

NICOTINE and HEALTH

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NICOTINE — and — HEALTH



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PART ONE



Nicotine and Its Health Effects

SUMMARY

MORTALITY RISKS AND CANCER RISKS VARY GREATLY BY PRODUCT

Cigarettes and smoking tobacco are the most deadly recreation products on shop shelves.

Nicotine has been widely used as a medicine since 1984 and is safe at the doses used in medicines.

Nicotine products do not cause lung or other cancers, nor lung or heart disease.

Tobacco smoking, in contrast, is the main cause of lung cancer and the main preventable cause of lung and heart disease.

POLITICAL AND REGULATORY APPROACH

The first requirement is to ensure smokers can buy recreational inhaled nicotine, as it is far safer than smoked tobacco. The next step is to ensure brands are true to label, effective, child-safe, and of minimal toxicity. Extreme regulatory caution, insisting on all nicotine being sold as a medicine while tobacco remains on sale as a recreational product, could inhibit smokers' desire to embrace nicotine as a recreational alternative to smoking.

ADDICTION SCIENCE

- Virtually all tobacco smokers are addicted.
- Cigarette smoking is highly addictive, more than nicotine by itself (*Chart 2: the continuum of addiction*).
- Nicotine is the main cause of addiction to tobacco, but it does not act alone, aided by the habits and rituals of the act of smoking, and possibly by other substances in tobacco and smoke.

This paper sets out the science of nicotine as it affects health. Nicotine is addictive, driving smokers to smoke for most of their lives, and indirectly shortening their lifespan by at least ten years. Nicotine, however, is not in itself a direct cause or even a minor cause of these smoking deaths or diseases. Indeed, smokers switching to far safer nicotine-vaporizer substitutes can reduce their risk while maintaining their addiction to nicotine.

Across the world, deadly cigarettes are sold with government approval for recreational purchase by adults in almost every country, yet nicotine products are not approved for recreational use. To understand the potential of nicotine products to help smokers and countries avoid the predicted one billion deaths from cigarette smoking this century, we need to understand the science behind nicotine.

INTRODUCTION

Tobacco for smoking was brought from the Americas to Europe by Christopher Columbus and others in the fifteenth and sixteenth centuries. Eventually, nicotine was isolated as the essential ingredient that had driven demand for tobacco since the 1700s, creating fortunes for the tobacco barons supplying Europe with nasal snuff and pipe tobacco. From the 1880s, with the invention of the cigarette machine, addictive tobacco/nicotine could be packaged in a standardized affordable cigarette, creating the fortunes of today's American and British tobacco multinationals (later joined by tobacco conglomerates in Japan and China). Today, nicotine continues to drive demand for the deadly cigarette.

Nicotine is the primary pharmacologically-active substance in tobacco and was first isolated chemically in 1828 and synthesized in the 1890s. Like caffeine and morphine, nicotine is an alkaloid—a biological, naturally occurring, nitrogen-containing compound. Nicotine is found in the *Nicotiana* or tobacco plant, part of the Solanaceae family of flowering plants which include edibles such as potato, tomato and chili peppers, and other highly toxic species such as deadly nightshade that contain insignificant amounts of nicotine. Nicotine makes up one to three percent of dried tobacco, and a cigarette contains about 10 mg of nicotine. Tobacco was used with little in the way of health effect until the widespread use of portable matches met up with the mass production of cigarettes around the turn of the last century. In the 1960s, the cigarette industry knew that nicotine was the addictive agent in cigarettes, a fact not officially recognized until the U.S. Surgeon General's landmark 1988 report.¹



GLOSSARY

Abuse potential

The risk that a substance would cause addiction.

ACC

Anterior cingulate cortex, the frontal part of the cingulate cortex on the medial (midline) side of the brain's hemisphere, which resembles a collar around the corpus callosum, is one of several brain regions involved in tobacco addiction.

Addiction continuum

Addiction, measured by difficulty in quitting, varies with the product. *Chart 2.*

Addiction to tobacco smoking

A periodic and regular compulsion to smoke tobacco.

Atomiser

The battery-powered heating coil of an electronic cigarette.

Delivery

The amount of a substance that a cigarette delivers to the mouth.

Denicotinized cigarette

(Denic) or Very Low Nicotine Content (VLNC) cigarette contains less than 2 mg of nicotine.

The electronic cigarette

The e-cigarette or e-cig is a battery-powered vaporizer of a solution of nicotine, propylene glycol or glycerol, with flavors, in various nicotine strengths including zero.

FA

Fractional anisotropy, a method of measuring brain cell organization in white matter.

FTND or FTCD

Fagerström test for nicotine dependence, now renamed the FTCD for cigarette dependence, a ten-point score measuring addiction to cigarettes.

FDA

Food and Drug Administration, which regulates tobacco and nicotine products, and NRT in the United States, except electronic cigarettes, which it intends to regulate.

HONC

Hooked on Nicotine Checklist, a ten-question list of symptoms of tobacco addiction.

Latency

The time from smoking the last cigarette until the need for the next cigarette is felt.

MAO

Monoamine oxidase, a natural enzyme that destroys dopamine, the pleasure-signaling molecule in the brain.

M RTP

Modified risk tobacco product. A product in development designed to claim reduced risk for smokers.

Nicotine addiction (or dependence)

A periodic and regular compulsion to use a nicotine product.

NRT

Nicotine replacement therapy, patch, gum, inhaler, lozenge.

PG

Propylene glycol, the main ingredient in most brands of e-cigarette liquid.

Risk Continuum

Risk of use decreases from high risk cigarettes (top bars in blue) to low-risk smokeless and nicotine products and non-smoking (bottom bars in green). *Chart 4* (see page 29). Harm reduction aims to move smokers down this scale of risk.

Smokeless tobacco

Does not generate smoke, and includes chewing tobacco, oral snuff, and snus.

Snuff, moist oral

Tobacco held in the mouth or, in the case of Swedish snuff, under the upper lip.

Tobacco addiction (or dependence)

A periodic and regular compulsion to use a tobacco product.

Tobacco harm reduction

Reducing harm by shifting from a high-risk product such as cigarettes, to a low-risk product (as in *Chart 4*).

TSNAs

Tobacco-specific nitrosamines, potent cancer-causing substances found in unburnt tobacco at approximately 1 microgram per gram (one part per million).

Vaping

The practice of inhaling vapor, a term used to distinguish e-cigarette use from smoking tobacco.

VG

Vegetable glycerine or glycerol. An alternative to PG in e-cigarette liquid.

VLNC cigarette

Very low nicotine content cigarette. A denicotinized cigarette. See above.

Yield

The amount of a substance (for example nicotine) in the smoke of a cigarette as measured by a smoke machine.

NICOTINE: PHYSICAL AND PHARMACOLOGICAL PROPERTIES

NICOTINE—AN ACUTE POISON

Nicotine at certain exposure levels is highly toxic, and toxic effects develop rapidly following acute overdose. The lethal dose for nicotine in adults is quoted as 40 to 60 mg.¹ Dermal absorption of 0.1 mg in young children is sufficient to cause symptoms.² Nicotine is more toxic when absorbed through the skin than from ingestion. For example, children swallowing two cigarettes (20 mg) recovered,¹ whereas 5 ml electronic cigarette liquid bottles contain 90 mg nicotine. Rarely, multiple nicotine patches on the skin have been used for attempted suicide, with serious results.³

Nicotine as an insecticide is highly toxic; on the other hand, it is one of the safest of medicines. As with many exposures, it all depends on the dose and the speed of delivery.

NICOTINE METABOLISM

Nicotine is metabolized in the liver, mostly by the enzyme CYP2A6, mainly breaking it down to cotinine—quite rapidly: nicotine has a metabolic half-life of two hours.¹ Cotinine's half-life is approximately 20 hours, making cotinine levels a good surrogate marker for whether a person is currently smoking tobacco or inhaling nicotine.

- **Estrogen.** Pre-menopausal women clear nicotine 21 percent more rapidly than men. Women using estrogen-containing oral contraceptives metabolize nicotine 28 percent more rapidly than non-users.⁴ Pregnant women clear nicotine 60 percent more rapidly than non-pregnant women.⁵
- **Race and ethnicity.** In the United States, whites metabolized nicotine most rapidly compared with blacks/African-Americans and Asians.⁶ Chinese-Americans clear nicotine from the body more slowly, and this may partly explain why they smoke fewer cigarettes.⁷
- **Adolescence.** At age 13 to 17 years of age, no gender differences in metabolism were found, but racial differences were similar to those for adults.⁶

NICOTINE DELIVERY TO THE BRAIN

Nicotine reaches the brain within seven seconds of taking a puff of smoke, and nicotine concentration in the brain reaches maximum values within five minutes of taking the last puff. The first cigarette of the day boosts brain nicotine tenfold, and a cigarette in the afternoon doubles it.

Nicotine is a small molecule and it can circulate with ease. Studies with radio-labeled nicotine show that when a cigarette is smoked some nicotine reaches the brain seven seconds after smoke enters the mouth.⁸ Nicotine concentration in the brain rises to more than half the maximum during the next 15 seconds,⁹ although it takes 3.5 to 4.8 minutes to finally reach maximum levels. During this time brain nicotine levels are increasing gradually and steadily. This is due to the slower absorption from the mucosal surfaces of the conducting airways before the smoke reaches the alveoli.

The rate of increase in brain nicotine is thus sufficient to markedly increase brain nicotine before each new puff is taken. After overnight abstinence, smoking just one cigarette will boost the amount of free nicotine in the brain tenfold, and during afternoon smoking one cigarette will double the amount of free nicotine in the brain.¹

The rapid increase in brain nicotine after every cigarette is believed to increase the addictiveness of smoking, compared, for example, to the use of a nicotine patch, which causes a very gradual rise in plasma nicotine to a low plateau, seldom causing addiction.



ADDICTION TO NICOTINE

A person is addicted to smoking or nicotine if the person experiences a recurrent and periodic wanting, craving, or needing for tobacco or nicotine.

Almost all people who smoke regularly are addicted, even shortly after starting to smoke.

Nicotine is the drug in tobacco that causes addiction. It alters the mood and can provide pleasurable effects. Due to its nicotine, the cigarette is also the most addictive product sold legally. The large majority of those addicted to nicotine or tobacco are smokers, and mostly they smoke cigarettes.

Nicotine is highly and rapidly addictive, and tobacco smoke is much more addictive than current nicotine medicinal products. Tobacco smoking is highly addictive partly because smokers are also addicted to their smoking behaviors and rituals, reinforced by the current culture of smoking and possibly, to a minor extent, reinforced by other addiction-promoting substances in tobacco. Nicotine in tobacco has a chemical or nicotine effect, and behavioral effects (hand/mouth movements). Smokers are bio-behaviorally addicted.

ADDICTION IN ADOLESCENCE

Only a few exposures to nicotine are required to produce neuroplastic changes in adolescent rats, and in adolescent humans, only a few cigarettes are required to produce symptoms of tobacco dependence.

In the largest study of adolescent addiction to smoking published so far, 7,482 adolescents interviewed at 14 to 15 years of age, had rapidly become addicted to smoking, as judged by symptoms of loss of control over their smoking.¹⁰ Addiction is assessed by questions on symptoms of loss of autonomy over smoking (the Hooked on Nicotine Checklist or HONC¹¹), validated against brain scans. We found that:

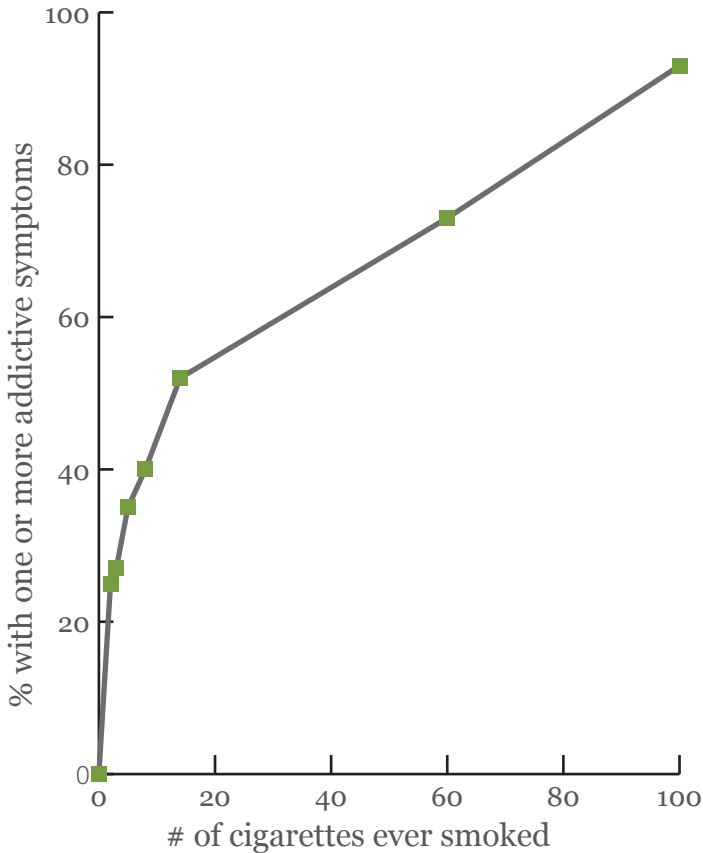
- One quarter lose some control over their smoking after smoking only one to two cigarettes.
- Forty percent lose some control after smoking one to nine cigarettes ever.
- At 10-19 cigarettes ever smoked, half reported some loss of control over their smoking.
- Of those 14- to 15-year-olds who had ever smoked 100 cigarettes or more, half had high scores for loss of autonomy (7 to 10 out of 10 on the HONC scale).¹⁰

Adolescent addiction cannot be dismissed as trivial, something they grow out of. It is intense, and in the majority who become lifelong smokers, it will shorten the lifespan of two-thirds of them,¹² and markedly affect their lifetime health status.”

