HOPE OR HAZARD?

What Research Tells us About "Potentially Reduced-Exposure" Tobacco Products

The Cancer Center
University of Minnesota

TTURC
Transdisciplinary Tobacco Use Research Center

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INTRODUCTION

Cigarette smoking remains a formidable public health challenge in the United States. According to the Centers for Disease Control and Prevention, cigarette smoking accounts for more than 400,000 deaths and about $100 billion in health care expenses annually.[1]

Not surprisingly, one of the most effective ways to address the health problems associated with cigarette smoking is through smoking cessation. About 41% of smokers make a quit attempt in a given year,[2] but only 4.7% actually quit for 3 months to a year.[2] Also discouraging, less than 10% are interested in taking action to stop smoking at any given time.[3] Given the difficulty smokers have in quitting, one can argue that interventions aimed at cigarette smoking prevention and cessation cannot be relied upon as the sole means for reducing cigarette smoking risks. Strategies must also be considered to bring about proven and comprehensive reductions in the harm that cigarette smoking poses to both smokers and the general public. Reduction in exposure to tobacco toxins—in other words, modifying tobacco products to be "less harmful"—has been regarded as a potential mechanism for reducing the health risks associated with cigarette smoking. However, the benefit of reducing exposure to some toxins and not others and the extent to which these toxins should be reduced remains problematic.

The goals of this report are to:

- describe the current state of science regarding **potentially reduced-exposure tobacco products (PREPs)**;
- comment on whether the marketing claims about PREPs are supported by the current published scientific literature; and
- outline what we need to know about PREPs in order to assess the claims made about (or the actual harm reduction offered by) these products.

BACKGROUND

Several tobacco products are currently on the market with claims of reduced exposure to specific toxins or reduced risk for disease. But none of these claims have been convincingly proven, nor were they evaluated by a public health agency prior to their appearance in the marketplace. The effects of these products and their marketing strategies on consumer perception must be carefully considered, especially given the tobacco industry's history of labeling tobacco products and making marketing claims about them.

For instance, in one study, smokers estimated on average that smoking "light" and "ultra light" cigarettes conferred a 25% and 33% reduction in risk, respectively, compared with regular brands,[4] and 27% of smokers in another study indicated that the risk of lung cancer was lower in those who smoked light cigarettes compared with those who smoked regular cigarettes.[5] (For more information on the definition of light and ultra light cigarettes, see page 6, "Filtration and dilution.") These findings raise significant concerns about the effect of "light"

and “ultra light” product labeling on public health, given the reality that research on light or lower-yield cigarettes has shown that the disease risk of these products is not significantly different than regular or medium-yield cigarettes.[6-8]

In a more recent study, when researchers assessed smokers’ perceptions of Eclipse, a currently available PREP, they found that 91% of smokers believed Eclipse was safer than regular cigarettes and 24% thought it was as safe as not smoking.[9]

From these and other studies, one can conclude that the likelihood of overinterpreting the marketing claims of PREPs or interpreting claims based on minimal scientific data is high—and that **this overinterpretation may also undermine some smokers’ individual cessation efforts by leading them to think that they may have a safe way to continue smoking**.[8] Moreover, the misreading of marketing messages may help promote non-smokers to start smoking and encourage former smokers to take up smoking again.

Therefore, it becomes imperative that independent researchers scientifically scrutinize such marketing claims and explore the effects that these claims have on consumer perception, consumer behavior, and ultimately, public health. Most importantly, it is essential that these claims, whether explicit or implicit, be supported by scientific-based evidence. **To date, limited research independent of the tobacco companies has been conducted or published to support the validity of the marketing claims employed in the promotion of PREPs.**

Demystifying the Data...

What are PREPs?
PREPs are potentially reduced-exposure products. They are tobacco products that have been modified or designed in some way to reduce users’ exposure to tobacco toxins. As a marketing tactic, some manufacturers claim that reduced exposure to tobacco toxins may lead to reduced risk of cancer or other adverse health conditions. However, these claims have not been convincingly demonstrated in independent studies.

What is meant by “reduced exposure” and “reduced risk” with respect to use of PREPs?
“Reduced exposure” indicates that use of the PREP has been shown to reduce exposure to nicotine or to certain tobacco toxins. “Reduced risk” indicates that these reductions in exposure have resulted in reduced risk of disease. To date, there is no evidence to suggest that there is enough of a reduction in tobacco toxin exposure with any of the existing PREPs to expect a significant reduction in disease risk, nor do we know the extent of toxin exposure reduction that is necessary to result in reduction of disease.

NONPHARMACEUTICAL TOBACCO PRODUCTS

Over the decades, tobacco companies have introduced a variety of products, manufacturing processes, and methods of tobacco consumption purportedly designed to reduce consumers' exposure to tobacco toxins.

FILTRATION AND DILUTION

The concept of reducing toxins associated with cigarette smoking is not new. Two primary methods to reduce toxins, both of which have been used for decades, are filtration (adding filters to the cigarettes) and dilution (which is achieved mostly through ventilation). Other methods to reduce **tar** and **nicotine** yields also exist, such as decreasing the length of cigarettes, increasing cigarettes' burn rate, decreasing the density of tobacco, or blending different kinds of tobacco. Most cigarettes sold in the United States today include cellulose acetate filters to trap certain smoke constituents. Use of these filters has been demonstrated to reduce tar and nicotine yields by up to 50% compared with nonfilter products.[10] Since the late 1960s, many cigarette manufacturers have also perforated their filters with lines of ventilation holes, which act to dilute the smoke as it travels through the filter. Perforation leads to lower yields of tar and nicotine in the cigarettes, according to machine-derived measurements. Tobacco manufacturers have labeled these lower-yield products "light" and "ultra light" cigarettes. But as evidence suggests (see page 14), smokers may be unwittingly compensating for the reduced nicotine delivery.

CIGARETTE-LIKE DELIVERY DEVICES (Eclipse, Accord)

Heating tobacco at a lower temperature, rather than burning it, results in lower-combustion products that, in theory, may lower the overall toxicity of the tobacco product. One example is Eclipse, which is similar in shape and size to a traditional cigarette but uses a carbon tip and a heat-insulated tube to prevent burning. When the carbon tip is lit, it heats the mixture of predominantly glycerin and small amounts of tobacco, and the vaporized substance passes through a charcoal filter. This "controlled burn" dramatically alters the composition of the "smoke" (i.e., smoke-like vapor) produced.[11] Another example is Accord, which contains a burning device powered by rechargeable batteries. The device is activated by a microchip that senses when a smoker is puffing on the cigarette. When signaled, the "puff-activated lighter" produces a controlled, timed burn that, like Eclipse, produces no ash.[11]

MODIFIED TOBACCO PRODUCTS (Advance, Omni, Quest)

Modified tobacco products marketed today are designed to reduce tobacco toxin exposure through one of three means:

- *Improved tobacco curing processes.* Some cigarette manufacturers use alternative curing methods to help reduce one class of known carcinogens called **tobacco-specific nitrosamines (TSNAs)**.[11] An example of a product that uses improved tobacco curing processes is Advance.

- *Chemical additives.* Some modified tobacco products purportedly reduce the presence of TSNAs and **polycyclic aromatic hydrocarbons (PAHs)**—another group of powerful cancer-causing agents—by adding constituents to the tobacco, such as palladium. (With the addition of palladium, tobacco can burn more efficiently. Theoretically, more complete burning of the tobacco reduces the concentration of certain carcinogens, such as PAHs.)[12,13] An example of such a product is the Omni cigarette.

- *Genetic modification of tobacco*. One product recently released by Vector Tobacco uses genetically altered tobacco that controls the level of nicotine produced. The brand name for this cigarette is Quest. The Quest cigarette line features three different "levels" of nicotine in its products.

Level one purportedly contains 17% less nicotine than an average light cigarette, level two contains 58% less, and level three is virtually nicotine-free. (These measurements are all machine-derived.)

