glycol.

3. Population Adjusted Dose (PAD)

Dietary risk is characterized in terms of the Population Adjusted Dose (PAD), which reflects the reference dose (RfD), either acute or chronic, that has been adjusted to account for the FQPA Safety Factor (SF). This calculation is performed for each population subgroup. A risk estimate that is less than 100% of the acute or chronic PAD is not of concern. Since toxicological endpoints for risk assessment were not identified based on the available data, RfDs and PADs have not been calculated for propylene glycol and dipropylene glycol.

4. Dietary and Residential Exposure

Dietary exposure (food and drinking water) could potentially occur from the use of propylene glycol and dipropylene glycol as a preservative in food packaging adhesives and from its use as an inert ingredient in agricultural pesticide formulations. Residential exposure could also potentially occur as a result of the use of propylene glycol and dipropylene glycol in and around the home as a sanitizer, disinfectant and pet treatment. However, risk estimates have not been calculated for potential exposures to propylene glycol and dipropylene glycol on food, in drinking water, or as a result of use in residential settings because there are no toxicological endpoints of concern according to a review of the available toxicity data.

5. Aggregate Exposure

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require "that there is a reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure will typically include exposures from food, drinking water, residential uses of a pesticide and other non-occupational sources of exposure.

Since toxicological endpoints for risk assessment were not identified based on the available data, an aggregate risk assessment was not conducted for propylene glycol and dipropylene glycol.

6. Occupational Exposure

The occupational exposure assessment for propylene glycol and dipropylene glycol addresses potential exposures and risks to humans who may be exposed in occupational settings. An occupational risk assessment is required for an active ingredient if: 1) certain toxicological criteria are triggered; and 2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete. For propylene glycol and dipropylene glycol, there is potential for exposure, however, there are no toxicological endpoints of concern, according to a review of the available toxicity data.

7. Human Incident Data

The Agency reviewed available sources of human incident data for incidents relevant to propylene glycol and dipropylene glycol. EPA consulted the following sources of information for human poisoning incidents related to propylene glycol and dipropylene glycol use: **(1) OPP Incident Data System (IDS)** - The Office of Pesticide Programs (OPP) **Incident Data System** contains reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992; **(2) California Department of Pesticide Regulation (1982-2004)** – The California Department of Pesticide Regulation pesticide poisoning surveillance program consists of reports from physicians of illness suspected of being related to pesticide exposure since 1982. **(3) National Pesticide Information Center (NPIC)** - NPIC is a toll-free information service supported by OPP that provides a ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991. **(4) National Poison Control Centers (PCC)** (1993 – 1996).

Although there are incidents that have been reported associated with propylene glycol or dipropylene glycol, there is no one reported incident involving propylene glycol or dipropylene glycol as an individual chemical exposure. Either no effects or minor effects (nasal irritation and sensitization) involved in these reported incidents. Since propylene glycol and dipropylene glycol are often formulated with other active ingredients, reported symptoms may result from reactions to the other active ingredients or the combination of propylene glycol and dipropylene glycol with other ingredients.

B. Environmental Assessment

A summary of the Agency's environmental review is presented below. For detailed discussions of all aspects of the environmental review, see the Product Chemistry, Environmental Fate, Ecotoxicology, and Toxicology chapters available in EPA's Pesticide Docket, EPA-HQ-OPP-2006-0831 at www.regulations.gov.

1. Environmental Fate and Transport

Propylene glycol and dipropylene glycol are aliphatic trihydroxy chemicals that do not contain any hydrolyzable hydrogen. For this reason, the Agency granted a waiver from the aquatic hydrolysis study. However, the Agency has relied on data and fate properties of propylene glycol and dipropylene glycol obtained from published literature to assess environmental health risks.

These data suggest that propylene glycol and dipropylene glycol are miscible in water, mobile in soils, low absorptivity to soil, and stable to abiotic hydrolytic degradation as well as soil and aquatic photolysis. In aerobic soils, propylene glycol degrades to CO_2 in 4 days, whereas biodegradation of dipropylene glycol may be a slower process according to biological screening tests. However, this process may still be an important mechanism for removal of dipropylene glycol from aerobic soil. The low KOW indicates that propylene glycol and dipropylene glycol are not likely to bioaccumulate in aquatic organisms. With a vapor pressure of 0.129 mm Hg at 25 °C, propylene glycol and dipropylene glycol exist almost entirely in the vapor phase in the atmosphere and degrade rapidly (half-life approximately 13-32 hours) by reaction with photochemically produced hydroxyl radicals. Therefore, the presence of propylene glycol and dipropylene glycol in the environment, including the atmosphere, do not pose a concern.

2. Ecological Risk

a. Toxicity (Hazard) Assessment

As a result of the Phase IV review of propylene glycol and dipropylene glycol for reregistration under FIFRA, ecological effects data requirements were waived due to its high volatility, known low toxicity, and available data. Data obtained from published studies provide additional confirmation of the low toxicity of the compound to fish and aquatic invertebrates (Table 4). As mentioned earlier in this document, no toxicological endpoints were selected for risk assessment based on the available mammalian database.

Table 4. Ecotoxicity of Propylene Glycol and Dipropylene Glycol

Species	Percent Active Ingredient	Test Type	Toxicity	Reference
Mysid (*Mysidopsis bahia)*	99.9	96-hour static acute	LC50 = 11,000 ppm	MRID #40228401 (Mayer, 1986)
Sheepshead minnow (*Cyprinodon variegatus*)	99.9	96-hour static acute	LC50 = 48,000 ppm	MRID #40228401 (Mayer, 1986)
Bluegill sunfish (*Lepomis macrochirus*)	unknown	96 hour static acute	LC50 > 10,000 ppm	Verschuren, 1983

Species	Percent Active Ingredient	Test Type	Toxicity	Reference
Menidia beryllina	unknown	96 hour static	LC50 > 10,000 ppm	Verschuren, 1983
Fathead minnow (*Pimephales promelas*)	unknown	96 hour flow-through	LC 50 59,900 - 77,400 ppm	Geiger et al., 1988

Adverse effects to nontarget organisms are not anticipated from the indoor use of propylene glycol and dipropylene glycol due to the low likelihood of exposure. The very low toxicity of the compound to aquatic organisms, as indicated by the high LC_{50} values in the table above, further supports the unlikelihood of adverse effects to fish and aquatic invertebrates.

b. Risk to Listed Species

Section 7 of the Endangered Species Act, 16 U.S.C. Section 1536(a)(2), requires all federal agencies to consult with the National Marine Fisheries Service (NMFS) for marine and anadromous listed species, or the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if they are proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to ensure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species means "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 C.F.R. § 402.02.

To facilitate compliance with the requirements of the Endangered Species Act subsection (a)(2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

For certain use categories, the Agency assumes there will be minimal environmental exposure, and only a minimal toxicity data set is required (Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered

and Threatened Species Effects Determinations, 1/23/04, Appendix A, Section IIB, pg.81). Chemicals in these categories therefore do not undergo a full screening-level risk assessment, and are considered to fall under a "no effect" determination. Due to the low likelihood of exposure and low toxicity of propylene glycol and dipropylene glycol, the Agency expects no effects to listed species or critical habitats and therefore makes a "No Effect" determination for this chemical.

IV. RISK MANAGEMENT, REREGISTRATION AND TOLERANCE REASSESSMENT DECISION

A. Determination of Reregistration Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether products containing the active ingredient are eligible for reregistration. The Agency has previously identified and required the submission of the generic (*i.e.* active ingredient-specific) data to support reregistration of products containing propylene glycol and dipropylene glycol. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of all supported products containing propylene glycol and dipropylene glycol.

