PREVENT DISEASE, SAVE LIVES

AN INTRODUCTION TO ORAL NICOTINE DELIVERY SYSTEMS (ONDS)

ORAL NICOTINE COMMISSION 2020 REPORT

The Oral Nicotine 2020 Report is an online, free-content publication to raise awareness and explain the role of oral nicotine delivery systems in tobacco harm reduction. For cigarette smokers who cannot or will not quit, switching to tobacco-free oral nicotine will help prevent tobacco-related disease and premature death.

This publication is dedicated to the community of oral nicotine consumers worldwide.

Written collaboratively by the members of the Oral Nicotine Commission and supported by Health Diplomats.

SUMMARY

This booklet is about a potential lifesaver. One of the most exciting opportunities yet to help prevent tobacco-related disease and premature death, by persuading cigarette smokers who can't quit, to switch to a simple, uncomplicated, tobacco-free substitute for combustible tobacco, in the form of oral nicotine pouches. This emerging product category of tobacco-free oral nicotine delivery systems, might be the breakthrough public health has been waiting for.

As an introduction to the first report of the Oral Nicotine Delivery Systems (ONDS) Commission, we note the very first article of the *World Health Organization's (WHO) constitution states that its objective shall be "enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition*[1]*".*

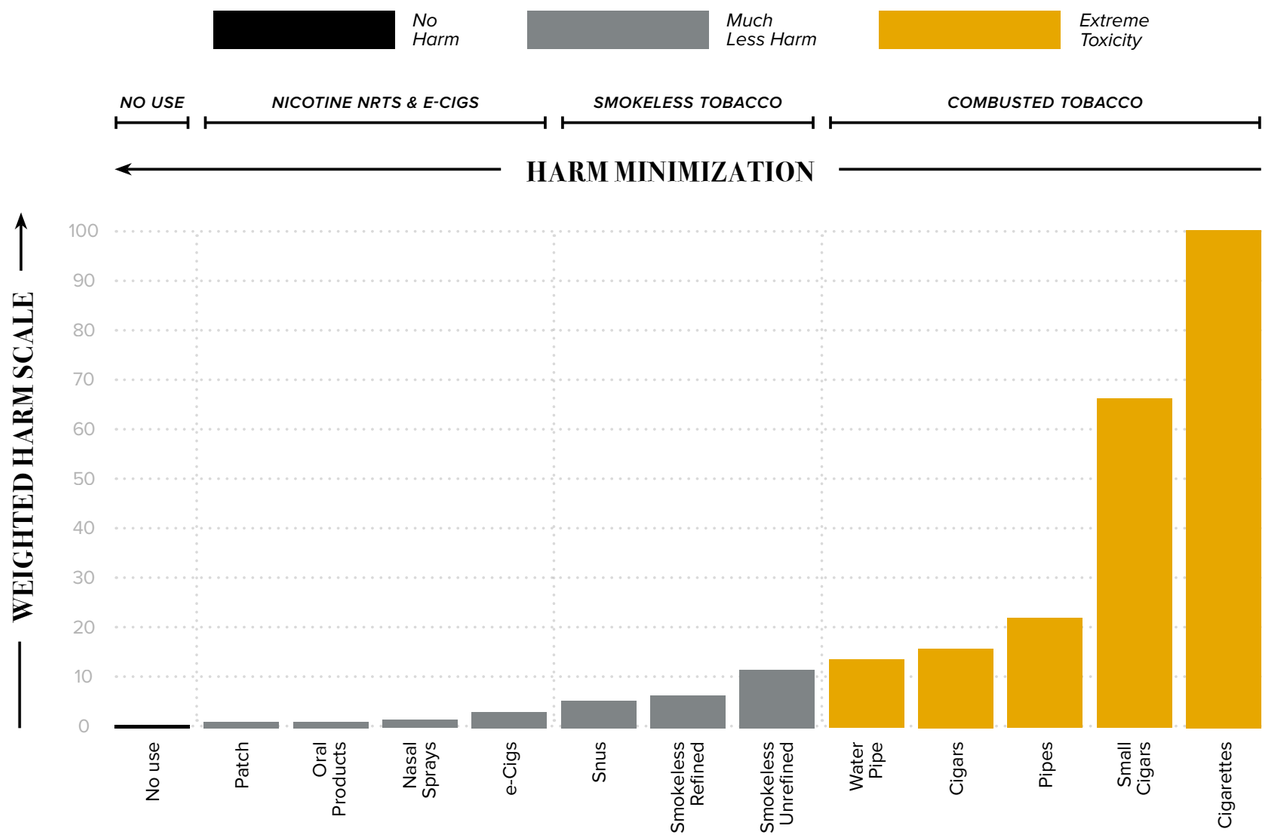
In the same spirit, Article 1 of the Framework Convention on Tobacco Control (FCTC)[2] – the ground-breaking international agreement that was signed in 2003 – states that *"tobacco control itself means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke".*