ORAL NONCOMBUSTIBLE TOBACCO PRODUCTS (e.g., Revel, Exalt, Ariva, Stonewall)

Many varieties of oral noncombustible tobacco products, or smokeless tobacco, are also available throughout the world. The two main types of smokeless tobacco that are used in the United States are moist snuff (a finely ground tobacco product) and chewing tobacco (a leaf, twist, or plug of tobacco).[14] US Smokeless Tobacco created Revel, small packets of tobacco about the size of a piece of chewing gum, which smokers can use when they are not able to smoke in public places. More recently, lozenges containing compressed low-nitrosamine tobacco have been developed and marketed (e.g., Ariva, Stonewall).

The health risks of smokeless tobacco products also vary across the spectrum of products marketed. In India, for example, use of smokeless tobacco is regarded as a primary cause of oral cancer. However, one manufacturer in Sweden, Swedish Match, uses a special process to kill the microorganisms in tobacco, and the snuff does not undergo fermentation. As a result, the levels of TSNAs found in Swedish moist snuff, or snus, (e.g., Exalt) are considerably lower than those in the most popular smokeless tobacco marketed in the United States. The absolute health risks of smokeless tobacco products are lower than cigarettes,[15] although smokeless tobacco still confers significant health risks, such as oral and pancreatic cancers and possibly esophageal cancer.[16]

Demystifying the Data...

What are the indicators of reduced exposure and reduced risk?
Some of the currently used indicators of reduced exposure may include the following:

- Reductions in cotinine in urine (which would indicate a reduction in nicotine exposure)
- Reductions in NNAL or NNAL-Glucs (which would indicate a reduction in exposure to NNK, a cancer-causing substance)
- Reductions in 1-HOP (which would indicate a reduction in pyrene, a substance that is reflective of cancer-causing compounds known as polycyclic aromatic hydrocarbons [PAHs])
- Reductions in carbon monoxide (which would indicate exposure to a potentially poisonous gas)

Indicators of reduced toxicity, injury, or harm may include:

- Reductions in urine mutagenicity
- Reductions in macrophages or bronchial inflammation
- Reductions in cardiovascular risk factors, such as high blood pressure or high blood cholesterol, C-reactive protein, and fibrinogen
- Reductions in incidences of lung cancer or other cancers, heart disease, noncancerous lung diseases or other diseases associated with tobacco use

CONCLUSIONS BASED ON AVAILABLE RESEARCH

Studies aimed at assessing the level of toxin exposure in PREPs have yielded potential concerns regarding their risk-reducing effects and have failed to produce solid evidence that any of the products currently marketed as a PREP actually reduce the risk of disease. (A summary of selected published data begins on page 14. For comparative information by product and product claims, see the table on page 22.) From the findings presented in these and other studies, one can draw the following observations and conclusions:

- ***Machine-derived methods to assess toxin exposure can overestimate the extent of toxin reduction compared with actual human exposure.*** This finding has repeatedly been observed with low-yield cigarettes. In more recent studies of modified tobacco products, Hatsukami and colleagues,[13] as well as other scientists, demonstrated that the U.S. Federal Trade Commission's (FTC's) testing methodology (machine-derived measurements) does not take into account the wide range of smoking behaviors that occur naturally among smokers. Reduction in intake of some carcinogens was less than anticipated by machine-derived yields. In addition, there was great variability in the amount of toxin exposure among smokers, and some smokers experienced an increase in exposure to TSNAs with the use of a modified tobacco PREP. The most accurate way to assess how these products alter or affect carcinogen exposure is to use human-derived measurements and to report the range of toxin exposures observed.

- ***To date, there is no evidence to suggest that there is enough of a reduction in tobacco toxin exposure with any of the existing PREPs to expect a significant reduction in disease risk, nor do we know the extent of toxin exposure reduction that is necessary to result in reduction of disease.*** Yet consumers do equate reduction in exposure with reduction in disease risk. Most studies that have been conducted are limited in the duration of use of the product as well as in the **biomarkers** used to assess toxin exposure or health risks. Furthermore, reliance on one or a few biomarkers is not sufficient, because it may not present an accurate picture of the potential harm associated with a product. Reductions of nicotine levels or other measures of toxin exposure may occur, but an increase in exhaled carbon monoxide may also occur (as in the case of Eclipse), which may increase the risk for heart disease.

- ***The technology is available to reduce harmful constituents in tobacco.*** We know this, in part, because conventional products sold in the United States have significantly higher levels of toxins than modified tobacco products sold in some other parts of the world. Although the extent of reduction in exposure to tobacco toxins may not necessarily lead to a proportional reduction in disease risk, if the technological capacity currently exists, all marketed tobacco products should meet performance standards that would reduce or eliminate toxins in tobacco products. It is important to note that most exposures to toxins in food products or in the environment are reduced as much as possible, thus allowing for maximum risk reduction. Such an effort toward maximum risk reduction has not been pursued heretofore with respect to toxin exposure from cigarettes. It is also important to note that even if performance standards are instituted, attainment of these standards should not necessarily warrant an exposure-reduction claim without evidence of actual reduction in health risks. Furthermore, even validated claims of health risk reduction may potentially produce public health harm if these claims increase smoking initiation, maintenance, or relapse.

POLICY IMPLICATIONS AND RESEARCH DIRECTIONS

- ***Consumers must be provided accurate information in order to make informed decisions about their use of and exposure to tobacco products.*** It is imperative that the consumer understand that reduced exposure does not necessarily translate into reduced disease risk. Modest reductions that were observed for the PREPs are unlikely to lead to clinically significant reduction in disease risk. The consumer needs to understand that risk for other diseases may remain unchanged, and, in some cases, may increase with some of these tobacco products. Consequently, reduced exposure claims should not be permitted if there is no evidence to show that the claimed reduction will actually occur in tobacco users and is likely to lead to a substantial reduction in disease risk. In addition, direct or implied health claims that are unsubstantiated may mislead a consumer about the "safety" of tobacco use and may diminish a tobacco user's interest in quitting, thereby leading to continued exposure to harm.

- ***To date, a limited number of studies have been conducted on recently marketed PREPs.*** These studies themselves are limited with regard to the number of participants, the duration of tobacco use, and the small number of toxin exposures and health effects measured. Therefore, it is apparent that a great deal of additional research must be conducted before any conclusions can be made regarding PREPs' potential to reduce disease risk.

WHAT IS NEEDED NOW

• ***Methods and measures to test these products.*** The fact that some existing data do not support the marketing messages or implied claims of the manufacturers of PREPs indicates the need for rigorous scientific investigation surrounding these products. Ultimately, the data that emerge can help educate consumers and inform public policy.

Establishing a science base involves:

- Identifying potential toxins present in both the product and its smoke;
- Conducting preclinical animal trials involving exposure to these products and their toxins;
- Developing a comprehensive panel of measures of disease risk that can be used to assess cigarette and smokeless tobacco products; and,
- Conducting human clinical trials to determine the level of toxin exposure, health effects of toxicity, addiction potential, and patterns of use. (For example, research protocols for assessment of human toxin exposure must be developed to augment the FTC machine-derived measurements currently used.)[11,14,17]

• ***Better understanding of consumers' perceptions regarding PREPs.*** Even before PREPs are released for purchase by the public, consumers' perceptions of them must be evaluated through premarket testing. The goal of this research would be to understand how marketing messages (including advertising copy and images) and the placement of those messages affect how the products are viewed. If valid information and messages pertaining to these products do exist, we must determine how those facts can be most effectively communicated so that consumers can make informed and rational decisions regarding the use of these products. Ultimately, exposure-reduction claims should be prohibited if consumer perception data showed consumers would misinterpret exposure-reduction claims to mean a concomitant reduction in risk.