- Most of these 7,482 students had not smoked 100 cigarettes or more in their lifetime, but of those who had, 93 percent had diminished autonomy over their smoking,¹⁰ as measured by the Hooked on Nicotine Checklist (HONC).¹¹

In lay language, soon after smoking the first cigarettes, the adolescent brain is rapidly hardwired to become addicted to smoking.

CHART 1. PERCENTAGE WITH ONE OR MORE ADDICTIVE SYMPTOMS AT AGE 14-15 YEARS, BY NUMBER OF CIGARETTES EVER SMOKED.¹⁰



Note: The numbers of cigarettes ever smoked is based on answer options for answer of:
1, 2, 3 to 3-4, 5-9, 10-19, 20-99, or 100 or more.

THE LATENCY PERIOD

The length of time that the last cigarette keeps the urge to smoke at bay may be days or weeks in beginning smokers, then gradually shortens to hours and even minutes. It, rather than plasma nicotine concentration, is a main determinant of how many cigarettes are smoked each day.

Activity of the brain's nicotine receptors sets the time for the next cigarette, not nicotine levels in the blood.

After the last cigarette of the day, and during the night, the liver continues to halve plasma nicotine concentration every two hours. Smokers with short latencies may feel the need to smoke immediately upon arising in the morning. However, many beginning smokers report long latencies, experiencing withdrawal symptoms only after several days have passed. The idea that smokers are smoking to maintain a minimum or trough nicotine concentration is an illusion created when the latency to withdrawal approximates the two-hour half-life of nicotine. The latency to withdrawal is a chief determinant of the time to first cigarette in the morning and the number of cigarettes smoked per day.¹³

Fifty percent of smokers, when asked how long they can last without a cigarette, will likely say two hours or less. (The average time, however, is likely to be much higher due to the much longer latencies of less experienced smokers.) Since cravings for a cigarette are unpleasant enough, smokers take care not to leave it too long, and tend to smoke another cigarette to head off feeling unmet need for the next cigarette.

Once the latency period is exceeded, circuits in the brain gradually escalate the urge to smoke.

THE URGE TO SMOKE

Strong urges to smoke (cravings) occur and recur, wax and wane, throughout the 24 hours.

Smokers experience a mini-version of “cold turkey” or withdrawal every morning and to a much lesser extent during the day. Every night, smokers stub out their cigarettes; most smokers abstain all night, and on awaking, their latency is exceeded (except for those who started to smoke more recently), and so their craving becomes intense. At this point, they may need a cigarette just to feel normal. Many rate the first cigarette of the day to be the most satisfying, and many smoke it within five minutes of waking. For the most addicted smokers the need is far more urgent than food or coffee. Time to first cigarette in the morning is one way to measure their degree of addiction.

Cravings decrease after a cigarette and increase before the next one. In smoke-free workplaces cravings increase towards lunchtime and then towards the afternoon break, and again before they leave work. Smoke-free buildings mean some smokers leave with a cigarette already on their lip and light up immediately after.

First comes the *wanting* (which is often interpreted as not being addicted; they smoke because they want to). Then comes the strong urge to smoke (*craving*). Then *needing* a cigarette to feel normal again. The sequence is the same every time, once the latency period is exceeded.¹⁴

After every cigarette, it is as if the brain has a built-in timer that starts quietly ticking until the next cigarette is desired. When this next cigarette is overdue, it is as if this clock starts ticking more loudly. Smokers describe this feeling as a thought that pops into their head that it's time for another cigarette. From initial latencies of four weeks, the latency period progressively shortens over the first few months or years of smoking. Eventually, when the latency is reduced to 24 hours or less, smokers are forced to acknowledge they want, crave (strongly desire), or need to smoke every day. They may try to quit and finally realize they are addicted.

Progressive shrinking of the latency period helps explain the difficulties smokers face.

For example, at less than seven hours, sleeping becomes difficult; at latency of less than one hour, students find lectures difficult to sit through. Latency can explain how smoking gradually changes a smoker's way of life. Eventually, latency stabilizes at a certain value for each individual. After quitting smoking, latency will lengthen again but may not return to its original value. The addiction may never entirely disappear—just one cigarette or cigar may cause relapse to smoking for many years.

As a result of various brain scans, several short questionnaires such as the Hooked on Nicotine Checklist (HONC)¹¹ are available for clinicians and researchers to use, fully validated against smokers' brain function at different brain sites known to be involved in addiction to tobacco, such as the anterior cingulate cortex on the inner side of the cerebral hemisphere.

ADDICTION IN ADULTS—THE ADDICTION CONTINUUM

The ultimate test of addiction is the degree of difficulty smokers experience when they try to quit.

Comparing drugs of addiction. On comparable criteria of addiction, a large national survey in the United States showed that cigarettes were far more difficult to quit than alcohol, cannabis, or cocaine.¹⁵

Comparing tobacco and nicotine products. Studies of smokers who took part in clinical trials of medicines to help them quit smoking were reviewed for overall success in helping people to quit. Generally, not much attention is paid to the smokers who took a dummy or placebo medicine to act as a control contrasted to those taking the test medicine; these people received no help from any active drug, and their success and failure reflects the addictive power of the addictive product they were trying to quit.

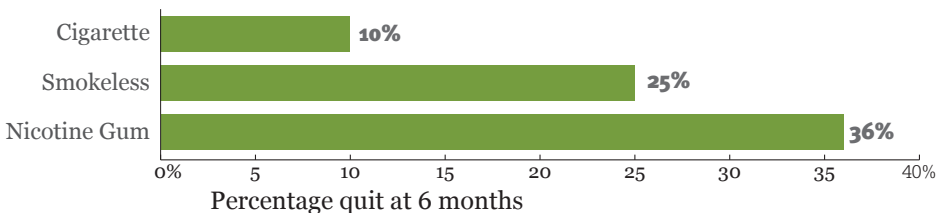
At six months, cigarette smokers who had received placebo had a 10 percent success rate in quitting. Relapse was very common. By contrast, 25 percent of smokeless tobacco users succeeded in stopping. Even better, those trying to give up nicotine gum had a 36 percent long-term cessation rate using the placebo dummy. The product they were trying to stop using, not the drug used, was the influential factor in the success rate of these control subjects—by definition, they received no active drug. Variation among smokers trying to quit using the same product were surprisingly small.¹⁶

Cigarettes are the most addictive tobacco product, and the most difficult to quit.

CIGARETTES: SOME “MUST HAVE,” SOME OPTIONAL

In seeking smoking pleasure, the smoker inhales nicotine and also toxicants with every puff—100 to 200 puffs per day. The pleasure is immediate, and the cycle is repeated. Not all cigarettes are pleasurable, but some are enjoyed more, typically the first cigarette of the day. Other cigarettes are optional extras, so if the price increases, the optional cigarettes are the first to be sacrificed.¹⁷ When the price threatens enjoyment of their must-have quota, the smokers must either pay more or quit.

CHART 2. THE ADDICTION CONTINUUM OF TOBACCO AND NICOTINE PRODUCTS. THE SUCCESS OF VOLUNTEERS TAKING PLACEBO MEDICATIONS AT 6 SIX MONTHS, IN QUITTING CIGARETTES, SMOKELESS TOBACCO AND NICOTINE GUM.¹⁶



MEASURING NICOTINE YIELD, CONTENT, DELIVERY AND ABSORPTION

NICOTINE YIELDS MEASURED BY SMOKE MACHINES

Today, commercial “yield” ratings remain misleading and deceptive; yields are no longer printed on cigarette packets in most countries; the filters remain ventilated; light and mild descriptors are out; and instead color-coded packets and new brand names identify the “light” cigarettes.

- In 1964, the first U.S. Surgeon General’s report warned that cigarette smoking causes lung cancer.
- In 1967, the U.S. Federal Trade Commission started publishing tar and nicotine ratings for cigarette brands. Many smokers, reluctant to quit, clung to a belief that a “low yield” cigarette would be a less harmful cigarette and trusted the ratings.
- From 1975 to 1990 manufacturers: 1) increasingly ventilated cigarette filters to entrain fresh air, giving an airy feel to the smoke, allaying health concerns; 2) re-engineered cigarettes to be more “elastic,” delivering more smoke and nicotine with less effort (more bang for the suck), having the effect of lowering the FTC ratings; and 3) advertised the resultant low tar ratings, thus increasing their sales. Smokers and public health authorities in many countries were deceived. A generation of smokers switched to low tar instead of quitting, as many might have done if they had known the truth.

It took from 1983 to 2005 for university nicotine laboratories to prove beyond doubt that machine yields of nicotine were misleading.

- In 1983, Benowitz in San Francisco showed that low nicotine ratings on cigarettes were not associated with lower nicotine concentrations in smokers’ blood.¹⁸
- In 2000, Djordjevic from the American Health Foundation in New York showed FTC ratings underestimated the nicotine and carcinogens in smoke by half and overestimated the proportional benefits of low yield cigarettes.¹⁹
- In 2004, a study of nearly a million U.S. smokers found no difference in lung cancer mortality in either men or women for tar ratings between low tar (8-14

mg) and very low tar (7 mg or less). Risk was only increased for tar yields above 21 mg of tar.²⁰

- In 2005, Hecht in Minnesota showed that smokers of regular, light, and ultra-light brands excreted very similar amounts of lung carcinogen breakdown products in their urine in the 24 hours after smoking. If light and ultra-light brands could not show evidence of reduced carcinogens absorbed in the first 24 hours, it was unlikely that they would reduce lung cancer risk 20 years later.²¹

In most countries today, the filters are still ventilated, yields are no longer printed on cigarette packets, and the yield ratings remain misleading and deceptive. Descriptors such as “light” are banned in many countries, but color-coded packets ensure retailers and smokers can still identify the “light” cigarettes, and smokers still ask for low tar (that is low nicotine). Smokers’ death rates have not diminished since the advent of “low yield” cigarettes.

NICOTINE CONTENT

Mean nicotine content of U.S. cigarettes is 10 mg²² and the minimum content required to maintain addiction can be set at 2 mg.²³ For commercial cigarettes, testing of the nicotine content of the un-burnt cigarette is the best guide to its addictiveness. Bench-top-tested nicotine content is significantly correlated with how much nicotine is absorbed from smoking it.²⁴ By contrast, traditional machine testing of commercial cigarettes is weakly correlated—if at all—with the amount of nicotine that is absorbed.¹⁸

NICOTINE DELIVERY

How much nicotine is delivered to the smoker’s mouth (mouth level exposure) can be estimated directly by analysis of cigarette filters in spent butts. This is possible since the smoke-machine yield of nicotine in the smoke and that remaining in the filter are related by the filter efficiency, which is specific for each brand. The method agrees well with values for nicotine derivatives measured in 24-hour urine, though for public health regulatory purposes, nicotine content is simpler, much less expensive, and adequate.

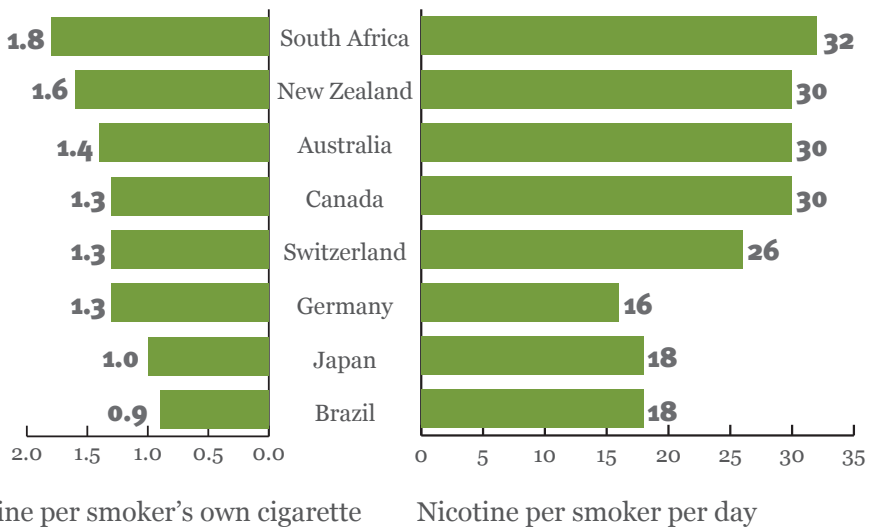
Nicotine delivery is the amount the smoker receives in the mouth. Smokers obtain 1 mg to 2 mg of nicotine per cigarette, based on analysis of smoked cigarette filters. The amount delivered varied with type of tobacco smoked, and up to twofold by country. For very low nicotine yield cigarettes, delivery was seven times the yield. Smokers of low yield cigarettes obtained two-thirds the amount delivered by higher yield brands; yield was a weak indicator of actual delivery.²⁵

Scientists at British American Tobacco (UK) analyzed 80,000 filters from spent butts from 5,703 smokers of their own brand of cigarette, including 106 brands

sold in eight countries. Each brand was analyzed for filter efficiency over a wide range of machine yields. Deliveries of nicotine into the mouth by cigarette and per smoker per day varied two-fold by country (*Chart 3*). Male smokers obtained nine percent more nicotine per day, partly due to different brands smoked.²⁵

In general, the study revealed that smokers were obtaining far more nicotine than ever disclosed on the cigarettes packet by smoke machine ratings. Smokers of flue-cured tobacco obtained a mean 31 mg of nicotine per day, while smokers of American blend obtained less, a mean 20 mg of nicotine per day. Low yield cigarettes delivered a mean 1.0 mg of nicotine per cigarette and 19 mg of nicotine per day, much more nicotine than smoke machine yield values indicated. Smokers of brands yielding over 6 mg of tar obtained 1.5 mg nicotine in the mouth per cigarette, a mean 29 mg nicotine per day.²⁴

CHART 3. NICOTINE MOUTH DELIVERY, LEADING BRANDS, EIGHT COUNTRIES, 2005²⁴



NICOTINE ABSORPTION

With dilution, nicotine evaporates off the particles in the smoke aerosol to circulate as gas molecules, which then are passively absorbed in the mouth and respiratory passages. The veins draining the bronchi are cross linked to the pulmonary veins, enabling rapid and effective absorption of nicotine (and presumably of toxicants), even from shallow puffing.