The Agency has completed its assessment of the dietary, drinking water, residential, ecological and occupational risks associated with the use of pesticide products containing the active ingredients propylene glycol and dipropylene glycol. Based on a review of these data, the Agency has sufficient information on the human health and ecological effects of propylene glycol and dipropylene glycol to make a decision as part of the tolerance reassessment process under FFDCA and reregistration under FIFRA, as amended by FQPA. The Agency has determined that propylene glycol and dipropylene glycol containing products are eligible for reregistration. Appendix A summarizes the uses of propylene glycol and dipropylene glycol that are eligible for reregistration. Appendix B identifies the generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of propylene glycol and dipropylene glycol, and lists the submitted studies that the Agency found acceptable.

B. Comments and Responses

Supporting documents for propylene glycol and dipropylene glycol were not issued for public comment per the Agency's public participation process because no toxicological endpoints were identified and, as such, a quantitative risk assessment was not conducted. To ensure that opportunity is presented to the public to comment on the risk management decisions and supporting documents for propylene glycol and dipropylene glycol, the Agency will implement a 60-day public comment period on this RED document.

C. Regulatory Position

1. Food Quality Protection Act Findings

a. "Risk Cup" Determination

Upon reviewing the available toxicity information, the Agency has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to propylene glycol and dipropylene glycol. This conclusion is based on the results of toxicity testing of propylene glycol and dipropylene glycol in which 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 observed. The Agency has concluded that the exemption from the requirement for a tolerance is appropriate and is considered reassessed as required by FQPA. An aggregate assessment was not conducted for exposures through food, drinking water and residential exposure since toxicological endpoints for risk assessment were not identified based on the available data. In reaching this determination, EPA has considered the available information on the special sensitivity of infants and children, as well as aggregate exposure.

b. Determination of Safety to U.S. Population

As part of the FQPA tolerance reassessment process, EPA has concluded that there are no endpoints of concern for oral, dermal, or inhalation exposure to propylene glycol and dipropylene glycol. This conclusion is based on the results of toxicity testing of propylene glycol and dipropylene glycol in which 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 observed. The Agency has determined that the established exemption from the requirement for a tolerance for propylene glycol and dipropylene glycol meets the safety standards under the FQPA amendments to section 408(b)(2)(D) of the FFDCA, and that there is a reasonable certainty no harm will result to the general population or any subgroup from the use of propylene glycol and dipropylene glycol. In reaching this conclusion, the Agency has considered 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 and dipropylene glycol, the Agency has determined that exposure to it does not result in human health effects of concern. Therefore, a quantitative risk assessment was not necessary for this pesticide.

c. Determination of Safety to Infants and Children

EPA has determined that the established exemption from a requirement for a tolerance for propylene glycol and dipropylene glycol, meet the safety standards under the FQPA amendments to section 408(b)(2)(C) of the FFDCA, that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children considers factors of the toxicity, use practices, and environmental behavior noted above for the general population, but also takes into account the possibility of increased dietary exposure due to the specific consumption patterns of infants and children, as well as the possibility of increased susceptibility to the toxic effects of propylene glycol and dipropylene glycol residues in this population subgroup.

In determining whether or not infants and children are particularly susceptible to toxic effects from propylene glycol and dipropylene glycol residues, the Agency considered the completeness of the database for developmental and reproductive effects, the nature of the effects observed, and other information. The FQPA Safety Factor has been removed (i.e., reduced to 1X) for propylene glycol and dipropylene glycol because there is no pre- or post-natal evidence for increased susceptibility following exposure.

d. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that EPA include evaluations of potential effects in wildlife. For pesticides, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, propylene glycol and dipropylene glycol may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

e. Cumulative Risks

Any risks summarized in this document are those that result only from the use of propylene glycol and dipropylene glycol. The Food Quality Protection Act (FQPA) requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common toxic mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the substances individually. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for propylene glycol and dipropylene glycol. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

2. Tolerance Exemptions and Summary

Propylene glycol and dipropylene glycol are exempted from the requirement of a tolerance when used as a diluent (solvent, cosolvent). The following tolerance exemptions for propylene glycol and dipropylene glycol are listed in 40 CFR 180.910 [formerly 180.1001(c)] and only for propylene glycol in 180.930 [formerly 180.1001 (e)]:

> 180.910. Propylene glycol and dipropylene glycol are exempted from the requirement of a tolerance when used as a diluent (solvent, cosolvent) in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations when applied to growing crops or to raw agricultural commodities after harvest.
>
> 180.930. Propylene glycol is exempted from the requirement of a tolerance when used as a defoaming agent (solvent, cosolvent) in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

In addition to the above, propylene glycol is approved by the Food and Drug Administration (FDA) as a preservative in food products as listed in 21 CFR, Part 184-Direct Food Substances Affirmed as Generally Recognized as Safe (GRAS):

> 184.1666(d). The ingredient is used in foods at levels not to exceed current good manufacturing practice in accordance with Sec. 184.1(b)(1). Current good manufacturing practice results in maximum levels, as served, of 5 percent for alcoholic beverages, as defined in Sec. 170.3(n)(2) of this chapter; 24 percent for confections and frostings as defined in Sec. 170.3(n)(9) of this chapter; 2.5 percent for frozen dairy products as defined in Sec. 170.3(n)(20) of this chapter; 97 percent for seasonings and flavorings as defined in Sec. 170.3(n)(26) of this chapter; 5 percent for nuts and nut products as defined in Sec. 170.3(n)(32) of this chapter; and 2.0 percent for all other food categories.

a. Codex Harmonization

Currently there are no Codex MRLs established for propylene glycol and dipropylene glycol.

D. Regulatory Rationale

The Agency has determined propylene glycol and dipropylene glycol are eligible for reregistration. Based on the available data, the Agency has concluded that propylene glycol and dipropylene glycol exhibit low toxicity and exposure to propylene glycol and dipropylene glycol used as both an active or inert ingredient do not present risks of concern to the Agency. Therefore, no mitigation measures are necessary at this time.

1. Listed Species Considerations

a. The Endangered Species Act

Section 7 of the Endangered Species Act, 16 U.S.C. Section 1536(a)(2), requires all federal agencies to consult with the National Marine Fisheries Service (NMFS) for marine and anadromous listed species, or the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if they are proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to insure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species means "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 C.F.R. § 402.02.

To facilitate compliance with the requirements of the Endangered Species Act subsection (a)(2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

For certain use categories, the Agency assumes there will be minimal environmental exposure, and only a minimal toxicity data set is required (Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered and Threatened Species Effects Determinations, 1/23/04, Appendix A, Section IIB, pg.81). Chemicals in these categories therefore do not undergo a full screening-level risk assessment, and are considered to fall under a "no effect" determination. Due to the low likelihood of exposure and low toxicity of propylene glycol and dipropylene glycol, the Agency expects no effects to listed species or critical habitats and therefore makes a "No Effect" determination for this chemical.

b. General Risk Mitigation

Propylene glycol and dipropylene glycol end-use products (EPs) may also contain other registered pesticides. Although the Agency is not proposing any mitigation measures for products containing propylene glycol and dipropylene glycol specific to federally listed species, the Agency needs to address potential risks from other end-use products. Therefore, the Agency requires that users adopt all listed species risk mitigation measures for all active ingredients in

the product. If a product contains multiple active ingredients with conflicting listed species risk mitigation measures, the more stringent measure(s) should be adopted.