• ***Better surveillance of these products.*** Postmarketing testing is equally as important as pretesting to determine the level of harm associated with use of these products. Even if a product is linked with decreases in uptake of toxins, the product may still pose harm to the user and to the population as a whole. The product may prompt a person to initiate smoking, cause relapse of tobacco use in former smokers, or prompt smokers to keep smoking when they might have otherwise quit. Longitudinal surveillance studies can also help determine how the use of these products affects public health.

• ***Government regulation of tobacco products and how they are marketed.*** Without government regulation, there is no way to be certain that any claims being made are accurate and that consumers are not being misled. Government regulation will also help ensure that there is a surveillance mechanism in place, such that when a tobacco manufacturer makes changes in one of its products, that product is retested and consumers are made aware of the change.

What we should ask the tobacco industry about "reduced exposure" and "reduced risk"

- What toxins in the PREP have been identified?
- What types of animal studies have been conducted to determine exposure to identified toxins and the effects of these toxins? What have these studies shown?
- What types of human studies have been conducted?
- What are the characteristics of the study population, and do they reflect the population most interested in using the product?
- What biomarkers have been used to test the product? To what extent are these biomarkers predictive of disease?
- What potential diseases do these biomarkers measure?
- What was the duration of the trials? Was the duration sufficient to stabilize smoking behavior?
- Were the trials conducted in a natural environment, or was smoking behavior controlled? Were participants allowed to use the products as they would normally, and how were these products used? Were they used in conjunction with other tobacco products? If so, what levels of toxin exposure were attained?
- What were the products with which the PREP was compared? Did they include a range of products, including light and ultra light cigarettes?
- What criteria were used to determine if the product significantly reduced toxin exposure?
- Were these criteria based on actual reduction in disease risk?
- Did an independent panel of experts determine that the product led to significant reduction in toxin exposure?
- What measures were taken to ensure that consumers were not misled about the "safety" of the product through marketing, placement, or advertising efforts?
- If labels that refer to harshness/smoothness/less irritation/ease of smoking experience are being used, what studies have been conducted to ensure that consumers do not misinterpret these labels as reducing exposure to toxins or being beneficial to health?
- What postmarketing surveillance system has been established to ensure that no harm to the public health occurs with the introduction of these products (e.g., increases initiation of tobacco use, maintains tobacco use among those interested in quitting, leads to relapse among previous smokers)?
- What steps will be taken if unintended health consequences do occur?

UNDERSTANDING THE RESEARCH ON PREPS

When examining human studies conducted with PREPs, one must consider the following design issues:

- ***The inclusion of a range of biomarkers for exposure and risk factors for disease states such as cancer, cardiovascular disease, and noncancerous lung disease.***

- ***The assessment of the addiction potential of the PREP***. Addiction potential can be measured by examining the extent of nicotine boost or nicotine levels, the time to reach maximum nicotine levels, subjective responses to the product, withdrawal symptoms from the product, or participants' preference for the product when given a choice among a number of products.

- ***The duration of the study.*** Duration of the experiment varies depending on the aims of the study. Addiction potential can be assessed in a laboratory session that may last for several hours. Studies examining the effects of products on biomarkers may last several weeks or a few months. The duration of the longer-term studies to assess the effects of products on toxin exposure and health risks should be adequate enough that tobacco use behaviors and patterns have been stabilized.

- ***The instructions for product use.*** Instructions for product use may range from controlled smoking in a laboratory setting to use of a product as would be smoked normally in a naturalistic setting. Controlled laboratory settings can provide comparative data on uptake of toxins, including nicotine, or subjective or physiological (e.g., heart rate) responses to a product when participants are using different products in the same way. Natural environment studies produce actual exposure to toxins when study participants use the products as they normally would. In these studies, participants may be asked to use solely the product that is assigned to them, or they may be allowed to use other products if they wish. The latter instruction would provide information on the pattern of overall tobacco use (e.g., potential concurrent use of tobacco products).

- ***The products with which the PREP is compared.*** Comparison groups typically include participants' own brand of cigarettes. Brands of cigarettes that are compared should include light and ultra light cigarettes. Ideally, the use of PREPs should also be compared with smoking cessation with or without nicotine replacement therapies.

- ***The population recruited for the study.*** The study population should reflect the population interested in using the product.

WHAT THE PUBLISHED RESEARCH SHOWS

The following is a brief summary of selected published findings regarding the toxicity of PREPs. (For detailed information by product and product claims, see table on page 22.)

FILTERS

Although filters are not covered in detail in this report, they deserve mention. On the basis of machine-derived measurements, ventilated filters in low-yield cigarettes were found to reduce nicotine and tar content. However, unlike with machine-testing environment, humans tend to compensate for these reductions by increasing the number of puffs they take from a cigarette, by increasing the volume of each puff, or by increasing the number of cigarettes smoked. They may also place their fingers or lips over the ventilation holes. (Research has shown that obstructing the holes in this way can increase tar, nicotine, and carbon monoxide to levels similar to those found in regular filter cigarettes.) Not surprisingly, therefore, changes in cigarette design (i.e., primarily with ventilation) over the last 50 years have not produced a public health benefit and have not decreased the rate of lung disease in the United States.[18] These findings are of concern because of the belief among consumers that smoking low-yield light and ultra light cigarettes confers a significant reduction in disease risk, including lung cancer.

CIGARETTE-LIKE DELIVERY DEVICES

Presently, the two cigarette delivery devices that "heat" rather than burn tobacco are Eclipse and Accord. R.J. Reynolds, the manufacturer of Eclipse, advertises that Eclipse "may reduce the risks of smoking-associated cancers and lower the risk of lung disease." They also say that "Eclipse is for smokers who have decided not to quit but who are interested in a cigarette that responds to concerns about certain smoking-related illnesses, including cancer. For many smokers, it may well be a better way to smoke."[19] The Eclipse Web site has a video that presents additional information, such as the findings that Eclipse results in 46% reduced bronchial inflammation and 36% less inflammation of the lower lung. The advertisements also indicate that R.J. Reynolds "[doesn't] claim that Eclipse presents less risk of cardiovascular disease or complications with pregnancy."[19] No claims have been made for Accord, although Accord is believed to result in "reduced toxins."[11]

Several studies have been conducted on the Eclipse cigarette, many of which have been funded by R.J. Reynolds. Rennard and colleagues[20] found that heavy smokers who switched to Eclipse for a 2-month duration experienced significant reductions in respiratory tract inflammation (35% improvement in alveolar inflammatory cells and 46% improvement in bronchitis index). However, the reductions did not reach the range of inflammation found in nonsmokers. Smokers using Eclipse generally maintained their prior nicotine levels, but their exhaled levels of carbon monoxide tended to increase. No other parameters associated with cardiovascular disease or pulmonary function changed with the switch to Eclipse. One of the limitations of this study was the recruitment of a small sample of very heavy smokers, which is unlikely to represent the population that will switch to Eclipse. Other tobacco-company—funded studies have found either an increase in carbon monoxide[21] or no mean change but wide variability in carbon monoxide levels.[22] Frampton and colleagues[21] examined 10 participants who smoked Eclipse for 2 weeks and 4 weeks and found no change in pulmonary epithelial permeability at 4 weeks, but they did note an improvement on a few biomarkers (e.g., HDL, lymphocyte activation). Two studies found a reduction in **urine mutagenicity**, with reductions ranging from 70% to 79% after smoking Eclipse for 1 week,[23,24] with one of these studies examining urine mutagenicity across varying tar categories. To date, it is unclear if this observed reduction in urine mutagenicity has any impact on health risks.

Several studies independent of funding from R.J. Reynolds have also been conducted. In a study comparing Eclipse with conventional cigarettes, Lee and colleagues[25] assessed puff volume and frequency, exhaled carbon monoxide levels, and plasma nicotine levels in 10 male smokers who smoked a single cigarette in a laboratory setting. Participants using Eclipse puffed more often and had larger, although statistically insignificant, increases in the levels of exhaled carbon monoxide, but less nicotine boost than with their own brand of cigarettes. They also rated the product as less satisfying and less rewarding and liked the product less than their own brand. Similarly, Breland and colleagues[26] conducted a laboratory study that controlled smoking behavior in 20 smokers. They observed a significantly increased **carbon monoxide boost** and decreased nicotine levels after the smoking session. The lower nicotine levels and self-reports of less satisfaction with Eclipse suggest that this product is likely to increase the number and duration of puffs from each cigarette and/or is less likely to sustain use compared with conventional cigarettes.