From the mouth

- Nearly half (46 percent) the nicotine in mouth smoke is retained in the mouth if the smoke is held within the mouth for just two seconds without inhaling. Thus within two seconds, nicotine evaporates from the smoke particles, and now in gas form rapidly attaches to the mucosa and is absorbed passively.²⁶
- The quantity absorbed from the mouth is insufficient to raise plasma nicotine concentrations.²⁶
- Cigarette blends with added diammonium phosphate (DAP) increased the proportion of nicotine retained in the mouth to nearly two thirds (64 percent) but did not increase nicotine levels in venous blood.²⁶ DAP could possibly affect smokers' perceptions of the strength of the smoke.

Shallow inhalation

- Shallow respiration (75 ml of air inhaled along with the mouth smoke) results in 80 to 90 percent retention of the nicotine in the mouth, throat, and bronchi due to evaporation and deposition of nicotine particles.²⁶
- Although 75 ml of air is insufficient to reach the alveoli, plasma nicotine increases to 10-15 ng/ml (70 percent of the level attained by deep inhalation) and no less rapidly than with deep inhalation.²⁶ This may be explained as follows:
- Nicotine evaporates from the smoke particles and is absorbed in gas form on to the mucosa of the throat and bronchi.
- Two thirds of the bronchial capillary blood is thought to drain via communicating veins into the pulmonary veins—the broncho-pulmonary circulation.²⁷
- Only one third of the bronchial capillary blood is pumped through the lungs first before reaching the systemic arterial circulation to the brain.

Deep inhalation—the rapid alveolar-arterial route

- Virtually all of the nicotine inhaled into the lungs is retained and absorbed, due to smoke reaching the alveoli from whence the pulmonary veins carry the

nicotine directly to the heart, for pumping immediately to the systemic circulation and to the brain via the carotid arteries.

- Increasing the alkalinity of the smoke by adding urea or diammonium phosphate during tobacco manufacture does not significantly increase plasma nicotine levels.
- Estimating five percent loss from mouth-spill of smoke before inhalation, and 98 to 99 percent efficiency of absorption for nicotine if the smoke is inhaled with 500 ml of air,²⁸ the average smoker would absorb 94 percent of estimated nicotine mouth level exposures in *Chart 3*, that is around 15-30 mg of nicotine per day.
- Deep inhalation means some nicotine reaches the brain within seconds while much is absorbed more slowly via the throat and bronchial veins and some rapidly via the alveoli and pulmonary veins. The result: plasma nicotine is increased to 15-20 ng per ml within five minutes.²⁶

HEALTH RISKS: NICOTINE VS. TOBACCO SMOKE

- In medicinal doses nicotine is very safe if used as intended.
- Long-term human studies of nicotine use show no increase in hospitalization, mortality, or cancer.
- Cigarette smoke causes cancer. Nicotine does not cause cancer.

THE SAFETY OF NICOTINE IN MEDICATIONS

The health sector routinely uses nicotine as a medicine to assist smokers in quitting. Serious adverse reactions to nicotine products are rare. Millions of smokers have used nicotine medications since nicotine gum was first sold over 25 years ago.

- Medicinal nicotine (nicotine replacement therapy, NRT) is quite safe if used as intended.
- Rats who inhaled nicotine for 20 hours a day five days a week for two years, giving a plasma concentration twice that in heavy smokers, suffered no increase in mortality, atherosclerosis, or tumours.²⁹

- Published data show that long-term NRT use is safe. The Lung Health Study of over 3,000 smokers and ex-smokers included a smoking cessation component in which participants used nicotine gum, and the fate of these people was followed for five years. This provided useful data on safety and long-term NRT use.³⁰

No increase in hospitalization or mortality was found in non-smokers regularly using nicotine gum.³⁰

NICOTINE AND BRAIN FUNCTION

Researchers at the National Institute of Drug Abuse conclude that repeated nicotine, as from a cigarette or a nicotine product, improves brain function (for an hour or two) to a small or moderate degree, improving fine movements, alertness, and short-term and working memory. This effect is not just due to correcting nicotine deprivation but holds true for non-deprived smokers, ex-smokers, and non-smokers.³¹

Some ex-smokers who complain they miss the positive stimulation smoking once gave them, or who have felt out of sorts ever since giving up smoking, could be at increased risk of returning to smoking, and might wish to discuss with their doctor whether taking nicotine would possibly relieve such symptoms.

With Parkinson disease, current cigarette smoking more than halves the risk of future Parkinson disease, while coffee drinking reduces the risk by one third, and nicotine in the smoke may be the active protective agent.³² Nicotine fed to rats protects the nigrostriatum, a part of the brain particularly affected in Parkinson disease, and particular subtypes of nicotine receptors in this part of the brain may be involved. Drugs including nicotine that act on these nicotine receptors are under investigation.³³

No one, however, is recommending smoking cigarettes to improve brain function since smoking triples the risk of stroke,¹² and smoking over 20 cigarettes a day in middle age was followed by an increased rate of cognitive decline.³⁴

THE DEADLY CIGARETTE

The risk from tobacco increases some twentyfold the moment it is lit and inhaled, compared to the lesser risk of consuming oral tobacco snuff.³⁵ Smoking tobacco is a killer—over five million globally this year and rising, with one billion cigarette deaths expected in this century unless the number of people smoking decreases.³⁶ In fact, the cigarette is the most deadly product sold for human consumption, killing two out of three long-time users prematurely.¹²

The cigarette's deadly nature is due to its smoke, while its addictiveness is due mainly to its nicotine.

SHORTENED LIFESPAN

As a group, smokers lose more than ten years of life compared with never-smokers. This is true for men and women.^{12,37}

- In the 1980s available evidence supported an estimate of one in four smokers dying prematurely. By 1994, the evidence indicated one in two smokers died early. Now, in 2013, the evidence is that two in three deaths of smokers are due to their smoking.^{12,37}
- By contrast, smokers who quit before the age of 40 years avoid 90 percent of this excess risk of dying early.¹²
- Cigarette smoke increases the risks of over 20 fatal diseases in the course of prematurely ending the life of two thirds of persistent smokers, and the effects may be delayed by 20 to 60 years or more.¹²
- At any age quitting prolongs a smoker's average lifespan, reducing mortality risk to that of a never-smoker within 10 to 15 years. Quitting smoking altogether remains the best advice, and nicotine medications are available to ease symptoms of the transition, but in one study using NRT for six weeks even with professional counseling did not reduce the risk of relapse.³⁸

COMBUSTION

Once the cigarette is lit, the high temperatures (800 degrees Centigrade) from the burning tobacco break up its complex plant molecules into smaller reactive molecules. These leading cancer-causing chemicals in smoke are mostly volatile small molecules, found in the gases and vapor, while the smoke solids or particulate contains the semi-volatiles. A few toxicants such as hydrogen cyanide are measurable in both fractions.

Inhaling half a liter of smoke every hour eventually causes many serious and fatal diseases. Only now, after studying the fate of men and women smokers for over half a century, have epidemiologists shown that most smokers die early because of their smoking,¹² compared with the longer lifespan of never-smokers of the same age.

VAPORIZATION

By contrast, vaporization of droplets of liquid nicotine occurs at lesser temperatures—well below 350 degrees Centigrade. Combustion destroys complex plant molecules in the tobacco and breaks them down to smaller molecules. Most of the very harmful toxicants and cancer causing substances found in tobacco smoke, and especially the volatile gases, are small molecules with a molecular weight under 100.³⁹

TOBACCO SMOKE AS AN AEROSOL

Tobacco smoke is a mixture of hot gases and organic vapors in which chemicals condense to form an aerosol of suspended droplets. Smoke testing uses a filter pad to trap the particles (particulate matter, or solids) accompanying the semi-volatile nicotine. The filter paper is stained by the trapped solids. Particulate minus the nicotine and water is called “tar,” whereas ash is the residue of burnt tobacco at the burning end.

“TAR”

The cancer potency of a cigarette’s smoke comes partly from the “tar” (the particulate or solids minus water and nicotine, or Total Aerosol Residue) that makes smoke visible.⁴⁰ This particulate contains the semi-volatiles and the potent nitrosamines NNK and NNN only found in tobacco, the heavy metals and some of the hydrogen cyanide, and the cancer-causing agent benzo[a]pyrene found in cigarette smoke. Nitrosamine carcinogens NNN and NNK vary by how tobacco is cured, and so tar can vary in cancer risk estimates from one brand to another. That said, there is still no consensus among researchers in the field that the level of a given constituent in a particular product is a reliable general indicator of the hazard posed by the use of the product.

GASES AND VAPORS

The harm from smoke is comes from both its invisible gases and vapor, and its solids (“tar”).

Constituents in the gas phase account for most of the estimated cancer and non-cancer risk in cigarette smoke.⁴⁰ The invisible gases and vapors make up over 95 percent of the mass of cigarette smoke,⁴¹ and the highest cancer risk index—for the gas 1,3 butadiene—is twice that of the next highest, acrylonitrile. These with the aldehydes, benzene, and small molecule organic volatiles, accounted for 70 percent of the estimated cancer risk.⁴⁰ The products of tobacco combustion in the smoke are found in virtually the same proportions across brands with respect to rank order. For example, among the harmful gases, carbon monoxide followed by acetaldehyde is always in the greatest quantity. Tobacco smoke has its own toxicant profile, compared with other types of smoke.

THE CONTINUUM OF RISK VARIES BY THE NICOTINE OR TOBACCO PRODUCT USED

In *Chart 4* (page 29) the risk of early death reduced from top to bottom from the blue bars for smokers above, to the green bars for chewers, snuff users, vapers, with never-smokers in smokeless homes with the least risk occupying the lowest green bar.

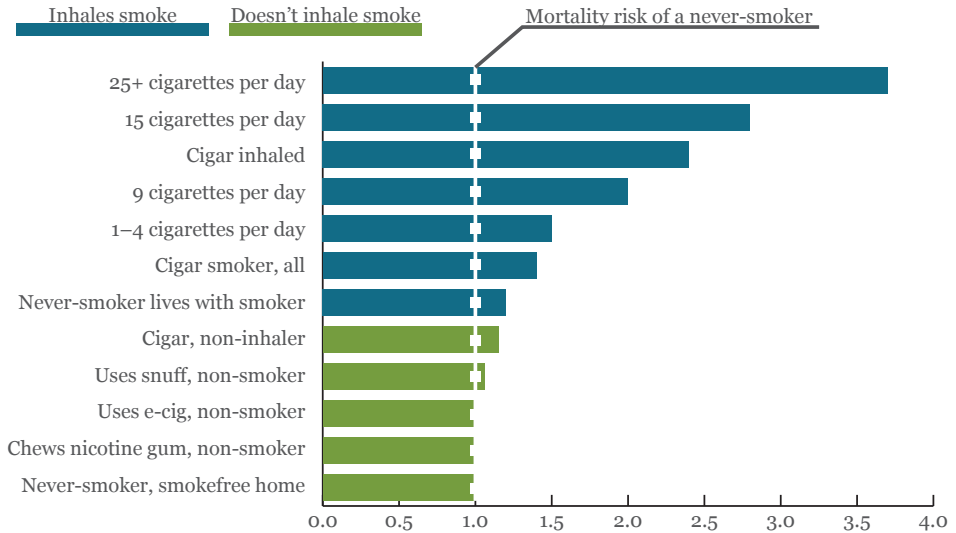
- Heavy cigarette smoking (25 cigarettes or more per day) nearly quadruples the risk of early death.
- Moderate smoking (15 cigarettes per day) triples the risk of early death.
- Very light smoking increases the risk of dying early by half.
- Cigarette smokers mostly inhale, incurring greater risks compared with cigars and pipe smokers (who generally do not inhale).
- Living with a smoker increases the risk 20 percent, presumably due to inhalation of secondhand smoke.
- Swedish moist snuff (snus) raises total death risk by 6 percent over that of a never-smoker.
- Never smokers who live in a home where no one smokes have the least risk.
- Those combining cigarettes with other products will have an intermediate risk.
- Electronic cigarette users' risk is expected to reside among the green bars in the lower part of *Chart 4*, as no smoke is inhaled.
- Inhaling tobacco smoke in any manner is more dangerous than using any other kind of tobacco or using nicotine in any form.
- Using nicotine products does not increase mortality risk above that of never-smokers.

THE PRECISE ROLE OF NICOTINE IN THE DEADLINESS OF THE CIGARETTE

When nicotine was used in the agricultural sector as an insecticide it was extremely poisonous and rapidly so. In the health sector, nicotine is used as a treatment for people trying to stop smoking and has few side effects. But its main role is as the addictive substance in tobacco and cigarettes, keeping people smoking for many decades, long enough for the gases and solids in smoke to eventually kill them.