This policy makes eminent sense – but it has proved near impossible to enforce. Smokers are dependent on the cigarettes, while governments are dependent on cigarette tax. For example, the largest tobacco manufacturer in the world is owned 100% by the Chinese government. Out of the 1.1 billion[3] people who smoke cigarettes worldwide, 300.8 million live there. If any government were able to force smokers to switch, it is in China. But imagine the dilemma of lost tax revenue. Another impediment is that global public health advocates tend to embrace the quit-or-die approach to smoking and completely disregard the obvious benefits of a harm reduction model. It is easier to blame it all on a big tobacco conspiracy.

The incontrovertible fact is that smoking of cigarettes and other combustible tobacco products remain the biggest single cause of non-communicable deaths in the world. According to the WHO, it caused 8 million deaths in 2017[4], and this is expected to increase for years to come.

Another reality is that nicotine is addictive, and one of the main reasons why people can't quit cigarettes. But if these consumers were to have access to alternatives that do not require combustion and still satisfy their need for nicotine, The Royal College of Physicians (RCP)[5] states that the hazard to health arising from example long-term vapour inhalation from the e-cigarettes available today is unlikely to exceed **5% of the harm from smoking tobacco**. With oral nicotine, there is no vapour, so the potential of even less harm.

In other words, tobacco and nicotine products can be stretched out along a harm continuum, with cigarettes at one end and tobacco-free, oral nicotine pouches on the other. In between are placed lower-risk smoke-free products such as heat-not-burn tobacco products, e-cigarettes, and smokeless tobacco pouches(e.g. Snus)[6]. Whereas for snus, there is a wealth of studies on its long-term effects, this evidence base is still being developed for the long-term effects of e-cigarettes and heated tobacco products.



Products along the harm minimisation continuum. Adapted from Nutt et al., 2014 and Abrams et al, 2018

Unfortunately, there seems to be a battle between those who want to promote tobacco harm reduction (THR) efforts and those who want to eliminate tobacco altogether – but this is unnecessary. Because THR has at its heart the very same guiding principles as those who want to eliminate tobacco altogether: to prevent or reduce tobacco-related health risks, diseases and premature deaths. In short, to save lives.

Given the net health benefits of switching from cigarettes to any of the less harmful products, this trend should be welcomed and accelerated. It is simple as that. And consumers – indeed, the public in general – should be educated about the relative harms of products that contain nicotine, and their benefits, too.

The best kept secret in tobacco control seems to be smoke-free oral tobacco and nicotine. For example, in Sweden where snus use has been displacing smoking, adult daily smoking prevalence has already fallen to 5% – compared to a European Union average of 26%. Yet, snus is still banned in all European Union countries (except Sweden), a fact made even more curious after a study by the Swedish Institutet för Tobaksstudier, or Institute for Tobacco Studies, using data from the WHO's 2012 Global Report on Mortality Attributable to Tobacco[7], concluded that if other EU countries practiced the same tobacco consumption patterns as Sweden – encouraging smokers to switch from cigarettes to snus, for example – no less than 355,000 lives per year could have been saved, most of them men over the age of 30. In particular, Swedish men have the European Union's lowest level of tobacco-related mortality, of any cause.[8]

Tobacco-free, oral nicotine pouches could become the most consequential tool in tobacco control, if the category can be underpinned with sound scientific characterisation and validation, regulated proportionately based on risk, and the relative risk accurately communicated to consumers.