Fagerstrom and colleagues examined the effects of Eclipse and a nicotine inhaler (a medicinal nicotine product) on smoking behavior and biomarkers of toxin exposure. These studies are important in determining the effects of concurrent use of a PREP and conventional cigarettes, which may reflect how smokers will actually use a PREP. In smokers not interested in quitting, Fagerstrom[27] observed the effects of Eclipse and a nicotine inhaler while participants smoked their own brand of cigarettes. Each product was used for 2 weeks. Eclipse reduced the number of cigarettes smoked per day but maintained nicotine concentrations and increased carbon monoxide levels, whereas the nicotine inhaler reduced both carbon monoxide levels and nicotine concentrations.

Demystifying the Data...

What does it mean to have a reduction in urinary mutagenicity?
Mutagenicity is damage to genes. This can be measured in urine using a simple test with bacteria. No data are available to indicate whether reductions in mutagenicity lead to a reduction in cancer risk in humans. No threshold for reduction in risk has been determined.

What do increases in nicotine boost signify?
Nicotine boost is the change in nicotine levels (as measured in a smoker's blood) before and immediately following use of a tobacco product. Increases in nicotine can have a reinforcing effect, such that the pleasurable effects from the tobacco product are experienced. Furthermore, the quicker the nicotine boost, the more addictive the product. Significant increases in nicotine boost, however, may cause adverse effects, such as dizziness and nausea. They may also lead to increased heartbeat and higher blood pressure.

What is the significance of higher levels of exhaled carbon monoxide?
Smoking tobacco increases the levels of carbon monoxide in the blood. When a smoker has higher levels of exhaled carbon monoxide after using a PREP, it indicates that even more carbon monoxide is reaching the bloodstream and circulating throughout the body. Increased blood levels of carbon monoxide interfere with the transport of oxygen in the blood. Carbon monoxide binds to hemoglobin with greater affinity than oxygen. Hemoglobin, which is in red blood cells, delivers oxygen to tissues, including heart muscle. Carbon monoxide levels can return to normal within a few days of quitting smoking.

RESULTS, CONTINUED...

In another study, Fagerstrom and colleagues[28] assessed the long-term use (8 weeks) of Eclipse and a nicotine inhaler when participants were given a choice of the products to use. Both Eclipse and the nicotine inhaler substantially reduced the number of cigarettes smoked per day (86% for Eclipse and 68% with the nicotine inhaler). However, similar to the findings from the prior study, Eclipse increased carbon monoxide levels, whereas the nicotine inhaler decreased carbon monoxide levels.

Several studies have also examined the effects of Accord. To evaluate the short-term effects of Accord, Buchhalter and Eissenberg[17] assigned 10 cigarette smokers to smoke either Accord or their own brand over a 2-hour period after abstaining for 8 hours. Results indicated that Accord users initially experienced insignificant reductions in cravings related to smoking (unlike the immediate reductions observed from their own brand of cigarettes), experienced reduced adverse physiological effects (e.g., the magnitude of heart rate increases and skin temperature decreases were not as great as those observed with participants' own brand), and were observed to have no significant increases in exhaled carbon monoxide. A subsequent study led by Buchhalter[29] confirmed these initial findings. Furthermore, this study showed that participants' carbon monoxide levels and heart rate were lower with the use of Accord than with ultra light cigarettes. Additionally, Accord did not suppress withdrawal symptoms and craving as well as the ultra light cigarettes. The authors speculated that this incomplete suppression of withdrawal symptoms may lead to increased frequency of smoking, which may offset health benefits derived from Accord.

In a study funded by Phillip Morris, Roethig and colleagues[30] randomly assigned 110 Marlboro Light smokers to 1 of 5 experimental conditions: (1) Marlboro Light (their own brand), (2) Marlboro Ultra Light, (3) Accord, (4) Oasis (a product similar to Accord, but with a charcoal filter; both Accord and Oasis are known as electrically heated cigarette smoking systems), and (5) no smoking. Participants were asked to participate in controlled smoking (i.e., allowed to smoke up to a certain maximum number of cigarettes determined by the rate of smoking of their own brand of cigarettes) for 8 days in a restricted clinical setting. Each of the 4 smoking conditions had 20 participants, and the no-smoking condition had 30 participants. The results showed that comparable numbers of cigarettes were smoked in each of the smoking conditions. The findings also showed a dramatic (70%) reduction in participants' urine nicotine levels with Accord and Oasis at Day 8 compared with baseline when they were smoking their own brand. Compared with baseline measurements, both Accord and Oasis users also showed reductions in urine mutagenicity levels (53% to 66% reduction), which were comparable to those of the no-smoking group (58% reduction); similar reductions in these groups were observed for exhaled carbon monoxide (80% and 93% reduction, respectively) and **carboxyhemoglobin** (93% and 95% reduction, respectively). The reductions in the Accord and Oasis groups were 2 to 3 times greater than those in the Marlboro Ultra Light group. This study also measured environmental tobacco smoke and showed that the levels of **respirable suspended particles**, carbon monoxide and **total organic compound** levels in the room air were comparable among both the Oasis and Accord groups and the no-smoking groups. Although this study was well-designed with appropriate comparison groups, the question that remains unanswered is whether the substantial reductions that were observed with Accord and Oasis would be seen if the smoking were not controlled, particularly in light of the dramatic decrease in urine nicotine levels observed.

One study compared effects across a variety of products, including comparisons between Eclipse and Accord. In a study conducted by Breland and colleagues,[26] 20 smokers who maintained

abstinence overnight were assigned to a controlled smoking procedure using (1) their own brand, (2) denicotinized tobacco cigarettes, (3) Accord, or (4) Eclipse. Accord suppressed craving less effectively and caused minimal carbon monoxide boost compared with smokers' own brand of cigarettes. Participants using Accord also puffed longer and took bigger puffs. Eclipse fully suppressed withdrawal but resulted in a 30% increase in carbon monoxide boost compared with their own brand. Concentration of nicotine in plasma increased with participants' own brand, Accord, and Eclipse. The greatest increase in plasma nicotine levels occurred with their own brand, then Eclipse, and finally, Accord.

In summary, these human studies show no conclusive evidence that Eclipse reduces carcinogens to a level that may result in reduced health risk. The studies that have been conducted tend to be small in number of participants, use study populations unrepresentative of the smokers who may use PREPs, and assess a limited number of biomarkers for tobacco toxin exposure. It is also unclear if any of the reductions that were observed among smokers, such as urine mutagenicity, would result in any beneficial effect, particularly given the often long history of smoking and the resulting damage already done among potential consumers of PREPs. Furthermore, urine mutagenicity is only one measure of the effects of uptake of carcinogens and toxins. No other measures of carcinogen uptake have been examined.

Results also show evidence that Eclipse may result in an increase in carbon monoxide levels, which may (or may not) potentially increase risk for cardiovascular disease if high levels are sustained. Accord, on the other hand, appears to result in minimal nicotine boost and significantly reduced carbon monoxide levels in short-term laboratory studies. Similarly, significant reductions in nicotine excretion levels and exhaled and blood carbon

Demystifying the Data...

What does it mean to have a decrease in carboxyhemoglobin?
When levels of carboxyhemoglobin decrease in the body, it indicates that the smoker is getting less carbon monoxide in the body than he or she did previously.

What is the threshold at which decreases or increases in toxin exposures become significant?
The threshold at which significant decreases (or increases) in toxin exposure occur is currently unknown.