The nicotine in its smoke is the prerequisite for its deadliness, by priming the brain for lifelong smoking many times a day. In the United States and the United Kingdom where smoking mortality has been tracked for over 50 years, the death rate for those who continue to smoke is three times as high as for those who never smoked.^{12,37}

CHART 4. THE CONTINUUM OF MORTALITY RISK. RELATIVE RISK OF MORTALITY FROM LIFETIME USE OF VARIOUS TOBACCO AND NICOTINE PRODUCTS, COMPARED TO THE RISK FOR A NEVER SMOKER.



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3. Cigar smoking risks: *Cigars, health effects and trends.* Monograph 9, National Cancer Institute USA, 1998, based on follow-up of one million US subjects for 12 years, including 22,000 cigar smokers, in Cancer Prevention Study I, 1959-72.

4. Non-smoker, lives with smoker: Secondhand smoke risk: Hill S, Blakely T, Kawachi I, Woodward A. *BMJ* 2004;328:988-89. Based on the fate of never smokers whether living with

a smoker or not in 1996 NZ census. Excess risk from living with a smoker, after adjusting for age, sex, ethnicity, marital status, and socioeconomic position, was 20 percent.

5. Uses snuff, non-smoker: Levy DT et al. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 2035-42. Estimated excess risk as 90 percent less than excess due to cigarettes. Re-estimated at 94 percent less: no increased risk of heart attacks.

6. Uses e-cigarette: Extra mortality risk due to electronic cigarettes is estimated at near zero, as for nicotine gum in (6) below, on the basis that nicotine is the active ingredient, neither nicotine nor its main carrier is propylene glycol cause cancer, and worldwide no deaths attributed as at March 2013 to electronic cigarettes in the medical literature since sales began in 2007. One non-attributed death was reported by BBC in 2012.

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TOBACCO HARM REDUCTION

NICOTINE REPLACEMENT THERAPY

Medicinal nicotine products (nicotine replacement therapy or NRT) such as nicotine patches, gum, lozenges and inhalers, reduce cravings for the next cigarette, and do not cause cancer, heart disease or lung disease.

Nicotine was licensed to treat smokers' symptoms such as the strong cravings due to abstinence experienced by smokers when they tried to quit smoking.

Clinical trials showed that smokers using NRT were more likely to quit successfully and on this basis NRT is now standard treatment for individual smokers attempting to quit.

However, outside of clinical trials NRT produced no marked reduction of smoking at population level. Public health people expected these results to translate into millions more smokers quitting, but in Europe in 2012 three times as many tried to quit without any aids as had tried using NRT. Quitting unaided remains the most popular method for successful quitting in almost every country. Taxation and media campaigns have been far more effective in reducing smoking.

Nicotine is FDA-approved for sale in nicotine dermal patches, nicotine gum, lozenges and inhalers. Pharmaceutical-grade nicotine, isolated from tobacco, is used to make these nicotine replacement therapy (NRT) medications. Nicotine in the past two decades has been the drug most widely used in developed countries to reduce the unpleasant effects of stopping smoking, and also to increase quitting success. Nicotine medications have enabled health workers to offer something tangible besides advice and cognitive therapy to smokers wanting to quit. In low-income countries such as China nicotine as a medicine or remedy remains generally far more expensive than smoking, and for most is simply unaffordable. One large study of nicotine taken by non-smoking pregnant women suggested a three percent increase in the incidence of minor musculo-skeletal malformations.⁴² But in view of the risks of relapse back to smoking or continuing to smoke, NRT use may be justified in pregnancy.

Nicotine gum was developed by the Swedish company Pharmacia and approved by the Food and Drug Administration (FDA) for sale in the United States in 1984. The nicotine patch was introduced in 1992, and both products became available over the counter from 1996. Nicotine in a nicotine patch delivers 21 mg of the drug over 16 to 24 hours—about 1.3 mg per hour—the total dose is similar to smoking, but plasma nicotine levels are slow to rise and cannot be increased to counter the urge for a cigarette. For this situation, nicotine gum can be used as needed in addition to the nicotine patch.

In scores of randomized controlled trials of smokers wanting to quit, nicotine medications increased quitting rates by 50-70 percent over the rates obtained with zero-nicotine placebos.⁴³ Population-wide, however, the effects were very modest.

- Taxation and media campaigns have been far more effective than NRT in reducing smoking.
- Quitting unaided remains the most popular method in almost every country.

NRTs were licensed as medicines to relieve symptoms, and as a medicine they are immaculately packaged, often expensively priced and limited to a few flavors. The packaging is designed to minimize appeal and risk of addiction and not become a substitute for smoking cigarettes. High costs involved in obtaining drug approval have favored the continued sale of products patented in past decades, without further innovation. Most do not succeed with NRT on the first attempt and so smokers recycle through NRT and back to smoking many times before most succeed by quitting unaided.

For smokers desperate to quit, NRT provided relief from cravings. Before 1996 in California, nicotine medications increased long-term quitting slightly—a 10 percent increase in sales of nicotine medications decreased cigarette sales by 0.04 percent, a 65-fold smaller effect than the response to a 10 percent real increase in cigarette price. Nicotine medication sales in dollars were only 1 percent of cigarette sales.⁴⁴

By 1999, nicotine medications had increased their sales greatly but were still not effective in increasing long-term successful cessation. Studies of over-the-counter NRT resulted in an absolute quit rate at six months of seven percent—a 93 percent relapse rate.⁴⁵ NRT by prescription gave similar results. Analysis of smokers in community settings shows they took their medication for only two weeks average, and only one in five received behavioral counseling.⁴⁶ Nicotine as a medication required additional support from health providers to be effective.

Nicotine medications were simply not popular enough or powerful enough to noticeably affect population-wide cigarette consumption.⁴⁴

By 2003, in the United States nearly two thirds of smokers attempting to quit did so unaided (cold turkey) with one third using nicotine medications, often supplemented by other methods.⁴⁷ In 2012, a survey of 4470 smokers across the

27-member European Union who had tried to stop smoking in the previous 12 months showed that

- 66 percent had tried to stop unaided,
- 22 percent had used NRT,
- 7 percent had used health services, and
- 7 percent had used electronic cigarettes.

Stopping unaided was three times as popular as using NRT. The success rate of each method has not been reported.⁴⁸ On this basis even if some medications were more efficacious, the popularity of unaided quitting delivers more ex-smokers.

Nicotine medications ease many smokers through the quitting process, but for reducing smoking prevalence media campaigns and tax/price increases have had significantly more impact. In fact, variations in nicotine medication sales have had no discernable measurable population effect on monthly smoking prevalence.⁴⁹

In 2013 in four countries of the International Tobacco Control four-country Survey (Australia, Canada, UK, and USA), a marginal reduction in prevalence can be credited to medications such as NRT. Noted high rates of relapse to smoking and stalled quit rates are best explained as due to increasing unresponsiveness to quitting, rather than to be due to NRT. In such a situation, new and different strategies will be needed⁵⁰—which is likely to mean increased access of smokers to new harm reduction products.

Nicotine medications have been widely sold for over 25 years to relieve the cravings when smokers quit. For creating a smoke-free 21st century, medicinal nicotine as currently marketed, despite widespread availability and good safety profile, remains a weak substitute for cigarette smoking⁵¹ and has failed to prove itself as the game changer many were looking for.

NICOTINE HELPS PREVENT CANCER BUT DOES NOT CAUSE IT

If smokers switch from smoking tobacco cigarettes to nicotine products, cigarette-caused cancers will be prevented, because those gases in smoke known to cause cancer, such as 1,3 butadiene, are no longer inhaled.

Cigarette smoke causes most lung cancers. Nicotine itself does not cause cancer.

As noted above, exposure of rats to nicotine vapor for two years designed to mimic twice the nicotine blood levels of heavy smokers produced no increases in tumours.²⁹

Experiments in mice have shown that low levels of exposure to nicotine, equivalent to those in humans who use nicotine medications (NRT), do not cause lung cancers.⁵²

The Lung Study in the USA followed thousands of ex-smokers for a total of 12.5 years. As these people had smoked for many years in the past, they were already prone to cancer. Yet, compared to those who quit smoking entirely, risk of cancer of the lung was increased only in those who continued to smoke, but not in those using nicotine gum.⁵³

NICOTINE DELIVERY FROM ELECTRONIC CIGARETTES

In 2012, some European brands delivered up to 50 micrograms of nicotine per puff, in the lower tobacco cigarette range, but most fell far short.⁵⁴ Some products are inconsistent in nicotine delivery across the same brand, the same variant, and by cartridge or label.

IN CARTRIDGE LIQUID

The nicotine content may range from zero through low, medium, and strong. The nicotine in the cartridge liquid in many brands was less than the label claimed. The usual strength was 18 mg or 1.8 percent of a 1 ml solution.⁵⁴

IN VAPOR

A study of 16 European brands has shown that nicotine content of the cartridge and vaporization efficiency can vary greatly by brand. On average 50 percent to 60 percent of the nicotine in the liquid was vaporized, and in many brands much less.⁵⁴ Brands tested delivered anything from 2.5 percent to 77 percent as much as the nicotine delivered by a regular cigarette.⁵⁴

DELIVERY OF NICOTINE

FDA scientists found that 33 puffs of 100 ml each from an electronic cigarette without pause delivered 1 mg of nicotine⁵⁵ (the same as one tobacco cigarette). Many experienced vapers achieve this sort of absorption.

NICOTINE IN ROOM AIR

One e-cigarette releases 3 millionths of a gram of nicotine per cubic meter of room air.⁵⁶ Modern laboratories can detect such traces.

ABSORPTION OF NICOTINE

E-cigarette vaping and smoking both result in similar levels of nicotine absorption as judged by serum levels of the nicotine-derivative cotinine. Fifteen smokers increased their cotinine levels by 61 ng/ml after actively smoking or

vaping. Similarly, passive smoking or vaping resulted in similar amounts of nicotine inhaled. Fifteen never-smokers increased their cotinine levels by 2.4 to 2.6 ng/ml after passive smoking or passive vaping.⁵⁷ (Toxic gases behave quite differently; for example, e-cigarettes do not emit carbon monoxide, whereas smoke does.)

Nicotine from electronic cigarettes used in planes or crowded situations is clearly not a health risk to those in close proximity. Measuring trace toxicants is difficult and no-one has so far succeeded in measuring toxicants in the blood of passive vapers. Airlines have understandably banned e-cigarette use, as security is their priority, and trains may ban them for passenger comfort, but restrictions on e-cigarette use indoors would be hard to justify on medical grounds, as e-cigarettes (no ash, no smoke, no second hand smoke) do not emit sidestream smoke. Propylene glycol, water vapor, and a trace of nicotine on the exhaled breath of e-cigarette users are not harmful for vapers or bystanders. Legislation could deter smokers from switching to less harmful vaping. In countries now enjoying smokefree laws and spaces, however, once the social norm is not to smoke, then by implication, the norm would be not to vape either.

We will take a more detailed look at e-cigarettes in Part 3 (and prior to that we will examine “smokeless tobacco” in Part 2).



CONCLUDING THOUGHTS ON PART 1

Cigarettes are deadly, and far safer alternative products are now available. The availability of lower-priced alternatives can be expected to greatly aid a switch away from cigarette smoking.

Quitting cold turkey is the commonest way to quit, but quitting by switching to using an electronic cigarette may be a more pleasant way to reach the same goal.

- Cigarette smoking should be much more highly taxed now that a safer and satisfying alternative product is now available. This is the tipping point principle.
- Electronic cigarettes should be made as accessible as cigarettes. Electronic cigarettes should be sold widely and lightly regulated to ensure product safety (whether by regulation as a medicine as in the UK, or under consumer law).
- Smokeless tobacco is of much lower risk than cigarettes, and health warnings and taxes should to reflect this.

Key messages

Smokers' need for nicotine is not disputed, but it is quite unnecessary for smokers to sacrifice their own lives to obtain their nicotine, when other products can provide nicotine and can even mimic the act of smoking.

Smokers smoke for the nicotine, primarily—but they die from the smoke. Specifically, the repeated inhalation and absorption of the toxic and carcinogenic volatile chemicals in the gaseous phase, and condensable substances in the solid phase—tar—eventually take the lives, prematurely, of about two-thirds of chronic smokers.

Nicotine is not a carcinogen; in fact, for the large majority of smokers, it is not toxic. But it is the nicotine that keeps them lighting up repeatedly over the course of days, weeks, months and years, and that causes them to fail repeatedly when they try to quit.

And many smokers, even many physicians, continue to falsely believe that nicotine is the main toxicant and cancer-causing agent in smoke. This fallacy needlessly complicates efforts to allow smokers to quit combustible tobacco and get nicotine in much less harmful forms.

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PART TWO



Smokeless Tobacco

Smokeless tobacco is arguably the only form of tobacco harm reduction about which we already possess substantial use data, thanks to its acceptance in Sweden. Let us therefore take a closer look.

SMOKELESS ORAL TOBACCO (MOSTLY SNUFF) CONTAINS AND SUPPLIES NICOTINE

In the United States, four percent of adults consume smokeless tobacco, mainly young men, compared with 19 percent of adults smoking cigarettes.