V. WHAT REGISTRANTS NEED TO DO

The Agency has determined that propylene glycol and dipropylene glycol are eligible for reregistration. No additional generic data are required at this time to support this decision.

For end use products containing the active ingredient propylene glycol and dipropylene glycol, the registrant needs to submit the following items for each product.

Within 90 days from the receipt of the product-specific data call-in (PDCI):

1. completed response forms to the PDCI (i.e., PDCI response form and requirements status and registrant's response form); and

2. submit any time extension or waiver requests with a full written justification.

Within eight months from the receipt of the PDCI:

1. two copies of the confidential statement of formula (EPA Form 8570-4);

2. a completed original application for reregistration (EPA Form 8570-1). Indicate on the form that it is an "application for reregistration";

3. a completed form certifying compliance with data compensation requirements (EPA Form 8570-34);

4. if applicable, a completed form certifying compliance with cost share offer requirements (EPA Form 8570-32); and

5. the product-specific data responding to the PDCI.

Please contact Marshall Swindell at (703) 308-6341 with questions regarding product reregistration and/or the PDCI. All materials submitted in response to the PDCI should be addressed as follows:

By US mail:
Document Processing Desk (PDCI)
Marshall Swindell
US EPA (7504P)
1200 Pennsylvania Ave., NW
Washington, DC 20460

By express or courier service:
Document Processing Desk (PDCI)
Marshall Swindell
Office of Pesticide Programs (7504P)
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

A. Manufacturing-Use Products

There are no currently registered propylene glycol and dipropylene glycol manufacturing-use products.

1. Additional Generic Data Requirements

The generic data base supporting the reregistration of propylene glycol and dipropylene glycol for the above eligible uses has been reviewed and determined to be substantially complete. Therefore at this time, there are no generic data requirements.

B. End-Use Products

1. Additional Product-Specific and Efficacy Data Requirements

Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. Registrants must review previous data submissions to ensure that they meet current EPA acceptance criteria and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then the study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product.

The Agency considers the terms "sanitizer" and "sanitization" to be public health claims, regardless of the use site or whether the specific organisms for which the product is efficacious against are identified or not. This policy was reiterated in the proposed Part 152/156 Antimicrobial Registration Requirements, 64 FR 50672-50730, September 17, 1999. Upon finalization of this proposed rulemaking, efficacy data will be required to support the continued use of the term "air sanitizer" on the product label.

Until the proposed Product Performance Guidelines for proposed Part 152/15 are finalized, testing requirements are being deferred for products of this type. Currently, efficacy requirements are satisfied by the chemical formula statement showing appropriate glycol content. For products containing at least 5% glycols (propylene glycol and dipropylene, dipropylene, and/or propylene glycols), quantitative chemical determinations must be performed, using an air sampling device, to show the concentration of glycol vapor achieved with the product in an enclosed experimental room or chamber when used as directed.

A product-specific data call-in, outlining specific data requirements, will be issued shortly. In the interim, no additional public health claims can be made unless supported by the appropriate efficacy data. A list of product-specific efficacy data requirements is listed in Table 5 below.

Table 5. Product-specific Efficacy Data Requirements

Guideline Number	Study Title
810.2100 (c,d,e)	Products for use on hard surfaces – AOAC use dilution/germicidal spray/carrier.
810.2100 (g)	Products for use on hard surfaces – virucidal activity method.
810.2100 (f)	Products for use on hard surfaces – fungicidal test.
810.2100 (l)	Products for use on hard surfaces – hard inanimate surface non-food.
810.2400 (b,l)	Chemical analysis.
830.7050	UV/Visible absorption.

VI. APPENDICES

US EPA ARCHIVE DOCUMENT

Appendix A: Use Patterns Eligible for Reregistration

Use Categories:
(1) Agricultural premises and equipment
(2) Food handling/ storage establishments premises and equipment
(3) Commercial, institutional and industrial premises and equipment
(4) Residential and public access premises
(5) Medical premises and equipment
(6) Human water systems
(7) Materials preservatives
(8) Industrial processes and water systems
(9) Antifouling coatings
(10) Wood preservatives
(11) Swimming pools
(12) Aquatic areas

Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
2. Food Handling/Storage Establishments Premises and Equipment				
Air Treatment (Eating Establishments)	1. 10807-43 - pressurized liquid - automatic dispenser	1. 7 ounce product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	1. information not given on label	1. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	2. 10807-37 & 10807-24 - pressurized liquid - manual spray	2. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	2. spray several times per day	2. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use

Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
3. Commercial, Institutional and Industrial Premises and Equipment				
Commercial Premises & equipment	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes; for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
Shower Room Premises	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes; for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
Air Treatment (Unspecified)	1. 9444-136- pressurized liquid - automatic dispenser	1. metered valve actuates every fifteen minutes - 7 ounce product treats a room up to 30 X 20 X 10	1. information not given on label	1. do not contaminate water, food or feed by storage or disposal
	2. 4822-293- pressurized liquid - manual spray	2. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9)	2. information not given on label	2. avoid contact with food and food utensils
Laundry Equipment	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

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Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
Air Treatment (Locker Room)	1. 10807-43- pressurized liquid - automatic dispenser	1. 7 ounces of product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	1. information not given on label	1. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	2. 9444-19- pressurized liquid - automatic intermittent aerosol dispenser	2. 6.2 ounces treats 6,000 cubic feet of closed air space.	2. sprayed at intervals	2. do not contaminate water, food or feed
	3. 10807-37 & 10807-24- pressurized liquid - manual spray	3. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	3. spray several times per day	3. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
Locker Room Premises	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes or for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
Air Treatment (Institutional)	1. 51838-1 - ready to use solution- automatic dispenser operation	1. 7 ounce product for each 6,000 cubic feet of closed air space	1. product sprayed at intervals	1. avoid contamination of food
	2. 51838-1- pressurized liquid - for manual operation	2. fill average size room with mist (approximately 15 sprays)	2. repeat application several times daily	2. avoid contamination of food
	3. 10807-37 & 10807-24- pressurized liquid- manual spray	3. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	3. spray several times per day	3. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	4. 4822-293- pressurized liquid - manual spray	4. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9)	4. information not given on label	4. avoid contact with food and food utensils
	5. 4822-531- pressurized liquid - wall mounted unit in continuous action aerosol can	5. one second spray for a 9.5 X 9 X 7 room	5. information not given on label	5. do not position near heat or electrical sources; do not spray directly onto surfaces; in case of contact with surfaces, wipe immediately with damp cloth.

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Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
	6. 44446-20- pressurized liquid - manual spray	6. spray for three seconds	6. information not given on label	6. wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
	7. 4822-531- wall mounted unit in metered dose aerosol can or pressurized liquid - hand held unit	7. using a 120 µl valve with .22 ounces of product: -1 time for 2.5 X 2.5 X 7 room -2 times for 4 X 3 X 7 room -3 times for 4.5 X 4 X 7 room -4 times for 5 X 5 X 7 room using a 185 µl valve- -1 time for 3 X 3 X 7 room -2 times for 4.5 X 4 X 7 room -3 times for a 5.5 X 5 X 7 room 4 times for a 6 X 6 X 7 room	7. information not given on label	7. do not position near heat or electrical sources; do not spray directly onto surfaces; in case of contact with surfaces, wipe immediately with damp cloth.

Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
	8. 10807-43-pressurized liquid - automatic dispenser	8. 7 ounce product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	8. information not given on label	8. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
Air Treatment (Commercial)	1. 51838-1-ready to use solution - for automatic dispenser operation	1. 7 ounce product for each 6,000 cubic feet of closed air space	1. product sprayed at intervals	1. avoid contamination of food
	2. 51838-1-ready to use solution - for manual operation	2. fill average size room with mist (approximately 15 sprays)	2. repeat application several times daily	2. avoid contamination of food
	3. 10807-43 - pressurized liquid-automatic dispenser	3. 7 ounce product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	3. information not given on label	3. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use

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Use Site	Formulation	Application Rate (Range)	No. of Applications	Use Limitations
	4. 10807-37 & 10807-24-pressurized liquid - manual spray	4. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	4. spray several times per day	4. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	5. 9444-19 - Pressurized liquid - automatic intermittent aerosol dispenser	5. 6.2 ounces of product treats 6,000 cubic feet of closed air space.	5. sprayed at intervals	5. do not contaminate water, food or feed
	6. 4822-293 - pressurized liquid - manual spray	6. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9)	6. information not given on label	6. avoid contact with food and food utensils
	7. 44446-20-pressurized liquid - manual spray	7. spray for three seconds	7. information not given on label	7. wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
	8. 51838-2 - pressurized liquid - automatic dispenser	8. spray for one second toward center of average size room (10 X 14 X 8)	8. repeat application several times daily	8. spray away from drapes, walls, plastic, vinyl, painted or varnished surfaces

Air Treatment (Transp Facilities)	1. 51838-1-ready to use solution - for automatic dispenser	1. 7 ounces of product for each 6,000 cubic feet of closed air space	1. product sprayed at intervals	1. avoid contamination of food
	2. 4822-293-pressurized liquid - manual spray	2. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9	2. information not given on label	2. avoid contact with food and food utensils
	3. 10807-37 & 10807-24 - pressurized liquid - manual spray	3. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	3. spray several times per day	3. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	4. 51838-1-ready to use solution - for manual operation	4. fill average size room with mist (approximately 15 sprays)	4. repeat application several times daily	4. avoid contamination of food

Air Treatment (Industrial)	1. 51838-1-ready to use solution - automatic dispenser	1. 7 ounces of product for each 6, 000 cubic feet of closed air space	1. product sprayed at intervals	1. avoid contamination of food
	2. 51838-1-ready to use solution - for manual operation	2. fill average size room with mist (approximately 15 sprays)	2. repeat application several times daily	2. avoid contamination of food
	3. 10807-37 & 10807-24-pressurized liquid - manual spray	3. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	3. spray several times per day	3. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	4. 10807-43-pressurized liquid - automatic dispenser	4. 7 ounces of product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	4. information not given on label	4. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use

4. Residential and Public Access Premises				
Air Treatment (Unspecified)	1. 9444-136-pressurized liquid - automatic dispenser	1. metered valve actuates every fifteen minutes - 7 ounce product treats a room up to 30 X 20 X 10	1. information not given on label	1. do not contaminate water, food or feed by storage or disposal
	2. 4822-293-pressurized liquid - manual spray	2. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9)	2. information not given on label	2. avoid contact with food and food utensils
Household (Premises & Contents)	44446-20-pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes or for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

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Air treatments (commercial/household)	4822-531-pressurized liquid - wall mounted unit in metered dose aerosol can or hand held unit	using a 120 µl valve with .22 ounces of product: -1 time for 2.5 X 2.5 X 7 room -2 times for 4 X 3 X 7 room -3 times for 4.5 X 4 X 7 room -4 times for 5 X 5 X 7 room using a 185 µl valve- -1 time for 3 X 3 X 7 room -2 times for 4.5 X 4 X 7 room -3 times for a 5.5 X 5 X 7 room 4 times for a 6 X 6 X 7 room	information not given on label	do not position near heat or electrical sources; do not spray directly onto surfaces; in case of contact with surfaces, wipe immediately with damp cloth.
Laundry Equipment	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toile
Automobiles	44446-20 - pressurized liquid - manual spray	spray into air conditioning system and spray for four to six seconds	information not given on label	shut off air conditioner after applying the product; wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

Shower Room Premises	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes or for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
Hard Nonporous Surface	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
Environmental Inanimate Hard Surfaces	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
Garbage Storage Premises & Containers	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes or for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
Bathroom Premises	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes or for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

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Air Treatment (Bathroom)	1. 10807-43- pressurized liquid - automatic dispenser	1. 7 ounces of product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	1. information not given on label	1. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	2. 9444-19- pressurized liquid - automatic intermittent aerosol dispenser	2. 6.2 ounce of product treats 6,000 cubic feet of closed air space.	2. sprayed at intervals	2. do not contaminate water, food or feed
	3. 44446-20- pressurized liquid - manual spray	3. spray for three seconds	3. information not given on label	3. wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet
	4. 10807-37- pressurized liquid - manual spray	4. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	4. spray several times per day	4. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use

	5. 51838-1- pressurized liquid - manual operation	5. fill average size room with mist (approximately 15 sprays)	5. repeat application several times daily	5. avoid contamination of food
	6. 4822-293 - pressurized liquid - manual spray	6. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9	6. information not given on label	6. avoid contact with food and food utensils
	7. 4822-531- pressurized liquid - wall mounted unit in continuous action aerosol can	7. one second spray for a 9.5 X 9 X 7 room	7. information not given on label	7. information not given on label
	8. 10807-24 - pressurized liquid- manual spray	8. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	8. spray several times per day	8. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use

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	9. 4822-531- wall mounted unit in metered dose aerosol can or pressurized liquid - hand held unit	9. using a 120 µl valve with .22 ounces of product: -1 time for 2.5 X 2.5 X 7 room -2 times for 4 X 3 X 7 room -3 times for 4.5 X 4 X 7 room -4 times for 5 X 5 X 7 room using a 185 µl valve- -1 time for 3 X 3 X 7 room -2 times for 4.5 X 4 X 7 room -3 times for a 5.5 X 5 X 7 room 4 times for a 6 X 6 X 7 room	9. information not given on label	9. information not given on label
Locker Room Premises	44446-20 - pressurized liquid - manual spray	spray surface until completely wet and allow to remain wet for 10 minutes or for air sanitization spray for three seconds	information not given on label	wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

Air Treatment (Locker Room)	1. 10807-43-pressurized liquid - automatic dispenser	1. 7 ounces of product contains 3400 controlled sprays that will last for 30 days when used on a 24 hour basis or 60 days if used 12 hours per day when set to dispense every 15 minutes (room size not specified)	1. information not given on label	1. do not use in nurseries or rooms where infants, ill or aged patients are confined; food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	2. 9444-19-pressurized liquid - automatic intermittent aerosol dispenser	2. 6.2 ounces treats 6,000 cubic feet of closed air space.	2. sprayed at intervals	2. do not contaminate water, food or feed
	3. 10807-37 & 10807-24-pressurized liquid - manual spray	3. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	3. spray several times per day	3. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
Birds (Caged) (Animal Treatment)	11715-20 - pressurized liquid- manual spray	spray lightly with one burst of 2 or 3 seconds	no more than 2 times per week	information not given on label
Pet Bird Cages (Enclosed Premise Treatment)	11715-20 - pressurized liquid-manual spray	thoroughly spray perches and cage	regular intervals	information not given on label