What does it mean to have similar levels of carbon monoxide, respirable suspended particles, and total organic compound levels in the room air of nonsmokers versus those who use an electrically heated cigarette smoking system, such as Accord or Oasis?
Having similar levels of these substances means that in these controlled experimental conditions, pollutants from environmental tobacco smoke were similar among nonsmokers and smokers of Accord and Oasis.

What does it mean when carbon monoxide levels decrease?
When bodily levels of carbon monoxide (measured by blood or breath samples) decrease, it indicates that the smoker is getting less carbon monoxide in his or her body. Having less carbon monoxide in the blood improves the body's ability to carry oxygen throughout the body. Specifically, some studies have shown that use of PREPs results in decreased levels of expired carbon monoxide in those who smoke them. However, further studies need to be conducted to determine at what level carbon monoxide must be reduced to decrease the risk of disease.

monoxide levels occurred in a controlled smoking study lasting several days. Furthermore, like Eclipse, lower levels of urine mutagenicity were observed with Accord, and these levels were comparable to not smoking. However, Accord also led to less suppression of withdrawal symptoms compared with smokers' own brand or Eclipse. Accord is unlikely to be a palatable product for most smokers because of the low levels of nicotine achieved by this product compared with conventional cigarettes; therefore, it is difficult to foresee smokers willing to switch from their own brand of cigarettes to Accord. No long-term natural environment or comprehensive biomarker study has been done with Accord.

MODIFIED TOBACCO PRODUCTS

Modified tobacco products involve reduction of one or more toxins in tobacco products. The two PREPs in this category that have been tested are Advance and Omni. Omni is no longer sold, but newspaper and magazine advertisements claimed that the product was "created to significantly reduce carcinogenic PAHs, nitrosamines, and catechols, which are major causes of lung cancer in smokers." On a Web site advertising Omni prior to its withdrawal from the market, its manufacturer, Vector Tobacco, indicated that smoking Omni produced a 53% reduction in exposure to **NNK** (a potent lung carcinogen) and a 15% to 20% reduction in **pyrene** (a marker for PAH exposure), as measured by machine-derived yields.[13] Advance has been advertised as "the innovative cigarette with a better formula for pleasure, giving you full, rich flavor and less toxins." [31]

As with the cigarette-like delivery devices, two types of studies have been conducted with modified tobacco products: short-term laboratory studies and longer-term natural environment studies in which participants were required to use only the assigned product. Most of these latter studies have focused primarily on the extent of exposure to cancer-causing agents, carbon monoxide, and nicotine. Breland and colleagues[32] examined the acute effects of Advance in 20 nonsmokers. After 4 8-puff smoking bouts, Advance delivered 11% less carbon monoxide and 25% more nicotine, but similar withdrawal suppression and heart rate increase, compared with participants' own brand. In another study led by Breland,[33] 12 participants were assigned to 1 of 3 experimental conditions (Advance, own brand, or no cigarettes) over the course of 5 days. Advance users had a 51% lower urinary concentration of nitrosamine metabolites compared with their own brand, and concordant with the previous study, a slight but significant decrease in carbon monoxide, but no change in **cotinine**, a biomarker of nicotine. Although this short-term study shows a reduction in exposure to a carcinogen, a study of longer duration is necessary to accommodate adjustments to smoking a novel cigarette product and stabilize participants' smoking behavior. Of note, other than exposure measures of nicotine, carbon monoxide, and one cancer-causing agent and measurement of vital sign (e.g., heart rate), no other studies have been published showing reductions in other toxins associated with use of Advance.

Two other studies of longer duration have focused on Omni cigarettes. Hughes and colleagues[12] randomly assigned 34 existing cigarette users to smoke either their own brand of cigarettes or the Omni cigarette; after six weeks, participants switched to the other experimental conditions (so all participants had an opportunity to use the Omni product). When using Omni, participants smoked the same number of cigarettes per day as they did when they were smoking their own brand of cigarettes, but their total cotinine levels were 18% lower. Carbon monoxide levels increased 21% with Omni. Levels of carcinogen metabolites of NNK (total **NNAL**) and pyrene (1-HOP, a marker for PAH) were 17% lower and 10% lower with Omni, respectively, but these findings were not statistically significant.

Hatsukami and colleagues[13] examined the amount of exposure to cancer-causing agents (assessed by

the presence of metabolites of NNK [total NNAL] and pyrene [1-HOP]) when tobacco users switched to either a "reduced exposure" tobacco product (snus or Omni) or medicinal nicotine. The researchers observed significant, albeit modest, reductions in NNK uptake (21% reduction in total NNAL), but only a 5% reduction in 1-HOP in the 22 smokers assigned to the Omni condition. Exposure to carbon monoxide and cotinine remained the same as before the switch occurred. Medicinal nicotine offered the greatest reduction in toxins.

Taken together, these studies show that Omni leads to minimal or only modest reductions in uptake of carcinogens, and either the same or increased levels of CO. It is unknown, although unlikely, whether the extent of this reduction would have any effect in reducing risk for cancer. Interestingly, in users of the Omni product, carcinogen exposure did not decrease as much as was advertised on the manufacturer's Web site. (Information appearing on the now-deactivated Omni Web site, which indicated a 53% reduction in NNK and a 15% to 20% reduction in pyrene, was based on machine-derived methods.)

In summary, no large, comprehensive, long-term, naturalistic study has been undertaken to examine the effects of using these modified tobacco products on biomarkers of exposure to cancer-causing agents and cancer risk. In addition, no studies have examined the effects of these cigarettes on biomarkers for other diseases, which would be important to rule out the possibility that one would see increased risk in other areas of health. To date, the studies have been either too short to determine actual exposure to carcinogens over the long term or have not shown a reduction that is likely to lead to reduced risk for cancer.

Demystifying the Data...

What does it mean to have lower levels of pyrene?
Lower levels of pyrene indicate a decrease in a smoker's exposure to potentially cancer-causing PAHs. Pyrene itself is not carcinogenic, but it is reflective of the presence of PAHs.

Do decreased levels of cotinine mean decreased exposure to carcinogens?
No. Cotinine, which is usually detected in urine, blood, or saliva, is a biomarker for exposure to nicotine, not carcinogens. With conventional cigarette products, there is a high correlation between carcinogen exposure and cotinine levels. However, modified tobacco products may reduce carcinogen exposure but maintain high nicotine levels, or the products may decrease nicotine levels but maintain high levels of carcinogens. A decrease in cotinine simply implies that the participant has absorbed less nicotine. Such measures of nicotine absorption are measures of exposure, but they are also measures of whether the product is delivering sufficient nicotine to satisfy the smoker.

What does it mean when levels of cotinine and nicotine are the same between those who used a PREP and those who smoked their own brand?
When measured levels of cotinine are the same for users of PREPs and users of their own brand of tobacco, it indicates that the uptake of nicotine with the PREP is similar to that with the smoker's own brand. This similarity suggests that the smoker's level of addiction to nicotine has not changed by switching to that particular PREP, unless the product is associated with slower delivery of nicotine.

SMOKELESS TOBACCO

To date, few studies have been conducted with smokeless tobacco and no studies have been published on oral compressed tobacco lozenges. Currently, two oral compressed tobacco lozenges exist on the market, Ariva and Stonewall. Both use StarCured tobacco. According to marketing claims, "The tobacco in Ariva is 100% Virginia StarCured tobacco, which the company reports contains the lowest levels of TSNAs in the world."[34] Other statements include "Star Scientific believes that Stonewall products offer enhanced flavor as well as reduced toxins, for adult tobacco consumers who want to make an informed choice about their use of smokeless tobacco products" and "Tobacco-specific nitrosamines levels in the Stonewall products are substantially lower than those found in any smokeless products currently sold in the United States."[35] While no claims have been made about reduced toxin exposure or reduced health risk among smokeless tobacco products, claims have been made that smokeless tobacco poses less risk than cigarettes. For example, Swedish Match, the manufacturers of Exalt and General (two Swedish smokeless tobacco products that have lower levels of TSNAs than conventional cigarettes sold in the United States), stated that the product's "continued appreciation by tobacco consumers in the U.S. will help in reducing the risks associated with cigarette smoking."[36]

Hatsukami and colleagues[13] examined the amount of exposure to cancer-causing agents (assessed by total NNAL) when smokeless tobacco users switched from their own brand of smokeless tobacco to General snus or to medicinal nicotine. Smokeless tobacco users assigned to snus reduced their total NNAL levels by about 50%, compared with 90% with medicinal nicotine. This finding indicates that there are smokeless tobacco products available with significantly reduced levels of a cancer-causing agent, NNK, compared with conventional and popular U.S. brands. However, use of these reduced-carcinogen products still results in significant exposure to a cancer-causing agent.