The complex challenge of reducing tobacco-related disease and death can only be solved by a whole-of-society approach, with all stakeholders playing their part – and a choice of reduced risk alternative for smokers. Oral nicotine pouches can be part of this solution. "Switch to the Pouch" can become a lifesaver.

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INTRODUCTION TO ONDS REPORT AND COMMISSION

WELCOME TO THE FIRST REPORT OF THE ORAL NICOTINE DELIVERY SYSTEMS (ONDS) COMMISSION – "ORAL NICOTINE – PREVENT DISEASE, SAVE LIVES"

> *The goal of the Commission, an independent body made up of leading figures in the international medical, scientific and public health policy communities, is to help build the evidence base and raise awareness of the benefits of oral nicotine among both governments, public health leaders and the public, thus countering negative, unfounded preconceptions and stereotypes. It will address policy, science, consumer issues and ONDS-relevant product innovations.*

Editorial independence is very important to the Commission. As far as possible, self- and crowdfunding will be the primary sources of funding. For this report, Health Diplomats has provided support in research, content development, editing and layout – but the Commission reports, analyses, conclusions and recommendations will remain completely independent of any potential funding.

This first edition of the report explains what ONDS are and what makes them different from cigarettes, oral tobacco-based snus and nasal snuff. More important, it provides insight into the benefits of ONDS for adult smokers who may choose to switch to this category of product.

Of course, no nicotine product is risk-free and the Commission recognizes that there may be health issues related to oral nicotine, given that this is a nascent category and the evidence base is still growing. Even medicinal nicotine replacement therapy (NRT) has certain risks.

But effectively, oral (pharma grade) nicotine pouches have exactly the same composition as NRT. Nonetheless, the risks are explained within the context of the health effects of snus, which has a delivery system similar to ONDS, but without the risk of either tobacco smoking-related cancers or heart and cardiovascular diseases[9].

Finally, this report touches on the interface between policy and science. It outlines and expands on preferred regulatory frameworks for the governments and public health officials involved in policy-making. Obviously, Sweden and its regulation of Swedish snus are referenced, because it highlights the graphic difference between the current level of tobacco smoking -related mortality in European Union (EU) countries and that of Sweden[10,11].

It is a staggering fact that 24 of the other 27 member EU states have a tobacco-related mortality rate twice as high, or more than Sweden. The key to this lower mortality rate appears to have been snus, because many smokers, most of them male, have switched over to snus.

Yet, snus is still a banned product in much of the rest of Europe – and other THR products such as ONDS remain on the periphery, whereas it could be playing a central role in the prevention of tobacco-related disease and premature death.

Dr. Delon Human
MBChB, MPraxMed, MFGP, DCH, MBA
Chair, Oral Nicotine Commission

delon@healthdiplomats.com

Dr. Human is a published author, international speaker and health care consultant specializing in global health strategy, corporate and product transformation, harm reduction and health communication.

He has acted as an advisor to three of the World Health Organization's (WHO) Directors-General and to Ban-Ki-moon when he was Secretary-General of the United Nations (UN). Until 2014 he served as Secretary-General and special envoy to the WHO/UN of the International Food and Beverage Alliance, a group of leading food and non-alcoholic beverage companies with a global presence. From 1997 to 2005, he served as Secretary-General of the World Medical Association (WMA), the global representative body for physicians.

He was instrumental in the establishment of the World Health Professions Alliance (WHPA), an alliance of the global representative bodies of physicians, nurses, pharmacists, dentists and physical therapists. In 2006, he was elected to serve as the Secretary-General of the African Medical Association (AfMA), the Africa Harm Reduction Alliance (AHRA) and is a fellow of the Russian and Romanian Academies of Medical Sciences.