Air Treatment (Pet Kennels & Enclosed Premise Treatment)	1. 4822-531-pressurized liquid - wall mounted unit in metered dose aerosol can or hand held unit	1. using a 120 µl valve with .22 ounces of product: -1 time for 2.5 X 2.5 X 7 room -2 times for 4 X 3 X 7 room -3 times for 4.5 X 4 X 7 room -4 times for 5 X 5 X 7 room using a 185 µl valve- -1 time for 3 X 3 X 7 room -2 times for 4.5 X 4 X 7 room -3 times for a 5.5 X 5 X 7 room 4 times for a 6 X 6 X 7 room	1. information not given on label	1. do not position near heat or electrical sources; do not spray directly onto surfaces; in case of contact with surfaces, wipe immediately with damp cloth.
	2. 4822-531-pressurized liquid - wall mounted unit in continuous action aerosol can	2. one second spray for a 9.5 X 9 X 7 room	2. information not given on label	2. information not given on label
	3. 4822-293-pressurized liquid - manual spray	3. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9	3. information not given on label	3. avoid contact with food and food utensils

5. Medical premises and equipment				
Air treatments (sickroom)	1. 4822-531- pressurized liquid - wall mounted unit in metered dose aerosol can or hand held unit	1. using a 120 µl valve with .22 ounces of product: -1 time for 2.5 X 2.5 X 7 room -2 times for 4 X 3 X 7 room -3 times for 4.5 X 4 X 7 room -4 times for 5 X 5 X 7 room using a 185 µl valve- -1 time for 3 X 3 X 7 room -2 times for 4.5 X 4 X 7 room -3 times for a 5.5 X 5 X 7 room 4 times for a 6 X 6 X 7 room	1. information not given on label	1. do not position near heat or electrical sources; do not spray directly onto surfaces; in case of contact with surfaces, wipe immediately with damp cloth.
	2. 4822-531- pressurized liquid - wall mounted unit in continuous action aerosol can	2. one second spray for a 9.5 X 9 X 7 room	2. information not given on label	2. information not given on label

Air treatment (hospital)	1. 51838-2 - pressurized liquid- manual spray	1. spray for one second toward center of average size room (10 X 14 X 8)	1. repeat application several times daily	1. spray away from drapes, walls, plastic, vinyl, painted or varnished surfaces
	2. 51838-1- ready to use solution - automatic dispenser	2. 7 ounces of product for each 6, 000 cubic feet of closed air space	2. product sprayed at intervals	2. avoid contamination of food
	3. 51838-1- ready to use solution - for manual operation	3. fill average size room with mist (approximately 15 sprays)	3. repeat application several times daily	3. avoid contamination of food
	4. 10807-37 & 10807-24 - pressurized liquid - manual spray	4. spray the room until a light fog forms - spray 6 to 8 seconds in an average room (10 X 10)	4. spray several times per day	4. food, food contact surfaces and utensils should be protected from exposure to the spray or rinsed with potable water before use
	5. 4822-293 - pressurized liquid - manual spray	5. spray upward in center of room for 10 seconds in average room of 12 X 12 X 9	5. information not given on label	5. avoid contact with food and food utensils
	6. 44446-20- pressurized liquid - manual spray	6. spray for three seconds	6. information not given on label	6. wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet

	7. 9444-19 - pressurized liquid - automatic intermittent aerosol dispenser	7. 6.2 ounces of product treats 6,000 cubic feet of closed air space	7. sprayed at intervals	7. do not contaminate water, food or feed
Hospital (Premises and Materials)	44446-20- pressurized liquid -manual spray	decontamination against HIV-1 of surfaces/objects soiled with blood/body fluids - 1800 ppm of active quaternary water for a contact time of 10 minutes at room temperature - use a 10 minute contact time for disinfection against all other bacteria and fungi claimed	information not given on label	dispose of infectious materials according to federal, state and local regulations

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Appendix B: Table of Generic Data Requirements and Studies Used to Make the Reregistration Decision

Guide To Appendix B

Appendix B lists the **generic** (not product specific) data requirements which support the re-registration of propylene glycol and dipropylene glycol. These requirements apply to propylene glycol and dipropylene glycol in all products, including data requirements for which a technical grade active ingredient is the test substance. The data table is organized in the following formats:

1. **Data Requirement** (Columns 1 and 2). The data requirements are listed by Guideline Number. The first column lists the new Part 158 Guideline numbers, and the second column lists the old Part 158 Guideline numbers. Each Guideline Number has an associated test protocol set forth in the Pesticide Assessment Guidance, which are available on the EPA website.

2. **Guideline Description** (Column 3). Identifies the guideline type.

Use Pattern (Column 4). This column indicates the standard Antimicrobial Division use patterns categories for which the generic (not product specific) data requirements apply. The number designations are used in Appendix B.

3.

(1) Agricultural premises and equipment
(2) Food handling/ storage establishments premises and equipment
(3) Commercial, institutional and industrial premises and equipment
(4) Residential and public access premises
(5) Medical premises and equipment
(6) Human water systems
Materials preservatives
(8) Industrial processes and water systems
Antifouling coatings
Wood preservatives
Swimming pools
(7) Aquatic areas

(9) 4. **Bibliographic Citation** (Column 5). If the Agency has data in its files to support a specific generic Guideline requirement,
(10) this column will identify each study by a "Master Record Identification (MRID) number. The listed studies are considered
(11) "valid" and acceptable for satisfying the Guideline requirement. Refer to the Bibliography appendix for a complete citation of
(12) each study.

DATA REQUIREMENT				CITATION(S)
New Guideline Number	Old Guideline Number	Study Title	Use Pattern	MRID Number
TECHNICAL GRADE ACTIVE INGREDIENT (TGAI) CHEMISTRY				
830.1550	61-1	Product Identity and Composition	2,3,4,5	43178601, 43179501
830.1600 830.1620 830.1650	61-2A	Starting Materials and Manufacturing Process	2,3,4,5	43178601, 43179501
830.1670	61-2B	Formation of Impurities	2,3,4,5	43178601, 43179501
830.1700	62-1	Preliminary Analysis	2,3,4,5	43178601, 43179502, 43858501
830.1750	62-2	Certification of Limits	2,3,4,5	43178601, 43179502
830.1800	62-3	Analytical Method	2,3,4,5	43178602, 43179502
830.6302	63-2	Color	2,3,4,5	43178603, 43179503
830.6303	63-3	Physical State	2,3,4,5	43178603, 43179503
830.6304	63-4	Odor	2,3,4,5	43178603, 43179503
830.7200	63-5	Melting Point	2,3,4,5	Not required
830.7220	63-6	Boiling Point	2,3,4,5	43178603
830.7300	63-7	Density	2,3,4,5	43178603
830.7840 830.7860	63-8	Solubility	2,3,4,5	43178603, 43179503
830.7950	63-9	Vapor Pressure	2,3,4,5	43178603, 43179503
830.7370	63-10	Dissociation Constant in Water	2,3,4,5	Not required

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DATA REQUIREMENT				CITATION(S)
New Guideline Number	Old Guideline Number	Study Title	Use Pattern	MRID Number
830.7550 830.7560 830.7570	63-11	Partition Coefficient (Octanol/Water)	2,3,4,5	43178603, 43179503
830.7000	63-12	pH	2,3,4,5	43178603, 43179503
830.6313	63-13	Stability	2,3,4,5	43178603, 43179503
830.6314	63-14	Oxidizing/Reducing Action	2,3,4,5	Not required
830.6315	63-15	Flammability	2,3,4,5	43178603, 43179503
830.6316	63-16	Explodability	2,3,4,5	Not required
830.6317	63-17	Storage Stability	2,3,4,5	43178603, 43179503
830.7100	63-18	Viscosity	2,3,4,5	43178603, 43179503
830.6319	63-19	Miscibility	2,3,4,5	43178603, 43179503
830.6320	63-20	Corrosion Characteristics	2,3,4,5	43178603, 43179503
830.6321	63-21	Dielectric breakdown voltage	2,3,4,5	Not required
ECOLOGICAL EFFECTS				
850.2100	71-1	Avian Acute Oral Toxicity Test - Quail/duck	2,3,4,5	43762301, 43888002 43760807
850.1075	72-1 c	Fish Acute Toxicity - Rainbow Trout	2,3,4,5	Open literature
850.1075	72-1 c	Fish Acute Toxicity - Fathead Minnow	2,3,4,5	Open Literature
850.1010	72-2 a	Acute Aquatic Invertebrate Toxicity	2,3,4,5	43762302, 43888003, 43760808