In another study led by Hatsukami,[37] researchers reviewed the studies and issues related to using smokeless tobacco as a means for decreasing exposure to tobacco toxins and reducing harm. Findings indicated that cigarette smoking produces more negative health effects than using smokeless tobacco and also has a higher addiction potential and rate of relapse. However, the authors note, smokeless tobacco is not without the potential for harm, and because smokeless tobacco is not subject to the same regulatory scrutiny as medicinal nicotine, lack of full disclosure regarding the toxins in smokeless tobacco could do more harm than good to public health. Furthermore, the individual and population effects of marketing smokeless tobacco in lieu of smoking are unknown.

As noted above, no studies have been published on Ariva or Stonewall.

Demystifying the Data...

What are the effects of maintaining nicotine levels?
When a smoker switches from his or her regular brand of cigarette to a PREP, it is possible that the level of nicotine (as measured by cotinine in urine, blood, or saliva) will be maintained—that is, remain the same. In such cases, it is likely that the PREP was able to suppress the symptoms of nicotine withdrawal because the level of nicotine absorbed in the body did not change. However, maintenance of nicotine levels may sustain addiction to the tobacco product, although how quickly the nicotine is absorbed also plays a significant role in the extent of addiction to the product. Maintaining high levels of nicotine may also contribute to risk factors for cardiovascular disease (e.g., high blood pressure).

What does a lower urinary concentration of total NNAL imply?
NNAL is a breakdown product of NNK, a potent lung carcinogen. When a smoker's urinary concentration of total NNAL (NNAL plus NNAL-Glucs) has decreased, it indicates that the uptake of NNK has also decreased. At this time, the health outcomes of such a decrease in NNK and NNAL are unknown.

What might a significant decrease in nicotine levels mean?
After switching from their own brand of tobacco to a PREP, smokers may experience a decrease in nicotine levels (as measured by cotinine in urine, blood, or saliva). As a result, these smokers may experience symptoms of withdrawal or less rewarding effects from the PREP. Reduced symptoms of withdrawal may have several implications. It may be good if the participant is trying to reduce addiction. On the other hand, decreased nicotine could lead the participant to modify his or her use of the product (e.g., use the PREP more frequently, take deeper puffs) so that more nicotine can be consumed. Finally, it may be an indication that smokers are unlikely to be satisfied with the PREP because it cannot deliver sufficient amounts of nicotine.

Potentially Reduced-Exposure Tobacco Products: Selected Product Claims and Published Research Results		
Product Information	**Product Claims**	**Research Results**
Product: Eclipse **Product Type:** Cigarette-like delivery device **Manufacturer:** R.J. Reynolds **Method for reducing toxin:** Heating (not burning) tobacco	Delivers lower levels of smoke; "may reduce the risks of smoking-associated cancers and lower the risk of lung disease"[38] "Eclipse is for smokers who have decided not to quit, but who are interested in a cigarette that responds to concerns about certain smoking-related illnesses, including cancer. For many smokers, it may well be a better way to smoke."[19] Eclipse results in 46% reduced bronchial inflammation and 36% less inflammation of the lower lung.[19]	<u>Lee et al (2004)</u>[25] *Participants**: 10 smokers *Experimental conditions*: Eclipse, own brand *Duration of exposure*: 5 smoking sessions separated by at least 24 hr; 1 cigarette per session *Study design*: Within-subjects† *Findings*: • Eclipse caused nonsignificant higher levels of exhaled CO (6.6 ppm) than own brand (4.5 ppm). • Eclipse had significantly smaller nicotine boost assessed 2 min after smoking than own brand (10.7 ng/ml vs. 16.4 ng/ml). • No significant difference in heart rate increases. <u>Breland et al (2002)</u>[26] *Participants*: 20 light and ultra light smokers *Experimental conditions*: Eclipse, Accord, denicotinized cigarettes, own brand *Duration of exposure*: 4 2.5-hour sessions, 4 8-puff smoking bouts *Study design*: Within-subjects *Findings*: • Eclipse significantly increased CO boost by approximately 30% (8.0 ppm for Eclipse vs. 5.6 ppm for own brand after first bout; 31.4 ppm vs. 23.6 ppm by end of session) and significantly decreased levels of nicotine compared with own brand (13.3 ng/ml vs. 18.9 ng/ml). • Heart rate increase similar to own brand. <u>Fagerstrom et al (2000)</u>[27] *Participants*: 40 smokers *Experimental conditions*: Eclipse, nicotine inhaler, usual smoking *Duration of exposure*: 2 weeks of Eclipse and 2 weeks of nicotine inhaler while smoking *Study design*: Within-subjects *Findings*: • Eclipse significantly reduced the number of cigarettes smoked per day from 19.1 to 2.1, but maintained nicotine concentrations and significantly increased CO levels from 21.0 ppm to 33.0 ppm. (Subjects using nicotine inhaler significantly reduced cigarettes per day from 19.1 to 4.8, CO intake from 21.0 ppm to 12.7 ppm, and nicotine from 16.8 ng/ml to 12.2 ng/ml). <u>Fagerstrom et al (2002)</u>[28] *Participants*: 38 smokers *Experimental conditions*: Eclipse, nicotine inhaler, usual smoking *Duration of exposure*: 8 weeks of nicotine inhaler (N=15) or Eclipse (N=10) while smoking, or smoking with own brand (N=13) *Study design*: Between-subjects‡ for Eclipse, nicotine inhaler or own brand (participants' choice for treatment condition) *Findings*: • Eclipse reduced the number of cigarettes smoked per day by 86% and increased CO levels by 45%. (Participants using nicotine inhaler reduced number of cigarettes smoked by 68% and CO intake by 47%.) ***The following published studies of Eclipse were funded by R.J. Reynolds tobacco company:*** <u>Rennard et al (2002)</u>[20] *Participants*: 12 smokers ≥ 40 cigarettes/day (8 nonsmokers used as controls)

Experimental conditions: Eclipse, own brand
Duration of exposure: 2 months of Eclipse
Study design: Within-subjects for Eclipse and own brand
Findings:
- Significant reductions in respiratory tract inflammation with Eclipse compared with own brand (e.g., visible decrease in inflammation in 11 of 12 participants, visual index score of 7.0 vs. 3.0 with switch, average of 35% improvement in alveolar inflammatory cells, average of 46% improvement in bronchitis index). Improvement in inflammatory markers did not reach the normal range.
- Greater proportion who rated themselves free of respiratory symptoms with Eclipse.
- No significant differences in serum cotinine or nicotine, peripheral blood measures (e.g., fibrinogen, hemoglobin, platelets), lung function, and vital signs were observed with Eclipse.
- CO tended to increase with use of Eclipse.

Frampton et al (2000)[21]
Participants: 10 smokers
Experimental conditions: Eclipse, own brand
Duration of exposure: 2 and 4 weeks of Eclipse
Study design: Within-subjects
Findings:
- No significant change in pulmonary epithelial permeability at 4 weeks.
- Increase in CO; increased high-density lipoprotein cholesterol, and reduced circulating lymphocyte activation with Eclipse.