Dr. Human qualified as a physician in South Africa and completed his postgraduate studies in family medicine and child health in South Africa and Oxford, England. His business studies (MBA) were completed at the Edinburgh Business School.

Dr. Anders Milton
MD, PhD

anders.milton@medhand.com

Dr. Milton is a physician with extensive experience in public service, a highly sought-after consultant in the healthcare sector and a former chair of the WMA. Currently the owner and CEO of Milton Consulting and current chair of the Snus Commission. He is the Chairman of the Board of three foundations that work with education for children and adolescents and a number of for-profit companies in the field of life science.

He served as President of the European Regional Network on HIV/AIDS (ERNA) for six years and chairs the boards of the pharmaceutical firms, Vironova AB, Toleranzia and Immune System Regulation.

Dr. Milton's resumé also includes stints as President and CEO of the Swedish Medical Association (SMA), and as President of the Swedish Red Cross, the People and Defence Foundation and the Swedish Confederation of Professional Associations (SACO). The Swedish government appointed him as the country's coordinator of national psychiatric treatment and care, as Chairman of a committee on Swedish HIV/AIDS policies and, following the disastrous tsunami in December 2004, as a member of its Catastrophe Commission.

Recently, he led as a member of the Catastrophe Commission formed following the December 2004 tsunami. Recently he led a Select Committee with a mandate to formulate best practice policies for organ donation and transplantation.

After graduating as both a medical doctor and a PhD, Dr. Milton served as a clinician in the department of nephrology at the University Hospital at Uppsala. Throughout his career, he has worked tirelessly to support of human rights, and to improve and enforce the ethics of medical practice and safe health care – of which effective pharmacotherapy is an integral

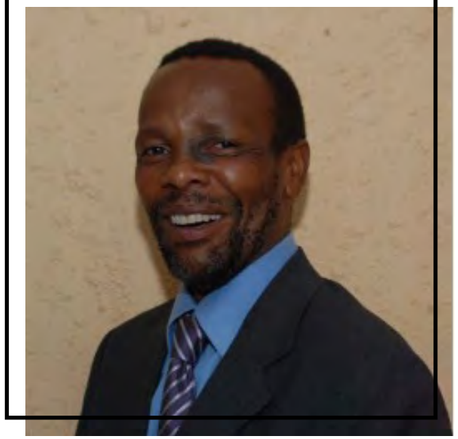
Prof. Solomon Tshimong Rataemane, MD

srataema@gmail.com

Prof. Solomon Rataemane is the head of the Department of Psychiatry at the University of Limpopo (MEDUNSA Campus) in Pretoria and was formerly Interim Executive Dean of the University's Health Sciences faculty. The chief psychiatrist at Dr. George Mukhari Hospital, he sits on the conflict management and resolution committee of the World Psychiatric Association and is a member of both the World Association for Social Psychiatry and the Colleges of Medicine of South Africa.

With a special interest in child psychiatry, mood disorders and addiction medicine, between 1995 to 2005, he served first as Deputy Chair, then Chair of the Central Drug Authority of South Africa from 1995 to 2005. He is the General-Secretary of the World Association of Psychosocial Rehabilitation, a global NGO in advocacy for persons with mental illness.

Dr. Rataemane was a co-investigator with the UCLA Substance Abuse Program to assess the efficacy of Cognitive Behaviour Therapy training for counsellors at SANCA Clinics in South Africa. He is a Board Member of the International Council on Alcohol and Addictions and serves on the Health Committee of the Health Professions of South Africa, assisting in physicians' own health management. Between 2007 to 2010, he was Deputy Chair of the Medical Research Council of South Africa, and he still serves as a member of the College of Psychiatry.



Dr. Kgosi Letlape, MD

dr.kgosi@gmail.com

An ophthalmologist by training, Dr. Kgosi Letlape is a past President of the World Medical Association, the global representative body for physicians around the world. He is the current President of the Africa Medical Association (AMA) and the immediate past chairman of the board of the South African Medical Association (SAMA).