DATA REQUIREMENT				CITATION(S)
New Guideline Number	Old Guideline Number	Study Title	Use Pattern	MRID Number
850.1300	72-4 a	Fish Early Life Stage	2,3,4,5	Not required
850.1400	72-4 b	Aquatic Invertebrate Life Cycle	2,3,4,5	Not required
Non-guideline	Non-guideline	Acute Aquatic Invertebrate Toxicity - Waterflea *(Ceriodaphnia dubia)*	N/A	Not required; Open literature
Non-guideline	Non-guideline	Acute Aquatic Invertebrate Toxicity - Waterflea *(Daphnia magna)*	N/A	Not required; Open literature
Non-guideline	Non-Guideline	Acute Aquatic Invertebrate Toxicity – Brine Shrimp *(Artemia salina)*	N/A	Not required; Open literature
TOXICOLOGY				
870.1100	81-1	Acute Oral - Rat	2,3,4,5	43760801, Open literature
870.1200	81-2	Acute Dermal - Rabbit	2,3,4,5	43760802, Open literature
870.1300	81-3	Acute Inhalation – Rat	2,3,4,5	43760803, Open literature
870.2400	81-4	Acute Eye Irritation - Rabbit	2,3,4,5	43760804, Open literature
870.2500	81-5	Acute Skin Irritation - Rabbit	2,3,4,5	43760805, Open literature
870.2600	81-6	Dermal Sensitization	2,3,4,5	43760806, Open literature
870.3100	82-1a	Subchronic (Oral) Toxicity –Rodent	2,3,4,5	46892504, 46892208, Open literature
870.3465	82-4	90-Day (Inhalation) Subchronic Toxicity	2,3,4,5	46892103
870.4100	83-1a	Chronic (Oral) Toxicity - Rodent	2,3,4,5	46892509, Open literature
870.4100	83-1a	Chronic (Inhalation) Toxicity - Rodent	2,3,4,5	Open literature

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DATA REQUIREMENT				CITATION(S)
New Guideline Number	Old Guideline Number	Study Title	Use Pattern	MRID Number
870.4300	83-5	Combined Chronic (Oral) Toxicity/Carcinogenicity - Rodent	2,3,4,5	46892504,46892101, Open literature
870.4300	83-5	Combined Chronic (Dermal) Toxicity/Carcinogenicity - Rodent	2,3,4,5	46892301
870.3700	83-3a	Prenatal Developmental Toxicity - Rodent	2,3,4,5	46892202, 46892203, 46892206, 46892207, 46892508, Open literature
870.3700	83-3b	Prenatal Developmental Toxicity – Non Rodent	2,3,4,5	46892205, Open literature
870.3800	83-4	Reproduction and Fertility Effects - Rat	2,3,4,5	46892204, Open literature
870.5100	84-2	Bacterial Reverse GeneMutation Assay Test	2,3,4,5	Open literature
870.5300	84-2	In Vitro Mammalian Cell Gene Mutation Test	2,3,4,5	Open literature
870.5375	84-2	Cytogenetics: In Vitro Mammalian Chromosome Aberration Test	2,3,4,5	Open Literature
870.5395	84-2	Cytogenetics: In Vivo Mouse Erythrocyte Micronucleus Assay	2,3,4,5	Open Literature
870.5450	84-2	Other Mechanisms: Rodent Dominant Lethal Assay	2,3,4,5	46892506, Open literature
870.6200	81-8	Neurotoxicity Screening Battery	2,3,4,5	Open literature
870.7485	85-1	Metabolism and Pharmocokinetics - Rodent	2,3,4,5	46892202, 46892201, 46893505, Open literature
870.7600	85-2	Dermal Penetration - Rodent	2,3,4,5	46892301
ENVIRONMENTAL FATE				

DATA REQUIREMENT				CITATION(S)
New Guideline Number	Old Guideline Number	Study Title	Use Pattern	MRID Number
835.2120	161-1	Hydrolysis of Parent and Degradates	2,3,4,5	Not required

Please Note: Although the Open Literature studies do not satisfy any of the Agency's testing guideline requirements, this information is considered adequate for characterizing the potential hazard from exposure to propylene glycol and dipropylene glycol. Therefore, no additional mammalian toxicity data will be required at this time.

Appendix C: Technical Support Documents

Additional documentation in support of this RED is maintained in the OPP docket, located in Room 119, Crystal Mall #2, 1801 South Bell Street, Arlington, VA 22202. It is open Monday through Friday, excluding legal holidays, from 8:30 am to 4:00 pm.

All documents, in hard copy form, may be viewed in the OPP docket room or downloaded or viewed via the Internet at the following site: http://www.epa.gov/edocket

These documents include:

1. **Propylene Glycol/Dipropylene Glycol** - Report of the Antimicrobials Division Toxicology Endpoint Selection Committee. (Memorandum: T. McMahon, Ph.D., Chair, July 20, 2004.
2. ***PROPYLENEGLYCOL/DIPROPYLENE GLYCOL:*** Revised Toxicology Chapter in Support of issuance of the Reregistration Eligibility Decision (RED) Document. PC Code for Propylene Glycol: 068603. PC Code for Dipropylene Glycol: 068604. CAS Registry Number for Propylene Glycol: 57-55-6: CAS Registry Number for Dipropylene Glycol: 25265-71-8. Reregistration Case Number: 3126, DP #: 327061. (Memorandum: M. Centra, Pharmacologist, February 5, 2007).
3. Data Evaluation Records (DER) for the Product Chemistry of Propylene Glycol. (Memorandum: N. Shamim, Chemist, December 10, 2003).
4. Data Evaluation Records (DER) for the Product Chemistry of Dipropylene Glycol. (Memorandum: N. Shamim, Chemist, December 10, 2003).
5. Science Chapter: Revised Environmental Fate Studies and Environmental Fate Assessment of Propylene Glycol (Memorandum: N. Shamim, Chemist, February 5, 2007).
6. Science Chapter: Revised Environmental Fate Studies and Environmental Fate Assessment of Dipropylene Glycol (Memorandum: N. Shamim, Chemist, February 5, 2007).
7. PROPYLENE GLYCOL AND DIPROPYLENE GLYCOL: Estimated Drinking Water Concentrations (Memorandum: N. Shamim, Chemist, July 2, 2004).
8. AD's Revised Occupational and Residential Exposure Chapter for the Propylene and Dipropylene Glycol Reregistration Eligibility Decision (RED) Document. Case No. 3126. PC Codes 068603, 068604. (Memorandum: T. Leighton, Environmental Scientist, February 5, 2007).
9. Propylene/Dipropylene Glycol Revised Ecological Hazard and Environmental Risk Characterization Chapter for the Reregistration Eligibility Decision (RED) Document, Case 3126. (Memorandum: K. Montague, M.S., Biologist, February 14, 2006).