Stiles et al (1999)[22]
Participants: 2 groups of 26 smokers
Experimental conditions: Eclipse, own brand
Duration of exposure: Laboratory testing after 2 weeks Eclipse, and when smoking own brand
Study design: Within-subjects
Findings:
- Wide variability in puffing and absorbed CO.
- Participants took significantly greater total puff volume when smoking Eclipse.
- No significant differences were observed in average absorbed CO between Eclipse and own brand.

Smith et al (1996)[23]
Participants: 20 smokers (14 nonsmokers used as controls)
Experimental conditions: Eclipse, own brand
Duration of exposure: 3 weeks own brand, 1 week Eclipse
Study design: Within-subjects
Findings:
- Eclipse resulted in 72% and 79% reduction in urine mutagenicity as measured in TA98 and YG1024 strains, respectively.
- Significant reductions in urinary cotinine (32%) were observed with Eclipse.

Bowman et al (2002)[24]
Participants: 67 smokers
Experimental conditions: Smokers of ultra low tar (N=11) vs. full-flavor low tar (N=41) vs. full-flavor tar (N=15) filtered cigarettes, Eclipse
Duration of exposure: 1 week usual brand, 1 week Eclipse, 1 week usual brand
Study design: Within-subjects
Findings:
- No difference in salivary cotinine when smoking own brand vs. Eclipse.
- Significant reductions (70%-77%) were observed in urine mutagenicity across all tar categories when participants switched to Eclipse.

Potentially Reduced-Exposure Tobacco Products: Selected Product Claims and Published Research Results (Continued)		
Product Information	**Product Claims**	**Research Results**
Product: Accord **Product Type:** Cigarette-like delivery device **Manufacturer:** Phillip Morris **Method for reducing toxin:** Heating (not burning) tobacco	No advertised claims. Reduced toxins reported at scientific meeting.[11]	*Buchhalter et al (2000)*[17] *Participants*: 10 light and ultra light smokers *Experimental conditions*: Accord, own brand *Duration of exposure*: 2 2-hour sessions (smoking at 30-minute intervals) *Study design*: Within-subjects *Findings*: • Accord resulted in marginal increase in CO intake (mean difference of 0.7 ppm). • CO intake with own brand was 25 times higher (mean difference of 18.0 ppm), which was significant. • More moderate heart rate increases occurred with Accord (78.4 bpm to 81.9 bpm) than with own brand (78.8 to 90.2 bpm). *Breland, Buchhalter et al (2002)*[26] *Participants*: 20 light and ultralight smokers *Experimental conditions*: Eclipse, Accord, denicotinized cigarettes, own brand *Duration of exposure*: 4 2.5-hour sessions, 4 8-puff smoking bouts *Study design*: Within-subjects *Findings*: • Accord led to significantly lower CO than own brand (1.6 ppm vs. 5.6 ppm after first bout, 8.2 ppm vs. 23.6 ppm by end of session). • Accord led to significantly decreased levels of nicotine compared with own brand (8.7 ng/ml vs. 18.9 ng/ml). • Generally lower heart rate increases with use of Accord (5.9 bpm with Accord after first bout, 13.0 bpm for own brand). *Buchhalter et al (2001)*[29] *Participants*: 32 light and ultra light smokers *Duration of exposure*: 4 2.5-hour sessions (smoking at 30-minute intervals) *Experimental conditions*: Accord, Merit Ultra Light, denicotinized cigarettes, own brand *Study design*: Within-subjects *Findings*: • Accord resulted in about 70% lower post-smoking CO levels compared with own brand (7.2 ppm vs. 24.1 ppm) and 63% lower than the ultra light cigarette (7.2 ppm vs. 19.6 ppm). • Heart rate increases were significantly lower than with own brand and ultra light cigarette. ***The following published study of Accord was funded by Phillip Morris tobacco company:*** *Roething et al (2005)*[30] *Participants*: 107 light smokers *Duration of exposure*: 8 days with controlled smoking to keep the smoking as constant as possible and confined to clinical site *Experimental conditions*: Marlboro Light (own brand), Accord, Oasis, Marlboro Ultra Light, no smoking *Study design*: Between-subjects, with 20 randomly assigned to each cigarette condition and 30 to the no-smoking condition *Findings*: • Accord and Oasis resulted in about 70% lower urine nicotine excretion at Day 8 compared with baseline, and Marlboro Ultra Light was associated with a 23% reduction; significant differences in changes from baseline were observed between the PREPs (Accord and Oasis) and both Marlboro Light and Ultra. • Accord and Oasis resulted in a 53% to 66% reduction in urine mutagenicity, compared with 58% for no smoking and

		26% for Marlboro Ultra Light. • Accord and Oasis resulted in 80% reduction in exhaled CO, compared with 93% reduction for no smoking group and 18% to 30% reduction (depending on time of day) for Marlboro Ultra Light. • Accord and Oasis was associated with 93% decrease in carboxyhemoglobin, compared with 95% in no smoking group and 39% in Marlboro Ultra Light. • Levels of respirable suspended air particles, CO, and volatile organic compounds in the air were similar between the rooms occupied by Accord and Oasis and no-smoking groups.
Product: Advance **Product Type:** Cigarette **Manufacturer:** Brown & Williamson; Star Scientific Tobacco **Method for reducing toxin:** Modified tobacco	"Great taste, less toxins"[31] "The innovative cigarette with a better formula for pleasure, giving you full, rich flavor and less toxins"[31] "StarCured tobacco curing process… consistently produces flue-cured tobacco with the lowest levels of TSNAs in the world."[34]	<u>*Breland, Evans, et al (2002)*</u>[32] *Participants*: 20 light and ultra light smokers *Experimental conditions*: Advance, own brand, unlit cigarette ("sham" smoking) *Duration of exposure*: 3 2.5 hour sessions, 4 8-puff smoking bouts *Study design*: Within-subjects *Findings*: • Advance delivered 11% less CO (23.4 ppm vs. 25.4 ppm) and 25% more nicotine than own brand (23.3 ng/ml vs. 18.6 ng/ml) at end of session, with both measures showing significant differences between Advance and own brand. • Heart rate was similar. <u>*Breland et al (2003)*</u>[33] *Participants*: 12 light and ultra light smokers *Experimental conditions*: Advance, own brand, no smoking *Duration of exposure*: 3 5-day conditions *Study design*: Within-subjects *Findings*: • Significantly lower (51%) urinary concentration of total NNAL with Advance compared with own brand (298.2 pg/ml vs. 603.9 pg/ml). • No significant difference in cotinine levels. • Slight but significant reduction in CO levels with Advance.
Product: Omni **Product Type:** Cigarette **Manufacturer:** Vector Tobacco **Method for reducing toxin:** Modified tobacco	"Reduced carcinogens. Premium taste… Introducing the first premium cigarette created to significantly reduce carcinogenic PAHs, nitrosamines, and catechols, which are major cause of lung cancer in smokers." (from magazine and newspaper advertisements) 53% reduction in NNK exposure and 15% to 20% reduction in pyrene as measured by machine determined yields[18]	<u>*Hatsukami et al (2004)*</u>[13] *Participants*: 22 smokers analyzed for Omni, 16 for nicotine patch *Experimental conditions*: Own brand, Omni, nicotine patch *Duration of exposure*: 4 weeks *Study design*: Within-subjects for own brand and product, between-subjects across products *Findings*: • A significant reduction in total NNAL (21%) with Omni compared with own brand. • A nonsignificant reduction in 1-HOP (5%) with Omni compared with own brand. • No significant differences in CO or cotinine. • Significant reductions in the nicotine patch group for total NNAL, 1-HOP, CO, and cotinine compared with own brand; lower levels were observed for nicotine patch compared with Omni for total NNAL and CO. <u>*Hughes et al (2004)*</u>[12] *Participants*: 34 smokers *Experimental conditions*: Omni, own brand *Duration of exposure*: 6 weeks of own brand and Omni *Study design*: Within-subjects *Findings*: Omni compared with own brand showed: • Significantly lower cotinine levels (18%). • Significantly greater CO boost (21%). • Nonsignificant reduction in total NNAL (17%). • Nonsignificant reduction in 1-HOP (10%).