Dr. Letlape has also served as executive director of the Tshepang Trust, a not-for-profit organization that pioneered the provision of treatment for HIV and AIDS patients in partnership with state hospital. The Trust was created at the behest of the late South African president Nelson Mandela, with funding from the U.S. Presidential Emergency Program for AIDS Relief by way of the Centers for Disease Control and Prevention.

In an effort to ensure access to healthcare for all, including less harmful products, . he co-founded the Africa Harm Reduction Alliance, with an aim to create awareness and teach people about the need to reduce harm and promote wellbeing.

Mr Joseph Magero: Tobacco Harm Reductionist (Kenya)

josephmagero@yahoo.co.uk

Joseph Magero is an avid tobacco harm reduction advocate. He has spent a decade working in tobacco control as the former director of Africa Tobacco-Free Initiative, but after extensive research, consultation, and direct engagement with ex-smokers, scientists and THR consumer advocates, he became convinced him that giving smokers the option of switching to significantly safer (and enjoyable) nicotine products could provide a vital addition in reducing smoking related diseases.

He was awarded 'Outstanding advocate of the year 2019' by The International Network of Nicotine Consumer Organizations (INNCO).

He is currently pursuing a master's degree in Public policy, and is the chairman of Campaign for Safer Alternatives, a regional organisation that advocates for the adoption of tobacco harm reduction policies in Africa. His commitment to a smoke-free future remains undiminished.

Dr Karl Olov Fagerström

PhD

karl.fagerstrom@hotmail.com

Dr. Fagerström, a founding member of the Society for Research on Nicotine and Tobacco (SRNT), started his own eponymous consulting firm in order to share with others his expertise in addiction, risk reduction and the benefits of nicotine. After studying at the University of Uppsala, he graduated as a licensed clinical psychologist in 1975. At that time, he started a smoking cessation clinic and invented the Fagerström 'Test for Cigarette Dependence,' which has become a standard measure for assessing the level of physical addiction to nicotine. In 1981, he was awarded a Ph.D. by the University of Uppsala, for a dissertation on nicotine dependence and smoking cessation.

Between 1983 and 1997, Dr. Fagerström worked for Pharmacia & Upjohn as the company's Director of Scientific Information for Nicotine Replacement Products (NRT). From 1975 on, he has helped to develop and improve NRT products such as the patch, spray, inhaler and pouch.

Dr. Fagerström's main research contributions have been in the fields of Behaviour Medicine, Tobacco and Nicotine , complete with 170 peer-reviewed publications. His current interests include better understanding the positive effects of nicotine and reducing harm and exposure to toxins for those who cannot give up smoking. In 1999, the WHO awarded him a medal for his outstanding efforts in the field of tobacco control and in 2013, the SRNT gave him an award for his work in clinical science.

Photo by Joseph Pearson on Unsplash

My own journey with Nicotine
-by Karl Fagerström, PhD

"My own journey with nicotine began as a smoker. I wasn't addicted, but smoked socially. When I reached my 20s, I asked myself why I was doing this in the first place? That was it. I quit. But I was lucky. Many others are not. They can't quit. Or they try multiple times with no success because they are addicted to the nicotine and need it get through work, or social situations and the stresses of everyday living.

Ever since I graduated from the University of Uppsala as a licensed clinical psychologist, I devoted my professional life to helping smokers quit because I understood their situation. I started a smoking cessation clinic and developed what has become a standard questionnaire doctors use to assess the level of nicotine addiction/dependency in patients (Fagerström 'Test for Cigarette Dependence'), thus allowing them to prescribe the correct drugs to the patients successfully. In 1983, I started working at Pharmacia & Upjohn as the company's Director of Scientific Information, helping to develop and improve NRTs such as Nicorette gum, nicotine patches, sprays, pouches and even an inhaler. In the mid-1997, I struck out on my own because I wanted to continue on this path, to explore how to provide consumers with even more choices and safer products. That's what oral nicotine pouches are about, a new way to deliver nicotine without the complications of tobacco.