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10. ***PROPYLENE GLYCOL/DIPROPYLENE GLYCOL:*** AD's Risk Assessment for Issuance of the Reregistration Eligibility Decision (RED) Document. Reregistration Case No.: 3126. PC Codes: 068603, 068604. CAS Registry No.: Propylene Glycol, 57-55-6; Dipropylene Glycol, 25265-71-8. (Memorandum: M. Centra, Pharmacologist/Risk Assessor, February 5, 2007).

Appendix D: Bibliography Citations

MRID Number	Citation
43176202	Davis, K. (1994). Product Chemistry Data of Propylene Glycol. Unpublished report prepared by RegWest Company, Greeley, CO. 21 p. Guideline Series 62/OPPTS 830.1760 and 830.1800
43176203	Davis, K. (1994). Physical and Chemical Characteristics of Propylene Glycol. Unpublished report prepared by RegWest Company, Greeley, CO. 68 p. Guideline Series 63/OPPTS 830.6302. – 830.7950.
43178601	Davis, K. (1994). Product Chemistry Data of Propylene Glycol. Unpublished report prepared by RegWest Company, Greeley, CO. 11 p. Guideline Series 61/OPPTS 830.1550, 830.1600, 830.1620, 830.1650,830.1670 and 830.1700.
43178602	Davis, K. (1994). Product Chemistry Data of Propylene Glycol:Lab Project Number:PG62. Unpublished Study prepared by RegWest Co. 21 p.
43178603	Davis, K. (1994). Physical and Chemical Characteristics of Propylene Glycol:Lab Project Number:PG63. Unpublished Study Prepared RegWest Co. 76 p.
43179501	Davis, K. (1994). Product Chemistry Data of Dipropylene Glycol. Unpublished report prepared by RegWest Company, Greeley, CO. 11 p. Guideline Series 61/OPPTS 830.1550, 830.1600, 830.1620, 830.1650 and 830.1670.
43179502	Davis, K. (1994). Product Chemistry Data of Dipropylene Glycol. Unpublished report prepared by RegWest Company, Greeley, CO. 21 p. Guideline Series 62/OPPTS 830.1700, 830.1760 and 830.1800.
43179503	Davis, K. (1994). Physical and Chemical Characteristics of Dipropylene Glycol: Lab Project Number: DPG63. Unpublished Study prepared by RegWest Co. 68 p.

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43760802 Robbins, G. (1995) Dipropylene Glycol: Acute Dermal Toxicity on Rabbits: Lab Project Number: B3435. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 23 p. The CSPA Glycols Joint Venture Project ID B3435. Work Assignment No. 2-28B.

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Appendix E: Generic Data Call-In

The Agency intends to issue a Generic Data Call-In at a later date.

Appendix F: Product Specific Data Call-In

The Agency intends to issue a Product Specific Data Call-In at a later date.

Appendix G: Batching of End-Use Products

Antimicrobial Division's Batching of Products Containing Propylene glycol and Dipropylene Glycol as the Active Ingredient for Meeting Acute Toxicity Data Requirements for Reregistration

In an effort to reduce the time, resources and number of animals needed to fulfill the acute toxicity data requirements for reregistration of products containing the active ingredient propylene glycol and dipropylene glycol, the Agency has batched products which can be considered similar in terms of acute toxicity. (The PC Code of propylene glycol is 068603; the CAS Registry Number is 57-55-6; The PC Code of propylene glycol is 068604; the CAS Registry Number is 25265-71-8). Factors considered in the sorting process include each product's active and inert ingredients (identity, percent composition and biological activity), product form (liquid, paste, solid, etc.), labeling (e.g., signal word, precautionary labeling, etc.) and acute toxicity data.

Using available information, batching has been accomplished by the process described in the preceding paragraph. Notwithstanding the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual product should the need arise.

Registrants of products within a batch may choose to cooperatively generate, submit or cite a single set of six acute toxicity studies to represent all the products within that batch. Registrants have the option of participating with all or some other registrants of products in their product's batch, to deal only their own products within a batch, or to generate all the required acute toxicological studies for each of their own products. If a registrant chooses to generate the data for a batch, he or she must use one of the products within the batch as the test material. If a registrant chooses to rely upon previously submitted acute toxicity data, he or she may do so provided that the data base is complete and valid by today's standards (see the attached acceptance criteria), the formulation tested is considered by EPA to be similar in terms of acute toxicity, and the formulation has not been significantly altered since submission and acceptance of the acute toxicity data. Registrants may not support their product using data conducted on a product from a different batch, unless this batching appendix specifically states so. The Antimicrobials Division must approve any new or canceled formulations (that were presented to the Agency after the publication of the RED) before data derived from them can be used to cover other products in a batch. Regardless of whether new data is generated or existing data is referenced, registrants must clearly identify the test material by EPA Registration Number. If more than one confidential statement of formula (CSF) exists for a product, the registrant must indicate the formulation actually tested by identifying the corresponding CSF.

In deciding how to meet the product specific data requirements, registrants must follow the directions given in the Data Call-In (DCI) Notice and its attachments appended to the RED. The DCI Notice contains two response forms which are to be completed and submitted to the Agency within 90 days of receipt. The first form, "Data Call-In Response," asks whether the registrant will meet the data requirements for each product. The second form, "Requirements Status and Registrant's Response," lists the product specific data required for each product, including the standard six acute toxicity tests. A registrant who wishes to participate in a batch must decide whether he or she will provide the data or depend on someone else to do so. If a registrant

supplies the data to support a batch of products, he or she must select one of the following options: Developing New Data (Option 1), Submitting an Existing Study (Option 4), Upgrading an Existing Study (Option 5) or Citing an Existing Study (Option 6). If a registrant depends on another's data, he or she must choose among: Cost Sharing (Option 2), Offers to Cost Share (Option 3) or Citing an Existing Study (Option 6). If a registrant does not want to participate in a batch, the choices are Options 1, 4, 5 or 6. However, a registrant should know that choosing not to participate in a batch does not preclude other registrants in the batch from citing his or her studies and offering to cost share (Option 3) those studies.

If a registrant would like to have the batching status of a product reconsidered, they need to submit detailed information on their product, including a detailed rationale for the inclusion of their product into a batch. An MSDS for each "inert" ingredient should be included where possible. However, registrants and manufacturers should realize that the more unique their formulation is, the less likely it is to be able to batch that product. AD/PSB notes that there were no registered Technical Grade Active Ingredient (TGAI) products to be reviewed in this batching chapter.

Table 1 displays the batch for the active ingredient Propylene glycol and dipropylene Glycol.

Table 1.

Batch	Registration Number	Percent Active Ingredient
1	51838-1	Propylene glycol and dipropylene Glycol ... 4.4% Propylene Glycol ... 4.4%
	51838-2	Propylene glycol and dipropylene Glycol ... 4.4% Propylene Glycol ... 4.4%
2	4822-293	Propylene glycol and dipropylene Glycol ... 6.0%
	4822-531	Propylene glycol and dipropylene Glycol ... 6.0%

Table 2 lists the products in the "No Batch" group. These products can not be batched because they were not considered to be similar to other the products in terms of acute toxicity or because there was insufficient information available to assist in making the decision.