Potentially Reduced-Exposure Tobacco Products: Selected Product Claims and Published Research Results (Continued)		
Product Information	**Product Claims**	**Research Results**
Product: Quest **Product Type:** Cigarette **Manufacturer:** Vector Tobacco **Method for reducing toxin:** Modified tobacco	"Step your way to nicotine-free!"[39]	No published studies available.
Product Revel **Product Type:** Oral tobacco packet **Manufacturer:** US Smokeless Tobacco **Method for reducing toxin:** Oral noncombustible	"A uniquely discreet way to enjoy real tobacco satisfaction instead of lighting up."[40] "Attention adult smokers: There's something to smile about!"[40]	No published studies available.
Product: General snus **Product Type:** Swedish snus **Manufacturer:** Swedish Match **Method for reducing toxin:** Oral noncombustible	No marketing claims available (in English)	*Hatsukami et al (2004)*[13] *Participants*: 19 smokeless tobacco users analyzed for General snus, 22 analyzed for nicotine patch *Experimental conditions*: Own brand, General snus, nicotine patch *Duration of exposure*: 4 weeks *Study design*: Within-subjects for own brand and product, between subjects across products *Findings*: • Significant reduction in total NNAL levels (48%) for General snus relative to own brand. • Significant reduction in total NNAL (89%-90%) and cotinine for nicotine patch; total NNAL was significantly lower for nicotine patch compared with General snus.
Product: Exalt **Product Type:** Swedish snus **Manufacturer:** Swedish Match	"Continued appreciation [of Exalt] by tobacco consumers in the U.S. will help in reducing the risks associated with cigarette smoking."[36]	No published studies available.

Method for reducing toxin: Oral noncombustible	"…a smokeless alternative for cigarette smokers."[41]	
Product: Ariva **Product Type:** Compressed tobacco lozenge **Manufacturer:** Star Scientific **Method for reducing toxin:** Oral noncombustible	"The tobacco in Ariva is 100% Virginia StarCured tobacco, which the company reports contains the lowest levels of tobacco-specific nitrosamines in the world."[34] "Ariva does not contain the hundreds of toxic chemical constituents found in tobacco smoke."[42]	No published studies available.
Product: Stonewall **Product Type:** Compressed tobacco lozenge **Manufacturer:** Star Scientific **Method for reducing toxin:** Oral noncombustible	"Star Scientific believes that Stonewall products offer enhanced flavor as well as reduced toxins, for adult tobacco consumers who want to make an informed choice about their use of smokeless tobacco products."[35] "Tobacco-specific nitrosamines levels in the Stonewall products are substantially lower than those found in any smokeless products currently sold in the United States."[35]	No published studies available.

* "Participants" represented a mix of regular, light, and ultra light smokers unless otherwise specified.
† "Within-subjects" means subjects are assigned to all of the treatment conditions.
‡ "Between-subjects" means subjects are assigned to one of the treatment conditions.

bpm, beats per minute; CO, carbon monoxide; ng/ml, nanograms per milliliter; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PAHs, polycyclic aromatic hydrocarbons; ppm, parts per million; TSNAs, tobacco-specific nitrosamines.

GLOSSARY

1-HOP (1-hydroxypyrene): A breakdown product (metabolite) of pyrene. Pyrene itself is not carcinogenic but is reflective of the amount of polycyclic aromatic hydrocarbons (PAHs) present in the body. 1-HOP can be measured as a biomarker for exposure to PAHs, which are potent carcinogens found in tobacco smoke and in other products of incomplete combustion.

Biomarker: A biomarker can be used to examine the extent of toxin exposure and the effects of this toxin exposure on the body. To determine whether or not a PREP may lead to harmful bodily effects may take years. Therefore, surrogate indicators or intermediary markers of health effects are necessary. Biomarkers provide an objective way for evaluating (1) exposure to carcinogens, nicotine, and other substances, (2) biological toxicity (e.g., alterations in DNA), and (3) indicators of injury (e.g., alterations in tissue) or harm (e.g., clinical symptoms). Although these biomarkers should be predictive of disease, few studies have been conducted to demonstrate that biomarkers specific to tobacco-related disease actually are predictive of disease.

Carboxyhemoglobin: A compound formed when inhaled carbon monoxide combines with hemoglobin in the blood. Carbon monoxide binds more tightly than oxygen, resulting in less oxygen that is transported in hemoglobin.

Carbon monoxide: A poisonous gas that is an indicator of exposure to tobacco smoke. Carbon monoxide is best used for assessing recent episodes of exposure. Increased blood levels of carbon monoxide interfere with the transport of oxygen in the blood.

Carbon monoxide boost: The increase in the measured levels of carbon monoxide that occur in the body as assessed before and immediately following use of a combusted or heated tobacco product (e.g., one cigarette).

Cotinine: A biomarker of nicotine in smokers and those exposed to environmental tobacco smoke. Cotinine is a metabolite of nicotine and because it stays in the body longer (i.e., has a longer half-life), it is considered a good indicator of nicotine exposure levels.

NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) and total NNAL (NNAL and its glucuronides): Metabolites of NNK, a potent tobacco-specific lung carcinogen. NNAL is easily detected in the urine of humans.

NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone): The most carcinogenic of the tobacco-specific nitrosamines. NNK has been shown to cause cancer in rodents.

Nicotine: A major known addictive ingredient in tobacco.

Nicotine boost: The increase in measured levels of nicotine that occur in the body as assessed before and immediately following use of a tobacco product (e.g., one cigarette or dip of smokeless tobacco).

Polycyclic aromatic hydrocarbons (PAHs): Cancer-causing compounds formed from the incomplete combustion of tobacco leaves and fossil fuels.

Potentially reduced exposure tobacco product (PREP): Tobacco products that have been modified or designed in some way to purportedly reduce users' exposure to tobacco toxins.

Pyrene: A substance that is noncarcinogenic but is reflective of PAH exposure.

Respirable suspended particles: Particulates that are small enough to reach the lower airways of the human lung.

Tar: The material from cigarette smoke, excluding nicotine and water, that can be collected on a fiberglass filter.

Tobacco-specific nitrosamines (TSNAs): Potent cancer-causing substances found in most tobacco products. An example of a TSNA is NNK.

Total organic compounds: An array of volatile organic compounds that can easily become vapors or gases. Many volatile organic compounds are hazardous air pollutants.

Urine mutagenicity: Mutagenicity is damage to genes. This can be measured in urine using a simple test with bacteria.

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Lead Author

Dorothy Hatsukami, Ph.D.
Forster Family Professor of Cancer Prevention
Professor of Psychiatry
University of Minnesota Cancer Center
Codirector, University of Minnesota
Transdisciplinary Tobacco Use Research Center
Minneapolis, Minnesota

Contributing Author

Stephen Hecht, Ph.D.
Wallin Professor of Cancer Prevention
University of Minnesota Cancer Center
Codirector, University of Minnesota
Transdisciplinary Tobacco Use Research Center
Minneapolis, Minnesota

Reviewers

David M. Burns, M.D.
Professor of Family and Preventive Medicine
Professor of Medicine
University of California, San Diego School of Medicine

Mitch Zeller, J.D.
Vice President for Policy and Strategic Communications
Pinney Associates
Bethesda, Maryland

Editor/Writer

Jeanne Mettner, M.A., E.L.S.
Planetary Ink
Minneapolis, Minnesota

Graphic Designer

Jenny Bondi
University of Illinois at Chicago
Chicago, Illinios

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University of Minnesota Transdisciplinary Tobacco Use Research Center
2701 University Avenue SE
Suite 201
Minneapolis, MN 55414

612.627.4848

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