Products like snus and ONDS are the best kept secrets, and the most underutilised tool in public health. It has prevented tobacco-related disease and premature death in Sweden, thereby saving millions of lives. Oral (tobacco-free) nicotine can do the same for the 1,1 billion smokers in the world.

Sweden, where I live, has a population of about 10 million, and when I started my career, around 10,000 people were dying each year because of diseases related to their smoking habit. People were smoking in restaurants, in their homes and around their children and grandchildren. And no one was worrying about it or trying to find alternatives. I realized that this was a practically untouched area that was ready for research and action. Because just as with alcohol and drugs, people addicted to smoking and nicotine need help.

In Sweden, snus was the key to changing the statistics. Up until the 1970s, although snus was around, cigarette smoking really dominated throughout the country. But when snus began to be advertised as a way to enjoy tobacco without disturbing others due to smoke, we noticed that the prevalence of smoking declined as the use of snus increased. (Studies have since linked the use of snus to Sweden having the lowest mortality rate in the EU because 54 per cent of the people who use it are ex-smokers, most of them men!)

All that said, snus, no matter if it is marketed as 'brown' or 'white,' where the tobacco is washed or treated to leach it of its original colour, does contain some potential carcinogens, such as tobacco-specific nitrosamines, but to a significantly lesser degree than chewing tobacco, snuff and cigarettes. And tobacco itself comes with some very bad baggage! Indeed, it can get really confusing. What sets pure oral nicotine (ONDS) apart is that there is no tobacco whatsoever, the nicotine is of pharmaceutical grade and effectively absorbed.

In a perfect world, everyone might simply quit smoking and get on with their lives, but this is not reality. We are living in the middle of a pandemic. People have lost jobs; they are uncertain about the future and stress levels are going through the proverbial roof. Even in the best of times, it is not helpful to tell people to do something because it is good for them. It is better to give them options that help them make better decisions for themselves. They deserve to have oral nicotine pouches as one of the choices to escape smoking.

ORAL NICOTINE: DESCRIPTION & EVOLVING SCIENCE

Oral Nicotine Delivery Systems, or ONDS, represent the next generation in smokeless, tobacco-free nicotine products. People trying to quit cigarettes, who like the effect of nicotine but want to forego the tobacco or may simply want to prevent those around them from inhaling second-hand smoke, may consider using these products. Oral nicotine pouches are essentially a tobacco-free version of Swedish snus, the moist, smokeless and pasteurized tobacco product . These tiny white, permeable nicotine pouches – like small teabags, contain nicotine, along with food-grade fillers, salt, water, and they come in different flavours. It is placed in between the upper lip and gum for it to work. No combustion is involved. Once in place, the saliva and general moistness of the mouth work to release the nicotine into the system. Once used, the pouch is usually disposed of into the disposable compartment of the can. It does not require refrigeration[12]. Unlike vaping products, no batteries are required.

The very fact that they do not require combustion (no emissions), and do not contain tobacco or the thousands of chemicals present in cigarette smoke (reduced exposure) mean that these products represent immense potential for the reduction of tobacco-related harm. Not only can it benefit individual health, but also play a major role in reducing the tobacco burden on population health.

It is not surprising that several major tobacco and nicotine companies have recognised this opportunity and are in the midst of shifting their business models away from cigarettes. In 2019 alone, five of them offered oral nicotine pouch products for sale.

AN ABBREVIATED HISTORY OF SMOKING AND NICOTINE

People still smoke cigarettes because they are accustomed to the habit and easily available, having been mass-produced in factories for over one hundred years. And they smoke despite the fact that when lit by a match, the tobacco in cigarettes combusts at a temperature of 900 degrees Celsius or higher. Although cigarette consumption ranges the world over, the average smoker lights ten to twenty cigarettes per day,[13] each time inhaling about 6,500 compounds into their lungs, causing significant damage.

Broken down, the act of smoking just one cigarette[14] looks like this: five minutes or so devoted to each one, with ten to fifteen inhalations that last two or three seconds each. In other words, a smoker will inhale for between twenty to forty-five seconds for each cigarette.