In Sweden, one gram of Swedish snuff (snus) held under the upper lip for over an hour delivers the same nicotine as a cigarette does in five minutes. Snus is very low in tobacco-specific nitrosamines (TSNAs) and in Sweden snus does not cause mouth cancer. No smoke is inhaled, and unlike a cigarette, snuff does not cause lung cancer, lung disease or heart attacks. Mortality risk is approximately 94 percent less than for cigarette smoking. Smokeless tobacco when used was twice as successful in helping U.S. smokers quit as any type of NRT medication. (*Chart 5*).

PREVALENCE OF USE

In the U.S., based on a tradition of chewing tobacco and oral snuff, four percent of adults in 2010 consumed one of these products, according to the National Health Interview surveys.¹ This compares with 19 percent of adults smoking cigarettes daily or less than daily in 2010. Snuff users have increased slightly over the decade, but chewing tobacco use has not.

Smokeless is mainly popular with men, young men (18-24 years of age) and the less educated. In 2009, prevalence of smokeless tobacco use among men in some states, such as West Virginia (17.1 percent) and Wyoming (16.9 percent), nearly reached the national level of smoking prevalence among all adults (20.8 percent) in that year. A minority of smokers reported also using smokeless tobacco.²

DOSAGE

British American Tobacco scientists report that nicotine in moist snuff is absorbed through the mouth mucosa achieving maximum blood levels in an hour, which is how long Swedish snus users held the pouch in the mouth. One gram of moist snuff results in nicotine absorption similar to that from a cigarette.³

MORTALITY RISK REDUCTION

Smokeless tobacco is safer, as no toxic volatiles are inhaled. Smokeless tobacco (Swedish snus) reduces the overall excess risk from smoking by no less than 94 percent, perhaps more. Ninety percent is the conservative default estimate.⁴ One estimate is for the risk to be 98 percent less than for smoking.⁵ Based on causes of death in the United States for 2007, we estimate the excess mortality due to smoking would be 94 percent reduced if snus reduced the smoking-attributable risk excess for lung cancer and respiratory disease 100 percent, for cardiovascular risk 90 percent, for mouth and throat cancer 90 percent and for pancreatic cancer 50 percent, respectively.⁶

HEART DISEASE

Current snus use was not associated with increased risk of acute myocardial infarction when eight studies were pooled (totaling 2.3 million years of follow-up), and although case fatality was higher in snus users, this may be confounded by lifestyle or socioeconomic factors.⁷

CANCERS

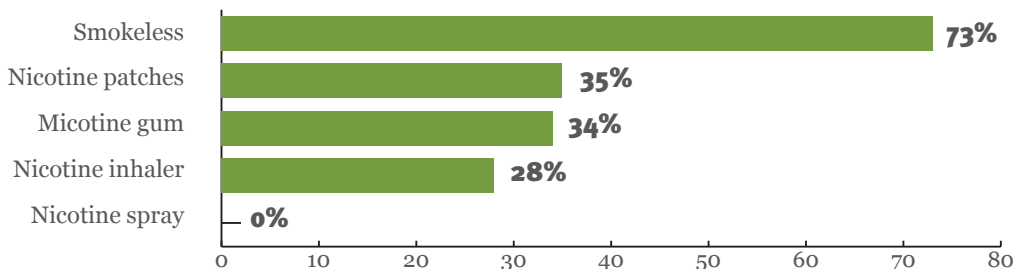
In Sweden, the new case cancer rate, counting lung, pancreatic, and mouth cancers in male smokers is some six times higher than for snus users.⁸ Smokeless tobacco risk for mouth cancer has been reduced to near zero levels, probably by attention to safe manufacturing practices designed to lower cancer-causing nitrosamines to levels stated in the industry's own Gothiatek voluntary standard in Sweden. Moist snuff carries less risk than for dry snuff, now little used.⁹ Smokeless tobacco has been intimately involved in reducing male smoking rates in Sweden and to a lesser extent in Norway; a process of Quit and Switch to snus.

SMOKELESS TOBACCO AS AN AID TO QUITTING

Smokeless tobacco can help smokers stop smoking and thus save lives, and not just in Sweden. In a 2008 report of US smokers using various products as quitting aids, 73 percent who used snus succeeded in quitting, twice the success rate for those using the nicotine patch, gum or inhaler (*Chart 5*). Less studied but also potentially beneficial is the e-cigarette, which we will examine in detail in Part 3.



CHART 5. METHODS FOR SUCCESSFULLY QUITTING SMOKING USED BY MEN IN THE 2000 NATIONAL HEALTH INTERVIEW SURVEY, USA



Rodu, Phillips¹⁰

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PART THREE



Electronic Cigarettes

Electronic cigarettes are nicotine inhalers designed to deliver nicotine without the toxicants in cigarette smoke. Manufacturing quality varies but is improving, and sales are rapidly increasing.

Mostly smokers want a safer way to smoke, or want e-cigarettes to help them quit.

Electronic cigarette vapor appears chemically incapable of causing cancer as cigarette smoke has done. E-cigarette vapor contains toxicants concentrations averaging less than one percent of the concentrations in tobacco cigarette smoke.

E-cigarettes consist of a mouthpiece, a cartridge containing nicotine in a liquid, atomizer and battery. They were invented in China, where most are still made—hand-made, under variable quality control—and exported all over the world. The liquid is equally important—nicotine in propylene glycol or glycerol, water, and flavors. Brands vary as to the proportions of PG and VG (vegetable glycerol) in the liquid. Many e-cigarette users tend to take one or two puffs quite frequently, as the e-cigarette generates no flame and can be kept in the pocket.

Electronic cigarettes make it possible to enjoy inhaled nicotine without health concerns, while enjoying flavors such as tobacco, menthol, coffee, or chocolate as desired, without even lighting up.

Most smokers will see electronic cigarettes simply as vastly safer cigarettes.

THE ELECTRONIC CIGARETTE MARKET

GROWTH OF ELECTRONIC CIGARETTE SALES

Electronic cigarettes were first sold outside of China in 2007, and global sales of electronic cigarettes reached an estimated two billion dollars in 2012, and are expected to eclipse the 2.4 billion dollar global sales of nicotine medications in 2013. The three leading electronic cigarette markets by value are the United States, Russia, and Germany.¹

In the United Kingdom electronic cigarette users are expected to number one million by 2013. In 27 European Union (EU) countries in 2012, one percent of adults used e-cigarettes regularly—about four percent of smokers,¹ a remarkable achievement within only five years. In the EU consumers spent an estimated €400-€500 million on electronic cigarettes in 2011.

In the United States annual sales have risen to between 250 and 500 million dollars² where six percent of smokers were using e-cigarettes in early 2012.³

First time nicotine vapers buy cigarette look-alike (analogue-equivalent) e-cigarettes with tobacco extract flavor, and in some countries these are sold under cigarette-similar brand names. This is sufficient to wean themselves off tobacco. Created to miniaturize the e-cigarette, small batteries require a personal battery-charging case to last through the day.

The next generation of e-cigarettes, designed for connoisseurs, are bulkier, look nothing like cigarettes, can cost \$100 to \$200, are often of stainless steel, and provide larger batteries. Running costs are minimized by using nicotine liquid from child-proofed 5 ml dropper bottles.

COMPETITORS, RIVALS, REGULATORS, AND HEALTH AGENCIES

The fledgling nicotine electronic cigarette industry as of 2013, faced opposition from many quarters:

- The cigarette industry's profits are now under threat as smokers switch from combustible tobacco to flameless electronic cigarettes. However, five major tobacco companies or their subsidiaries are now selling or plan to sell electronic cigarettes, including Altria.⁴
- The pharmaceutical industry's medicinal nicotine sales and profits will diminish as smokers use electronic cigarettes as another kind of NRT.
- Medical practitioners, quit-line advisors, and smoking cessation workers are required by law to use licensed medicines from the pharmaceutical industry. They will learn about e-cigarettes informally from patients.
- Major anti-smoking groups in the United States currently oppose the sale of e-cigarettes. They are funded by the pharmaceutical industry. They deeply distrust the tobacco industry.
- Governments looking to recoup future excise losses on declining tobacco sales could be tempted to tax e-cigarettes. This would make electronic cigarettes less price-competitive and would have the unwanted side effect of protecting tobacco sales.
- The World Health Organization's Conference of the Parties to the WHO FCTC (Framework Convention on Tobacco Control) as of 2012 encouraged Parties (nations) to ban e-cigarettes, even including non-nicotine e-cigarettes, because they could "undermine the de-normalization of tobacco use upheld by WHO FCTC" and because their use "could be considered a direct or indirect promotion of tobacco use" and "could hamper implementation of Article 8 (protection from

exposure to tobacco smoke).”⁵ As of 2013, almost no country has legislation in place to allow sale of nicotine products as a medicine or a tobacco product. Many countries have responded with reflexive bans rather than creative, flexible regulation. Bans of e-cigarettes, based on harms that are minor compared to smoking, are likely to perversely protect tobacco sales from competition.

- Regulators have problems with electronic cigarettes, as they are neither combustible tobacco products nor medicines. E-cigarettes neither pay tax like tobacco products nor conform to medicinal and pharmaceutical standards. UK law requires medicine regulators to promote public health, but in other countries medicine safety policy may not consider the reduction of tobacco sales as part of their brief.
- Smokers too, have had problems with the first generation electronic cigarettes; they want legal access to purchase better quality, longer lasting batteries, nicotine to match the label, efficient vaporization of nicotine, adequate puff generation, and at a lower price.



PUFFING PATTERNS

Vapers tend to take larger and stronger puffs, and pause less between puffs compared with smoking tobacco cigarettes, to maximize nicotine from each puff of e-cigarette vapor.⁹⁸

Two separate small studies measured puffs with the Cress Micro device (*Chart 6*) show that whereas the average smoke flow or puff velocity of tobacco cigarette smokers was 34 ml per second^{6a} a faster flow of 52 ml per second was required to activate the atomizer of common brands of electronic cigarettes in FDA’s laboratories.

Goniewicz and other Polish scientists studied ten experienced vapers and recorded an average 70 ml per puff, greater than the 59 ml per puff noted for 22 tobacco cigarette smokers. Duration of puff noted with tobacco cigarettes^{6a} and e-cigarettes⁹⁹ was 1.8 seconds, but some brands have atomizers that take longer to heat.

METHODS FOR BENCH-TOP COMPARISONS OF E-CIGARETTE BRANDS

E-cigarettes glow only when puffed and require more draw: tobacco cigarettes smolder between puffs. The puffing regimes used to machine test tobacco cigarettes had to be adjusted for the shorter interval between electronic cigarette puffs.

Until puffing parameters standards for testing electronic cigarettes are standardized internationally, Goniewicz’s observations in *Table 3* are the de-facto standard except that 3 seconds should be allowed as duration of puff, to prevent under-reporting of toxicants from some brands.

CHART 6. CLINICALLY OBSERVED PUFF PATTERNS OF TOBACCO AND ELECTRONIC CIGARETTES

Using Cress Micro flow meters.	Factory-made tobacco cigarettes ^{6a} n=22	Nicotine electronic cigarettes ⁷ n=10
Puffs per cigarette or session	14	15
Volume per puff, ml	59	70
Duration of puff, seconds	1.8	1.8
Inter-puff interval, seconds	19	10
Smoke flow, ml per second	34	52 to activate ⁶

CLINICAL HARM AND SAFETY REPORTS

We know of no deaths due to use of these devices despite open sale of these devices since 2007 in the United States and the United Kingdom and in other countries, even though sales have greatly increased. Two cases of exploding lithium batteries have been reported globally.

ADVERSE EVENTS REPORTED TO FDA

From 2008 to 2012, eight out of 47 reports of adverse events on electronic cigarettes received by the FDA were serious. These included pneumonia, heart failure, and burns to the face from a battery explosion, and possibly an infant choking fatally on a cartridge refill, chest pain and rapid heart beat.⁸

MAJOR RESPIRATORY EFFECTS

Most vapers are former smokers, many with chronic lung disease. One death in a UK user due to interstitial pneumonia was reported in 2010, but the coroner returned an open verdict as to whether this was due to e-cigarettes. One case of lipoid pneumonia was reported, suspected to be due to glycerin-based fluids in the electronic cigarette vapor.⁹

MINOR RESPIRATORY EFFECTS

Mild mouth and throat irritation and weak dry cough may occur after inhalation, but as in the Sicilian clinical trials described below, respiratory symptoms waned over time. These randomized controlled trials followed participants for six and 12 months, and found no serious adverse events attributable to electronic cigarettes.