Table 2. The "No Batch Group" of Products Containing Propylene glycol and dipropylene Glycol as an Active Ingredient

Registration Number	Percent Active Ingredient
9444-19	Propylene glycol and dipropylene Glycol ... 6.000% Dipropylene Glycol ... 4.000% n-Alkyl dimethyl benzyl ammonium chloride ... 0.20%
9444-136	Propylene glycol and dipropylene Glycol ... 9.15% Dipropylene Glycol ... 3.43% n-Alkyl dimethyl benzyl ammonium chloride ... 0.17%
10807-24	Propylene glycol and dipropylene Glycol ... 4.5% Propylene Glycol ... 3.0% n-Alkyl dimethyl benzyl ammonium chloride ... 0.10%
10807-37	Propylene glycol and dipropylene Glycol ... 3.00% Dipropylene Glycol ... 3.00% n-Alkyl dimethyl benzyl ammonium chloride ... 0.10% n-Alkyl dimethyl ethylbenzyl ammonium chloride ... 0.10%
10807-43	Propylene glycol and dipropylene Glycol ... 7.7% Propylene Glycol ... 5.13% n-Alkyl dimethyl benzyl ammonium chloride ... 0.17%
11715-20	Propylene glycol and dipropylene Glycol ... 0.10% Propylene Glycol ... 0.10% Pyrethrins ... 0.09% Piperonyl butoxide ... 0.18% n-Octyl bicycloheptene dicarboximide ... 0.30%
44446-20	Propylene glycol and dipropylene Glycol ... 6.00% n-Alkyl dimethyl ammonium chloride ... 0.10% n-Alkyl dimethyl ethylbenzyl ammonium chloride ... 0.10% Isopropanol ... 50.20%

Appendix H: List of All Registrants Sent the Data Call-In

A list of registrants sent the data call-in will be posted at a later date.

Appendix I: List of Available Forms

Pesticide Registration Forms are available at the following EPA internet site:

http://www.epa.gov/opprd001/forms/

Pesticide Registration Forms (These forms are in PDF format and require the Acrobat reader)

Instructions

1. Print out and complete the forms. (Note: Form numbers that are bolded can be filled out on your computer then printed.)

2. The completed form(s) should be submitted in hardcopy in accord with the existing policy.

3. Mail the forms, along with any additional documents necessary to comply with EPA regulations covering your request, to the address below for the Document Processing Desk.

DO NOT fax or e-mail any form containing 'Confidential Business Information' or 'Sensitive Information.'

If you have any problems accessing these forms, please contact Nicole Williams at (703) 308-5551 or by e-mail at williams.nicole@epa.gov.

The following Agency Pesticide Registration Forms are currently available via the internet at the following locations:

8570-1	Application for Pesticide Registration/Amendment	http://www.epa.gov/opprd001/forms/8570-1.pdf
8570-4	Confidential Statement of Formula	http://www.epa.gov/opprd001/forms/8570-4.pdf
8570-5	Notice of Supplemental Registration of Distribution of a Registered Pesticide Product	http://www.epa.gov/opprd001/forms/8570-5.pdf
8570-17	Application for an Experimental Use Permit	http://www.epa.gov/opprd001/forms/8570-17.pdf
8570-25	Application for/Notification of State Registration of a Pesticide To Meet a Special Local Need	http://www.epa.gov/opprd001/forms/8570-25.pdf
8570-27	Formulator's Exemption Statement	http://www.epa.gov/opprd001/forms/8570-27.pdf

8570-28	Certification of Compliance with Data Gap Procedures	http://www.epa.gov/opprd001/forms/8570-28.pdf
8570-30	Pesticide Registration Maintenance Fee Filing	http://www.epa.gov/opprd001/forms/8570-30.pdf
8570-32	Certification of Attempt to Enter into an Agreement with other Registrants for Development of Data	http://www.epa.gov/opprd001/forms/8570-32.pdf
8570-34	Certification with Respect to Citations of Data (PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf
8570-35	Data Matrix (PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf
8570-36	Summary of the Physical/Chemical Properties (PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf
8570-37	Self-Certification Statement for the Physical/Chemical Properties (PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf

Pesticide Registration Kit www.epa.gov/pesticides/registrationkit/

Dear Registrant:

For your convenience, we have assembled an online registration kit which contains the following pertinent forms and information needed to register a pesticide product with the U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP):

1. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of 1996.

2. Pesticide Registration (PR) Notices

a. 83-3 Label Improvement Program--Storage and Disposal Statements
b. 84-1 Clarification of Label Improvement Program
c. 86-5 Standard Format for Data Submitted under FIFRA
d. 87-1 Label Improvement Program for Pesticides Applied through Irrigation Systems (Chemigation)
e. 87-6 Inert Ingredients in Pesticide Products Policy Statement
f. 90-1 Inert Ingredients in Pesticide Products; Revised Policy Statement
g. 95-2 Notifications, Non-notifications, and Minor Formulation Amendments
h. 98-1 Self Certification of Product Chemistry Data with Attachments (This document is in PDF format and requires the Acrobat reader.)

Other PR Notices can be found at http://www.epa.gov/opppmsd1/PR_Notices

3. Pesticide Product Registration Application Forms (These forms are in PDF format and will require the Acrobat reader).

a. EPA Form No. 8570-1, Application for Pesticide Registration/Amendment
b. EPA Form No. 8570-4, Confidential Statement of Formula
c. EPA Form No. 8570-27, Formulator's Exemption Statement
d. EPA Form No. 8570-34, Certification with Respect to Citations of Data
e. EPA Form No. 8570-35, Data Matrix

4. General Pesticide Information (Some of these forms are in PDF format and will require the Acrobat reader).

a. Registration Division Personnel Contact List
b. Biopesticides and Pollution Prevention Division (BPPD) Contacts
c. Antimicrobials Division Organizational Structure/Contact List
d. 53 F.R. 15952, Pesticide Registration Procedures; Pesticide Data Requirements (PDF format)
e. 40 CFR Part 156, Labeling Requirements for Pesticides and Devices (PDF format)
f. 40 CFR Part 158, Data Requirements for Registration (PDF format)
g. 50 F.R. 48833, Disclosure of Reviews of Pesticide Data (November 27, 1985)

Before submitting your application for registration, you may wish to consult some additional sources of information. These include:

1. The Office of Pesticide Programs' website.

2. The booklet "General Information on Applying for Registration of Pesticides in the United States", PB92-221811, available through the National Technical Information Service (NTIS) at the following address:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161

The telephone number for NTIS is (703) 605-6000.

3. The National Pesticide Information Retrieval System (NPIRS) of Purdue University's Center for Environmental and Regulatory Information Systems. This service does charge a fee for subscriptions and custom searches. You can contact NPIRS by telephone at (765) 494-6614 or through their website.

4. The National Pesticide Information Center (NPIC) can provide information on active ingredients, uses, toxicology, and chemistry of pesticides. You can contact NPIC by telephone at (800) 858-7378 or through their website: http://npic.orst.edu/.

The Agency will return a notice of receipt of an application for registration or amended registration, experimental use permit, or amendment to a petition if the applicant or petitioner encloses with his submission a stamped, self-addressed postcard. The postcard must contain the following entries to be completed by OPP:

1. Date of receipt;
2. EPA identifying number; and
3. Product Manager assignment.

Other identifying information may be included by the applicant to link the acknowledgment of receipt to the specific application submitted. EPA will stamp the date of receipt and provide the EPA identifying file symbol or petition number for the new submission. The identifying number should be used whenever you contact the Agency concerning an application for registration, experimental use permit, or tolerance petition.

To assist us in ensuring that all data you have submitted for the chemical are properly coded and assigned to your company, please include a list of all synonyms, common and trade names, company experimental codes, and other names which identify the chemical (including "blind" codes used when a sample was submitted for testing by commercial or academic facilities). Please provide a chemical abstract system (CAS) number if one has been assigned.