LUNG FUNCTION

In 2012 a detailed study of thirty Greek smokers vaping an electronic cigarette for five minutes found an increase of airway resistance and a decrease in the fraction of expired nitric oxide (FENO) that was greater than for sham use. The effects were about half that measured by the same authors in smokers exposed to second-hand cigarette smoke in a car.^{10 11}

The reduction in FENO was not confirmed by a further study in Greece in 2013 using a robust repeated measures design. Lung function was measured by spirometry before and after 30 minutes of active smoking or vaping, and after one hour of passive smoking or passive vaping. Lung function was not significantly decreased in 15 smokers using e-cigarettes, or in 15 never-smokers inhaling the vapor of e-cigarettes or inhaling smoke; lung function was, however, significantly decreased seven percent by active tobacco smoking.¹²

MINOR SYMPTOMS

One study examined 543 posts (mostly symptoms) from 481 users of an electronic cigarette forum in 2011. The comments were 80 percent negative, and 20 percent positive—as might be expected, as these sections are designed to deal with complaints. The authors found that the generally negative short-term effects reported by e-cigarette users “appear relatively minor compared to more serious long-term conditions (e.g., cancer and stroke) that occur in conventional smokers.”¹³

GENERAL HEALTH EFFECT

Most vapers responding to an online survey recruiting in 2013 mainly from the same e-cigarette forum, as above, believed their health has been improved by switching. Of over 1,044 vapers (38 percent vaping for more than one year), and despite eight percent still smoking tobacco cigarettes, and 15 percent an occasional cigarette: 73 percent reported improved ability to exercise, and 66 percent improved in their ability to do strenuous jobs after switching to e-cigarettes. Smoker's cough afflicted 67 percent but on e-cigarettes, only afflicted three percent.¹⁴

CARDIOVASCULAR EFFECTS

- Arterial stiffness is not increased from vaping, as it is from smoking a cigarette.¹⁵
- Red and white blood cells are not increased in the peripheral blood in the first hour after an e-cigarette either actively or passively inhaled, as they were after smoking a cigarette or passively inhaling cigarette smoke.¹⁶
- Nicotine administered by electronic cigarette can relieve chronic idiopathic neutrophilia (high white cell count, often due to smoking) by inducing successful smoking cessation.¹⁷

EFFECTS ON THE BRAIN

Nicotine in e-cigarettes reduces the urge to smoke and improves mood, working memory,¹⁸ and prospective memory (remembering to execute a delayed intention at a given time),¹⁹ consistent with previous research on nicotine.^{31 in Part One}



TOXICOLOGICAL PROFILE OF E-CIGARETTE LIQUID AND VAPOR

ACUTE POISONING RISK FROM E-CIGARETTE LIQUID

As little as 10 mg of nicotine is a fatal dose for a child and 40 to 60 mg for an adult. Small 10 ml bottles of liquid for electronic cigarettes routinely contain 180 mg and skin absorption can be rapid. Child-proof caps are becoming routine, but regulators should insist on fully child-proof designs.

Even 10 mg of nicotine—the amount found in 0.5 ml to 2 ml of bottled liquid nicotine used for filling electronic cigarettes—is enough to kill a child. Since the taste is bitter swallowing is less likely, and skin absorption is the main risk for adults and children. In 2012 bottled nicotine was sold on the Internet in concentrated solutions containing up

to 8 g of nicotine, and 10 ml bottles of nicotine of 18 mg per ml were widely sold. These bottles are sold with child-proof caps, but the device itself needs to be fully child-proof.

In the future, regulators are likely to only approve product designs that eliminate any possibility of child access to nicotine liquid.

TOXICOLOGICAL PROFILE OF E-CIGARETTE LIQUID

The chemistry of the liquid can change as it is vaporized, so tests of the liquid are not adequate for a full safety report.

The most complete review of toxicology of e-cigarette liquid and vapour to date is that of Burstyn. Over 9000 observations of highly variable quality were extracted from peer reviewed and gray literature. He estimates actual exposures of vapers to possible contaminants in vapour, using the formula mg per puff x 150 puffs per day. For the few carcinogens detectable and measurable in the vapour, such as acetaldehyde and formaldehyde, exposure was estimated in micrograms per day, and for tobacco specific nitrosamines as a few nanograms per day.²⁰

E-CIGARETTE VAPOR

E-cigarette fluid or “juice” is liquid over a wide range of temperatures, but when small quantities are vaporized by the e-cigarettes atomizer (heater), the puff of aerosol or mist comprises particles containing water and propylene glycol.

a) The particle size of the e-cigarette aerosol. Measurements of particle size and number are comparable with tobacco smoke. An aerosol is a suspension of liquid or solid particles in a gas. The undiluted particles of average mass in the e-cigarette aerosol have particle diameters in the range 0.25-0.45 microns, and particle numbers are in the 10^9 per cm^3 range.²¹ With dilution in room air the particles evaporate and the mist becomes an invisible vapor.

A further study argues that similar particle size should result in similar deposition patterns, and based on the International Commission of Radiological Protection respiratory tract model, estimate seven to eighteen percent alveolar particles depositing in the alveoli, with 73-80 percent lost by exhalation. These particles would be propylene glycol.²²

b) Intense testing of the Ruyan e-cigarette aerosol. Although the Ruyan classic brand is sold in few countries today, it remains the brand most intensively tested. In 2008-9 Health New Zealand arranged for 62 toxicants to be tested, courtesy of British American Tobacco UK, with laboratory assistance from Labstat International ULC, Canada.

- Of 62 toxicants, 51 were non-detectable. The rest were found in negligible amount.

- No carbon monoxide (CO) was found in the vapor (nor increased in exhaled breath).
- 1,3 butadiene, the leading carcinogen in cigarette smoke was not detected.
- Hydrogen cyanide, the leading cardiovascular toxicant was not detected.
- Tobacco-specific nitrosamines (NNN, NNK) were detected, but at low levels—equivalent to the daily dose from using the nicotine patch and gum and over 300 times less than in Marlboro full flavor cigarette smoke.²³

Toxicants in electronic cigarette vapor vary from negligible to non-detectable.

c) Volatiles and nitrosamines in 12 European e-cigarette brands. In 2013, Goniewicz and other Polish researchers reported tests on 12 brands of e-cigarette for presence of three aldehydes, toluene, xylene, two tobacco specific nitrosamines, and three heavy metals. Goniewicz tested 10.5 liters of vapor per toxicant.

The vapors contained toxicants at levels nine to 450 times lower than in cigarette smoke, and concentrations were in many cases comparable with trace amounts found in a medicinal inhalator. There was 30- to 40-fold variation in the range of toxicant yields across the 12 brands.²⁴

Electronic cigarette brands high in nicotine yield were not the highest in toxicant yields, thus judicious choice of brands could select the most effective and safest brand.

Regulation can encourage manufacturers to manufacture only the most satisfying and the safest e-cigarettes, by excluding all others from the market.

Further study of six brands showed that acetaldehyde was present in the vapor of all six, but at a thousand-fold less than in cigarette smoke. Those e-cigarette brands with glycerol in the liquid all generated acrolein and formaldehyde in the vapor. Brands containing propylene glycol but not glycerol did not generate acrolein or formaldehyde,²⁵ but this requires confirmation. Increasing the voltage, taking longer puffs, or dripping liquid onto a hot heating coil (atomizer) greatly increased formaldehyde in the vapor.²⁶ New style e-cigarettes with higher or adjustable voltage may produce more toxicants, and test results on these second generation e-cigarettes are not yet available.

d) Analysis of the vapor for metals and nanoparticles.

Carcinogens: Cadmium, nickel and hexavalent chromium are grade 1 human carcinogens that are found in e-cigarettes. Cadmium levels are low. Nickel and chromium are widely used as the alloy for the heating element. Heavy metal

concentrations in e-cigarette vapor are low (*Chart 7*), 25-84 times lower than in Marlboro full flavor cigarette smoke,²⁷ and one to three times greater than in medicinal Nicorette inhalator vapor.

Tin: Talbot’s group purchased and examined a popular unnamed U.S. brand minutely and found tin particles in the aerosol, attributed to the solder.²⁸ High use (880 puffs daily) exposure per day was equivalent to only four percent of the upper limit for occupational eight hours continuous exposure.²⁹

Nickel: Values for this brand and the other e-cigarette brands were mostly lower and not, as claimed, higher²⁸ than for cigarette smoke (*Chart 7*).

Nanoparticles: This group at the University of California used electron microscopy to study the heating coil (atomizer) of this unnamed leading U.S. e-cigarette brand in detail, and found the aerosol contained tin and other metals as particles (*Chart 7*), some present as very small nanoparticles (< 100 nM diameter, which can penetrate cell membranes). The e-cigarette studied produced 4 billion nanoparticles per litre of vapor as opposed to 36 billion per litre of cigarette smoke.²⁸ Some nanoparticles contained heavy metals.

CHART 7. HEAVY METALS IN SMOKE AND NICOTINE VAPORS, MEAN CONCENTRATIONS, AND ESTIMATED DAILY EXPOSURE.

	Cigarette ^{27, 30, 31}	Nicorette nicotine medicinal Inhalator ²⁴	European (12 e-cigarette brands) ²⁴	Unnamed US electronic cigarette brand ²⁸	Daily dose estimate At 880 e-puffs/day	Permitted Daily Exposure ³⁰
	Ng / litre	Ng/litre	Ng/litre	Ng/litre	Ng/day	Ng/day
Cd	160	3	8	NR	400	1500
Chr	0.2-500	NR	NR	14	620	25000
Ni	0, 136, 151	18	18	10	440	1500
Pb	105	4	9	34	1500	5000
Sn	NR	NR	NR	39	1720	NR

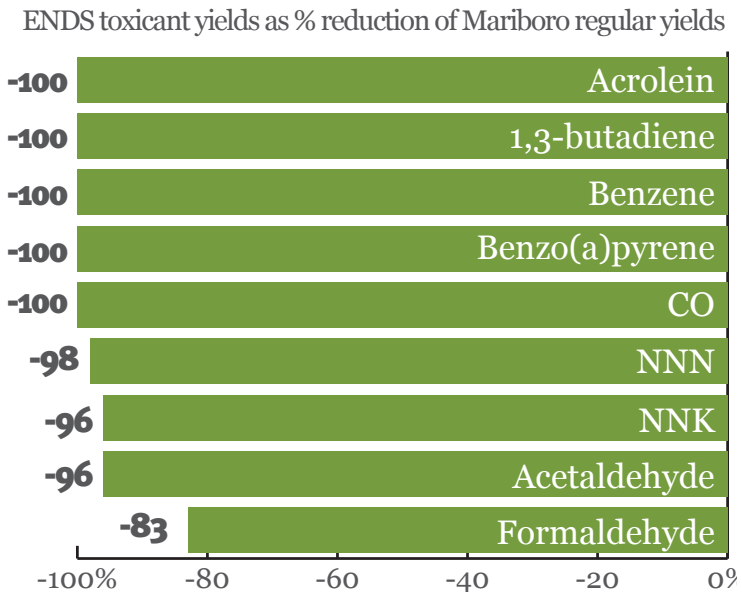
NR = not reported. E-cigarette puffs calculated at 50 ml / puff. Sn = tin. Nanogram (ng) =one billionth of a gram.

Metallic concentrations and metallic fine particulate in e-cigarette aerosols even at high e-cigarette use were below the permitted maximum for daily exposure, and in the much the same range as for the medicinal inhalator. The great variation in metal values across brands, suggests that regulation of e-cigarettes would minimize vapers' toxicant exposures.

Relative harm reduction: Switching from inhaling cigarettes smoke to inhaling e-cigarette vapor would greatly reduce toxicant exposure. The World Health Organization prioritized nine leading chemicals for “modest reduction” in cigarette smoke over the coming years.³² By contrast, *Chart 8* shows the percentage by which these cigarette gas emissions would be reduced by use of the Ruyan classic e-cigarette brand, based on that brand's emissions. The electronic cigarette on this basis is capable of achieving complete or near complete reductions in all nine toxicants, rather than the modest reductions proposed for cigarette smoke.

CHART 8. EXPECTED REDUCTION IN LEADING TOXICANTS INHALED IF THE SMOKER SWITCHED FROM SMOKING TO VAPING

(for nine toxicants prioritised by World Health Organization's TobReg Committee for reduction,³² nicotine adjusted, comparing the Ruyan Classic e-cigarette with Marlboro king size regular^{23, 27})



RISKS OF LONG-TERM USE OF NICOTINE E-CIGARETTES

- Assessment of mortality from smoking required 50 years of follow-up. With e-cigarettes, although e-cigarette vapor contains negligible cigarette-type toxicants, regulation is needed to minimize human exposure.
- The question arises as to whether e-cigarettes if used by millions over their lifetimes, could cause serious diseases not yet known. But diseases have causes, and the priority is to eliminate or reduce vapers' exposure to toxicants already known.
- **Cigarette type toxicant gases.** The aldehydes acrolein, acetaldehyde and formaldehyde though in negligible quantity in e-cigarette vapor, remain the main concern. If improved atomizers cannot greatly reduce these toxicants, charcoal filters could do so.
- **Risk of cancer from heavy metals.** The known carcinogenic heavy metals, cadmium, nickel, and chromium, are measurable in aerosol (*Chart 7*) and comparisons are needed to compare the levels of metals in smokers' and vapers' body fluids, for the levels of carcinogen-derivatives known as DNA adducts.
- **The active ingredient,** pharmaceutical grade nicotine, has been used safely for over 25 years in nicotine gum.
- **The main carrier, propylene glycol (PG),** has very low toxicity. Maximum advisable dose of PG as a solvent for intravenous drugs has been estimated to be 69 g per 24 hours,³³ which is equivalent to the PG in 100 e-cigarette cartridges, whereas vapers mostly report consumption in the range of 0.5 to 5 cartridges per day. PG is metabolized to lactate and up to half is excreted unchanged in the urine. PG has been used in asthma inhalers, in foods and in skin products. Glycerol also has a good safety profile and is an excipient for at least one therapeutic inhalational product. Neither PG nor glycerol cause cancer.
- **What can be done?** Regulation is needed to ensure 1) high purity for liquid ingredients, 2) minimal inhalation of toxicants, and 3) child-proofing to prevent acute poisoning.



NICOTINE DELIVERY FROM ELECTRONIC CIGARETTES

In 2012, some European brands delivered up to 50 micrograms of nicotine per puff, in the lower tobacco cigarette range, but most fall far short.²⁴ Some products are inconsistent in nicotine delivery across the same brand, the same variant, and by cartridge or label.

In cartridge liquid. The nicotine content may range from zero through low, medium, and strong. The nicotine in the cartridge liquid in many brands was less than the label claimed.²⁴ The usual strength was 18 mg or 1.8 percent of a 1 ml solution.

In vapor. E-cigarettes generate similar absorption of nicotine as tobacco smoke whether smoked actively or passively, as measured by serum levels of the nicotine-derivative cotinine (61ng/ml for active smoking, 2.4 to 2.6 ng/ml for passive smoking, using 15 smokers for active smoking/vaping, and 15 never-smokers for passive smoking/vaping).¹²

A study of 16 European brands has shown that nicotine content of the cartridge and vaporization efficiency can vary greatly by brand. On average 50 percent to 60 percent of the nicotine in the liquid was vaporized, and in many brands much less.²⁴ In bench-top testing a day's nicotine delivery from electronic cigarettes was compared with a tobacco cigarette brand. From 300 puffs of one e-cigarette cartridge (20 episodes of 15 puffs) nicotine delivery varied from 0.5 mg to 15.4 mg, as against 20 mg from 20 Marlboro king size full flavor tobacco cigarettes. The brands tested thus delivered anything from 2.5 percent to 77 percent as much as the nicotine delivered by a regular cigarette.²⁴

Delivery and absorption of nicotine. Our first clinical testing of the Ruyan e-cigarette brand in 2008-9 showed low plasma absorption of nicotine. Later brands tested on experienced users have shown absorption equaling tobacco cigarettes. FDA scientists found that 33 puffs of 100 ml each from an electronic cigarette without pause delivered 1 mg of nicotine⁶ (the same as one tobacco cigarette).

When e-cigarette users take more frequent puffs the atomizer stays hot and adequate nicotine is absorbed.

In an Internet survey in 2011, 31 subjects (16 percent) returned a vial of saliva for analysis. These experienced vapers used five nicotine refills per day, taking a median 200 puffs a day. Median cotinine level in these vials was 322 ng per ml, which equates to 26 mg of nicotine per 24 hours,³⁴ comparable to cigarette smoking.

PASSIVE INHALATION OF ELECTRONIC CIGARETTE VAPOR IN ROOM AIR

Electronic cigarettes used in planes or crowded situations are clearly not a health risk. Their use may annoy those close by. Once people enjoy the benefits of smokefree laws, the social norm is not to smoke, and by implication, not to vape either. Airlines have banned them, as security is their priority. E-cigarettes do not produce sidestream smoke.

One e-cigarette releases 3 millionths of a gram of nicotine per cubic meter of room air. Modern laboratories can detect such traces, but it is of no clinical consequence.

Similarly, the chemistry of fine particulates in e-cigarette vapor argues against it being harmful to health.

A cigarette smolders to produce sidestream smoke when not puffed, but the heating element of an e-cigarette is only red-hot during each puff, and there is no sidestream smoke emitted. Any “second-hand” vapor is exhaled propylene glycol with a trace of nicotine.

In a recent study, smokers accustomed to using both types smoked first an e-cigarette then a tobacco cigarette. Nicotine in the room air was three micrograms/ m^3 after the electronic cigarette, and 32 mcg/ m^3 after the tobacco cigarette. For carbon monoxide and volatile gases, the exposure levels for e-cigarettes were in the same range as for not smoking.³⁵

Nicotine in room air after vaping an e-cigarette is only 3 millionths of a gram per cubic meter of air.

In another study, the toxicants profile of four brands of electronic cigarette when applied to a poorly ventilated room of 40 m^3 showed no significant risk against hazard and cancer risk indices, whereas the tobacco cigarette tested showed significant risk.³⁶

Fine particulates. Visible electronic cigarette vapor, a white aerosol or mist, is exhaled from the mouth, disperses and vanishes within seconds to become an invisible vapor. The visible e-cigarette vapor consists of droplets (< 1 micrometer diameter) of propylene glycol (PG) and glycerol in the same proportions as in the liquid.³⁷ Fine particulate is able to penetrate into the gas-exchange areas of the lung, but size is not the only factor, and the nature of the particulate is important. No harm has been reported due from water-soluble e-cigarette vapor or from the

salt and water content of sea spray aerosol³⁸ —or from PG mist, which was found safe for inhalation by hospitalized children over months, and was highly effective in killing respiratory bacteria and the influenza virus.³⁹ Unlike diesel, coal, and cigarette smoke, electronic cigarette vapor on the evidence is not harmful to health because of its particulates.

FREQUENTLY ASKED QUESTIONS

The answers to these questions will influence policy makers as to whether they want:

- ***e-cigarettes banned or not*** (prohibition of e-cigarettes only leads to a grey market, and to a policy at odds with the government's tobacco control aims)
- ***e-cigarettes sold as recreational products and medicines***, or only as medicines.

QUESTION 1. DO E-CIGARETTES LEAD CHILDREN INTO SMOKING?

On the evidence to date, the answer is no. The percentage risk of never smokers using e-cigarettes (whether adolescents or adults) is near zero (*Chart 9*). However, *Chart 9* surveys were carried out before mass media advertising of e-cigarettes had become established in early 2013.

In 2013, never smokers in Britain reported 0 percent (<0.5 percent) use of e-cigarettes, whether adolescents or adults. Thus the chances of a never smoker becoming addicted to e-cigarettes at any age in 2013 were virtually zero. This is confirmed by surveys in other countries. (*Chart 9*)

Any e-cigarette use was confined mainly to smokers. Two percent of adolescent smokers used e-cigarettes more frequently than weekly and half used them less frequently.

QUESTION 2. DOES VAPING ACT AS A GATEWAY TO CIGARETTES?

- Less than 0.5 percent of never smokers have taken up e-cigarettes and fewer still have moved from e-cigarettes to smoking. (*Chart 12*)
- Although an important theoretical possibility, the risks so far are close to zero.
- Adolescents face real and greater risks from continuing to start smoking tobacco.

CHART 9. PREVALENCE OF E-CIGARETTE USE IN NEVER SMOKERS

Year	Ages surveyed	Survey	Number surveyed	Prevalence % use in past month
2010	18 and over	US National Online survey	2,649	0.3
2010	18-49	US Legacy Longitudinal smoker cohort study, phone survey ⁴⁰	3,658	0.0
2010-11	15-24	Poland, national sample, school surveys ⁴¹	13,250	1.4
2013	Adults	Great Britain, national survey ⁴²	12,701	0
2013	11-18	Great Britain national survey ¹³⁵	1,428	0

- Fortunately never-smoking adolescents have shown no interest so far in vaping.
- Gateways allow two-way traffic; many smokers are increasingly using e-cigarettes to exit smoking.

What can be done?

Various policies can be employed to protect adolescent never smokers from e-cigarettes:

- Prevention of glamorized e-cigarette advertising would discourage never-smokers from trying e-cigarettes (even though a ban might discourage smokers from switching to e-cigarettes).
- Cigarette taxes could encourage smokers to switch to vaping, as could graphic health warnings on tobacco packaging.
- Prohibit retailers from selling e-cigarettes—as is the law for tobacco sales.
- Require manufacturers to warn consumers with package warnings that say, for example, “This product contains nicotine and is addictive. Nicotine is not known to cause cancer.”

QUESTION 3. DO ELECTRONIC CIGARETTES NORMALIZE OR DENORMALIZE SMOKING?

CHART 10. DIFFERENT VIEWPOINTS ON WHETHER E-CIGARETTES DENORMALIZE SMOKING

A health promotion view

Vaping mimics and role-models smoking, and should be discouraged.

A child

There is no cigarette smoke odor, no lighting up, no use of a cigarette lighter, and, as is especially likely to be remembered, no ash dropped.

A smoker

The e-cigarette is a cigarette look-alike, and he or she is likely to try it—and may like it, possibly leading to quitting by switching.

Family view

A successful switch to e-cigarettes will denormalize smoking for that smoker and for family, home, friends, and children.

Market view

By reducing cigarette sales in the U.S. in 2013, e-cigarettes are beginning to seriously denormalize the sale of cigarettes.⁴³

Research view

Now that research shows that e-cigarettes increase smoking cessation,⁴⁴ it proves also that e-cigarettes denormalize being a smoker.

QUESTION 4. IS VAPING LESS ADDICTIVE THAN SMOKING?

4.1 Addiction to e-cigarettes in never smokers: development of addiction may be no less rapid than with first cigarettes.

A person who has not previously inhaled nicotine and who starts using e-cigarettes might expect to become addicted as rapidly as adolescents smoking their first cigarettes (*Chart 3*). In fact as e-cigarettes are less harsh, it is possible that e-cigarette nicotine could be inhaled more easily and more rapidly, making for a more rapid onset of addiction.

As *Chart 10* shows, zero percent of never-smoking adolescents are using e-cigarettes but more may do so if e-cigarette companies continue to glamourize e-cigarettes in the mass media.

4.2 Electronic cigarettes decrease addiction to tobacco.

For ex- or current smokers, vaping is less addictive than smoking; e-cigarette use reduces cravings for, and consumption of, tobacco.

In 2009 a randomized controlled trial at the University of Auckland showed that a nicotine electronic cigarette reduced the urge to smoke for up to an hour, more than a zero-nicotine electronic cigarette, and more than a nicotine inhalator, but not nearly as much as a tobacco cigarette.⁴⁵

In 2013 an online survey of 1,027 e-cigarette users, 95 percent of those who were now ex-smokers reported craving for tobacco cigarettes had decreased since they switched. Cravings for tobacco decreased 70 percent in the 14 percent still smoking tobacco. In over half of those still smoking tobacco, tobacco consumption “decreased dramatically.”⁴⁶

Vapers who had quit smoking altogether by using e-cigarettes, however, had started to smoke at an earlier age, which may explain their higher addiction scores than vapers who also smoked.)⁴⁶

On interviewing vapers as to current and past experiences, a hundred experienced vapers gave their average time from waking to first vape as 38 minutes, as against 24 minutes average from waking to the first cigarette when they used to smoke.⁴⁷

4.3 Most e-cigarette users quit e-cigarettes without becoming permanent vapers.

Of those using e-cigarettes for quitting tobacco, only a minority become long term vapers. In its 2013 population survey in 2013, Action on Smoking and Health London found that while eight percent of ex-smokers had quit smoking using e-cigarettes, five percent used them temporarily, and only three percent still used e-cigarettes.⁴²

Product improvements and promotions could increase the proportion of vapers who take up vaping long term.

QUESTION 5. DO E-CIGARETTES RESULT IN DUAL USE?

Is dual use a problem? Dual use of cigarettes is harmful, as even a few cigarettes a day increase mortality risk (*Chart 4*), and so to obtain the full health benefit from using e-cigarettes, the switch needs to be complete. On the other hand, dual use may be the norm at the start of the switching period.

What can be done? Taxation on tobacco and graphic health warnings encourage people to fully quit smoking. Regulation of e-cigarette packaging and health warnings on e-cigarette packaging could warn vapers of the dangers of an incomplete switch.

What not to do. Restricting access to e-cigarettes would favor reversion to smoking.



CHART 11. PERCENTAGE OF E-CIGARETTE USERS WHO CURRENTLY SMOKE: DUAL USE

Year	Ages surveyed	Survey	Number surveyed	Prevalence: % smoking
2010	18 and over	US National Online survey ⁴⁰	2,649	4.1 (past 30 days)
2010	18-49	US Legacy Longitudinal smoker cohort study, phone survey ⁴⁰	3,658	6.1 (ever use)
2010	Adults	US Consumer Styles. Past month users of e-cigarettes ⁴⁸	115	6.3
2010-11	15-24	Poland, national sample, school surveys ⁴¹	13,250	15.3
2011	Adults	Experienced vapers, face to face interviews, some cigarette use in past 30 days ⁴⁷	104	22
2013	Adults	Online survey of vapers ¹⁴	1044	8.0
2013	Adults	Great Britain, national population-based survey ⁴²	12,701	11.0
2013	Adults	On-line survey of e-cigarette users. ¹⁸	1338	14

ELECTRONIC CIGARETTES FOR SMOKING CESSATION

Electronic cigarettes fit where cigarettes once did, with much less harm. Many may vape for life, just as many smoke for life.

E-CIGARETTES AS QUITTING AIDS IN BRITISH ADULTS IN 2013

Approximately 20 percent of British adults in 2011 smoked cigarettes.⁵⁰ *Chart 12* shows that 7 percent of adults (35 percent of smokers) still smoked after trying vaping, while approximately 1 percent (100,000) of adults (3 to 8 percent of smokers) had used vaping to successfully quit smoking.

For British smokers from 2012 to 2013, the percentage of smokers who had ever vaped increased from 22 percent to 42 percent and the number vaping and quit increased from one percent to three percent approximately of the smoking population. Thus for the extra 16 percent of smokers taking up vaping, an extra two percent quit and were still vaping, which would tend to lock in the decision to quit. A decline in national smoking prevalence in 2013 would be expected if the survey results are correct.

ELECTRONIC CIGARETTES AS QUITTING AIDS IN EUROPE

In 2012, a survey of 4470 smokers across the 27-member European Union who had tried to stop smoking in the previous 12 months showed that 66 percent had tried to stop unaided, 22 percent had used NRT, 7 percent had used health services, 7 percent had used electronic cigarettes.⁵⁰ Data was not available on the success rate for these recent quit attempts.

In Europe during 2011-12 electronic cigarettes as an aid for quitting attempts, became as popular as health services.

ELECTRONIC CIGARETTES AS QUITTING AIDS IN THE UNITED STATES

In a nationally representative survey in 2011 of 1,836 smokers and recent ex-smokers, 8 percent had used e-cigarettes in the past month, but there was no association of use with increased quitting of tobacco. However, unsuccessful quitters were more open to using e-cigarettes in future, and those intending to quit in future had a higher interest in e-cigarettes than those not planning to quit.⁵¹

Of 2,476 ever users of e-cigarettes using tobacco cessation quit lines in various states in 2011-12, 31 percent of callers had used e-cigarettes. Most callers were mailed NRT, but e-cigarettes were not FDA approved and not part of the treatment protocol. Of those using e-cigarettes for a month or more, 22 percent quit for the past 30 days; for never users of e-cigarettes, 31 percent quit, but due to confounding factors the authors did not draw firm conclusions about the effectiveness of e-cigarettes for quitting.⁵²

In a focus group, 11 e-cigarette users, asked open-ended questions about e-cigarettes, said e-cigarettes helped quit smoking by providing bio-behavioural feedback, social benefits, hobby elements, personal identity, and distinction between smoking cessation and nicotine cessation.⁵³

ELECTRONIC CIGARETTES IN PATIENTS WITH SCHIZOPHRENIA

Bupropion or varenicline may not be suitable to prescribe for mentally ill patients for smoking cessation, and some form of nicotine is required. In Sicily, e-cigarette use over 52 weeks decreased average cigarette consumption from 30 to 15 per day, without significant side effects and without increase in symptoms for 14 patients with

CHART 12. EVER USERS OF ELECTRONIC CIGARETTES, BRITISH ADULTS, 2013*⁴²

Smoking and vaping status	Percentage of smokers or of ex-smokers*	Estimated % of adult population*
Has not tried vaping	65 percent of smokers	13.0
Remained a smoker after trying vaping	24 percent of smokers	4.8
Smoker and vaper	11 percent of smokers	2.2
Ex-smoker, ex-vaper	5 percent of ex-smokers	1.2
Ex-smoker and vaper	3 percent of ex-smokers	0.7
Ever –vapers	45 percent of smokers	8.9
Current vapers		2.9
Exclusively vapers		0.7

*Based on the 91 percent of smokers who were aware of e-cigarettes

chronic schizophrenia patients who smoked not intending to quit. Two quit smoking and were still quit when surveyed.⁵⁴ This is a small non-randomized study without controls, and the first of its kind.

RANDOMIZED CONTROLLED TRIALS (RCTS)

Trials up to 2013 have been encouraging though not proof that electronic cigarettes help smokers quit. Additional, larger studies are presently planned, recruiting or underway.

Against the conventional wisdom, these or similar devices are reported to succeed with and without nicotine, despite low levels of plasma nicotine initially reported, and with and without a desire to quit, though the numbers are small. A problem for clinical trials is selecting a product that guarantees to deliver sufficient nicotine.

Randomized controlled trials are considered the gold standard.

1) In 2009, a cross-over RCT trial at the University of Auckland evaluated the electronic cigarette's ability to reduce the urge to smoke in overnight tobacco-deprived smokers and found that the nicotine electronic cigarette had a similar effect to a medicinal nicotine inhaler, despite low plasma nicotine levels attained. The zero nicotine e-cigarette also reduced the urge to smoke.⁴⁵

2) In 2011, a RCT with six months follow-up at the University of Catania, Sicily on 40 smokers who had failed to quit smoking in a hospital programme showed that the e-cigarette substantially halved cigarette consumption for the total cohort, and 22.5 percent quit smoking altogether, without causing significant side-effects.⁵⁵

3) A further RCT with 12 months follow-up of 300 smokers in Sicily who were *unwilling* to quit showed that 13 percent quit on high nicotine cartridges as against four percent who quit on zero nicotine at 12 months, and all groups reduced cigarette consumption.⁵⁶

4) The Auckland New Zealand trial, the first to compare e-cigarettes with nicotine patches, shows comparable success in helping smokers to quit and no serious reactions due to e-cigarettes.⁴⁴

Of 657 smokers randomly allocated to e-cigarettes or nicotine patch use for 13 weeks, and after three months further follow-up, 7.3 percent quit smoking using nicotine e-cigarettes, 5.8 percent using nicotine patches, and 4.1 percent using placebo e-cigarettes (The differences were not significant). More than half the nicotine e-cigarette users reduced cigarette consumption by half, significantly more than for patch users. Nine in ten users of e-cigarettes said they would recommend it to friends wishing to quit smoking.

Adverse reactions were no different for e-cigarettes and nicotine patch, and no major reactions were attributable to either product. Of smokers allocated to use e-cigarettes, 40 percent liked their cigarette-like qualities, sensory familiarity and perceived health benefits, taste, absence of cigarette odor, and ease of use.

The e-cigarette used in this trial provided only 20 micrograms of nicotine per standard puff vs. up to 50 micrograms from cigarette look-alike brands currently sold internationally. Moreover, users consumed an average one e-cigarette refill daily, around 20 percent of the nicotine from cigarette smoking.

STAGES OF SWITCHING TO QUIT

Some smokers wanting to quit smoking may buy electronic cigarettes as cessation aids and use them to Quit and Switch. Success is aided by making an executive decision to stop smoking.

Stage 1. Switching and stopping smoking. Cigarette consumption is reduced, e-cigarette consumption increases.

Stage 2. Fully smoke-free, and reducing nicotine. Free of the risks of smoking, the ex-smoker now decides at leisure what nicotine strength of e-cigarette is most satisfying, and continues for three to six months to ensure no relapse.

Stage 3. Nicotine and tobacco-free. Uses a zero nicotine e-cigarette, and not smoking any tobacco, the ex-smoker may now choose to continue with nicotine free e-cigarettes or to dispense with them. A nicotine-free substitute can assist quitting.⁵⁷

REGULATION OF ELECTRONIC CIGARETTES

Among countries where e-cigarettes are sold there is widespread agreement on the need for some regulation, and widespread disagreement as to the whether they should be sold for pleasure or medications or both, and whether the regulation should be light or heavy.

Countries with bans in place may eventually permit sales once they see e-cigarette sales reducing tobacco cigarette sales in Europe and the U.S.

Under the 2009 U.S. Family Smoking Prevention and Tobacco Control Act, nicotine, even when sold on its own is considered a tobacco product because it was made from tobacco. U.S. courts have held that nicotine electronic cigarettes come under that same Act, rather than under the Food, Drug, and Cosmetic Act⁵⁸; however, the Food and Drug Administration regulates all tobacco, nicotine, and nicotine replacement therapy (NRT) products and has also asserted its intention to regulate electronic cigarettes.

Important questions remain.

1) Whether nicotine electronic cigarettes should be banned from sale in the meantime - and how long the ban should continue: Canada, Australia and New Zealand have banned sales of nicotine electronic cigarettes but permit import for personal use. In Canada despite the sales ban in 2009, by 2013 at age 16-30 years 33 percent of smokers had tried electronic cigarettes; 14 percent of smokers had used them in the past 30 days, as had one percent of non-smokers.⁵⁹ In New Zealand, the legal sale of non-nicotine electronic cigarettes means wasteful purchases by desperate smokers, with no provable public health benefit because the active ingredient is banned. Prohibition as a practical policy for e-cigarettes is discussed extensively but found untenable by Etter, a political scientist and professor of public health (see Bibliography).

2) Whether e-cigarettes should be sold to deliver nicotine for recreation and pleasure, and sold as freely as cigarettes; or sold only as medicines.

3) Whether regulation can be light-touch so as to raise standards and not so onerous that improved products cannot reach the smoker:

- **General sale provisions** under consumer protection laws usually require the product to be reasonably safe, to be fit for purpose, and to be true to label. In Sweden the industry has adopted a voluntary standard for snus, the

Gothiateg standard. The standard has been raised over time. Such a standard could be useful for e-cigarettes. Some electronic cigarette brands could progress to regulation.

Tobacco firms already control 99 percent of the nicotine supply, and the firms could soon dominate the growing e-cigarette market. Unless constrained by the laws of the country concerned, tobacco firms could raise electronic cigarettes prices and their profit, decreasing the incentive for smokers to switch to safer products, and protecting firms' tobacco cigarette sales revenue from competition.

- **Medicinal regulatory standards** require medicines to be free of toxicants, and for the manufacturer to certify that the medicine is produced under license at a site operating under good manufacturing practices. With current designs and materials it may be difficult to completely eliminate all toxicants from e-cigarette vapor, but the door should be left open should any manufacturer be able to afford to take safety and manufacturing responsibility to a higher level.
- **Light-touch** regulation is likely to require some proof of drug efficacy, and the standard (pharmacokinetic) method is to measure plasma nicotine during and after use of the drug. This is costly, and few brands have been tested.

In Sweden, tobacco cigarettes, cans of snus, nicotine patches, and gum can all be sold across the counter in the same shop. Electronic cigarettes could be sold the same way.

MANUFACTURING STANDARDS

Several refills may be required daily but the content per refill is not standardized. One cartridge may produce 150 to 300 puffs or more of vapor, but there is no standard or regulation to enforce this, or to ensure adequate nicotine delivery.

Electronic cigarettes vary in quality, and the product is still evolving. A switch from selling cartridges to selling disposable cartomizers (cartridge-atomizers) has ensured atomizers no longer need replacement. Reducing e-cigarette length and weight to mimic a tobacco cigarette has resulted in smaller batteries with lower capacity, but which often do not last a full day's vaping. Vaporization efficiency of popular electronic cigarette brands, if improved to match the best now available, would further increase the readiness of smokers to switch.

THE TIPPING POINT: NICOTINE E-CIGARETTES VERSUS TOBACCO

Cigarette volumes sold in the United States are now decreasing more rapidly than before, partly due to electronic cigarette sales, which are credited with an additional one percentage point decrease below the usual trend over recent years. As sales of electronic cigarettes continue to increase, cigarette volumes sold are likely to decrease slightly more steeply. Four major tobacco companies will be selling electronic cigarettes by the end of 2013; they will soon dominate that market and ensure increased quality of product, wide distribution, and further increases in electronic cigarette sales.

What is not clear is the proportion of current smokers who eventually become vapers and how long will they vape before losing interest and becoming ex-vapers.

Will the new vapers simply use electronic cigarettes to quit smoking, or will they go on to enjoy vaping as a safe way to continue to enjoy inhaling nicotine?

In either case, there are public health benefits, because fewer cigarettes are smoked. Cigarette makers will aim to make e-cigarette nicotine refills attractive enough to generate repeat sales.

The recent move of five major tobacco manufacturers (Altria, British American Tobacco, Imperial Tobacco, Lorillard, and Reynolds American) into the electronic cigarette market means electronic cigarettes are here to stay, as these firms have the capacity to rapidly fund, develop, and market improved products that can overcome current regulatory barriers. These firms also have the networks to sell nicotine refills daily, possibly jostling for display space alongside cigarettes at the nearest corner shop.

The tipping point may have been reached in the United States in the first quarter of 2013, when increasing electronic cigarette sales accounted for an estimated one percent decrease (out of a six percent decline) in national industry-wide cigarette sales (equal to 600 million cigarettes not sold).⁶⁰

By showing they can reduce cigarette consumption, e-cigarettes will gain public support and public health credibility. E-cigarettes will still need much further research and regulations to guarantee safety of the product.

The achievement of the public health community has been to make cigarette smoking less popular and less desirable, so that cigarette sales have declined, so that the manufacturers are seeking alternatives to replace the revenues lost. As virtually any alternative is safer than cigarettes, their moves into less harmful

products such as electronic cigarettes and smokeless tobacco are difficult to criticize. Their motive is still profit, but the move would be good for public health. The public health community may regard it as galling and an affront to natural justice that its *bête noire*, the tobacco industry, whose products have killed 100 million people last century, will now be applauded for selling harm reduction electronic cigarettes.

Public health people are now well positioned to propose tougher than ever policies to reduce the continued sale of deadly cigarettes and encourage research and sale of less harmful substitutes. By advocating an approach based on “out with the bad, in with the good” they can expect increasing public support.



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Key messages for policy makers

The current confusion around nicotine and misinformation around the risks of smokeless would be greatly improved by wide publicity for statements such as these:

MORTALITY RISKS AND CANCER RISKS VARY GREATLY BY PRODUCT


- Cigarettes and smoking tobacco are the most deadly recreation products on shop shelves.
- Two thirds of persistent smokers die from their smoking, losing on average, over 10 years of lifespan.^{12, 37 in Part One}
- Nicotine has been widely used as a medicine since 1984 and is safe at the doses used in medicines.
- Nicotine products do not cause cancer or lung cancer, lung or heart disease.
- By contrast, tobacco smoking is the main cause of lung cancer, the leading cause of cancer deaths.

ADDICTION SCIENCE

- Virtually all tobacco smokers are addicted.
- Cigarette smoking is highly addictive, and more than nicotine by itself (the spectrum of addiction, *Chart 2*).
- Nicotine is the main cause of addiction to tobacco, but it does not act alone, aided by rituals and behavioral habits and possibly by other substances in tobacco and smoke.

INFORMATION FOR SMOKERS

Smokers switching to electronic cigarettes can reduce inhaled toxicants by approximately 99 percent. Smokers switching to smokeless can reduce their risk of dying sooner than non-smokers by about 95 percent.



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In this publication the American Council on Science and Health sets out the science of nicotine as it affects health.

Nicotine is addictive, driving smokers to smoke for most of their lives, and indirectly shortening their lifespan by at least ten years. Nicotine, however, is not in itself a direct cause or even a minor cause of these smoking deaths or diseases. Indeed, smokers switching to far safer nicotine-vaporizer substitutes can reduce their risk while maintaining their addiction to nicotine.

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