When smoking a cigarette, the combustible compound (smoke) is inhaled into the respiratory tract through the upper airways, then passes into the lungs[15]. From here, the alveoli – small airway sacs in the lung – help absorb the nicotine into the bloodstream, which in turn transports it to the brain. In all, the entire process – from inhaling to that kick or nicotine high – occurs in a speedy twenty seconds or so.[16]

Depending on the situation, nicotine has a dual action and can both help to relax people or improve alertness and concentration[17]. Many people, doctors and public health officials included, mistakenly believe nicotine is as harmful as tobacco and the chemicals used in cigarettes – or, at the very least, they don't distinguish it as different. But even though it is addictive, nicotine does not cause tobacco smoking-related diseases such as lung cancer, stroke and COPD[18]. In a way, it is emblematic of the battle between those who want to eradicate smoking altogether versus pragmatists who advocate for smoker access to less harmful alternatives than cigarettes, if they are unable to quit.

How do ONDS users get their nicotine? Unlike the speedy hit from smoking, with a pouch, the nicotine's pathway is more circuitous, entering through the mouth's oral mucosa into the general bloodstream, which then carries it to the brain, within a few minutes[19].

TYPICAL CONSUMER USAGE PATTERNS: CIGARETTES, SNUS AND ONDS

As cigarettes burn down to the filter, there is less ventilation from the tobacco rod so that the nicotine and flavours intensify. With ONDS and snus, it is the exact opposite, with the

flavour at its most intense in the beginning, then diminishing as the pouch contents dissolve.

While a cigarette lasts about five minutes, snus users tend to hold each pouch under their upper lips for up to an hour; ONDS users typically keep each pouch in their mouths for about half that time.[20]

Early data from testing suggest that ONDS deliver nicotine as quickly and to a similar concentration compared with existing smokeless products, with no significant adverse effects[21]. This suggests the efficacy of ONDS in reducing withdrawal symptoms and helping smokers reduce or stop combustible tobacco use, in the same way as existing smokeless products. The biggest difference between the two – a potential game-changer when it comes to harm reduction – is of course that the latter contains tobacco.

Although consumption data varies in markets around the world, in Sweden, where snus has been used for more than two hundred years, users tend to go through about twelve pouches a day, while those who use ONDS consume between five to seven pouches a day.

For public health, great importance is placed on the appeal and interest among adults in a new consumer nicotine product. Their priorities are whether it positively or negatively impacts tobacco cessation and whether never users would initiate use, or dual use (with other tobacco products) might be possible. A study by Pluphanswat et al, 2020, investigated the appeal and interest among adults in a new oral nicotine products (ONDS). Non-users of tobacco showed very little interest in the ONDS. Smokeless tobacco users were not only more interested to buy this product, but became the largest group of regular users. The most popular reason for using ONDS was "less harmful to my health than other tobacco products", followed by "ease of use"[22]

Currently, ONDS are sold in many markets around the world under different brand names, including ZYN (Swedish Match), Velo/LYFT (British American Tobacco/R.J. Reynolds), Nordic Spirit (JTI), On! (Altria) and ZoneX (Imperial Tobacco)

THE EVOLVING SCIENCE OF ORAL NICOTINE (ONDS)

Although this is a nascent category and much research still needs to be done, data is available from tests conducted for years on similar products such as snus. Not only is there proof of concept, but 4 decades of epidemiological proof that Swedish snus is significantly less harmful than cigarettes.

Developing a research plan for ONDS should address at least the following areas:

- ***Differential risk of the Oral Nicotine (ONDS) category:*** Ideally, a science-based framework for a "category risk index" should be established. Nutt et al proposed the Multi-criteria Decision Making Analysis (MCDA) method as framework, and argued that non-combustible nicotine is 95% less harmful than cigarettes[23]. The EU's General Risk Assessment methodology[24] should also be considered, but in all cases, independent scientific endorsement is needed.

- ***Youth use:*** Few potential risks are more important to global public health than youth initiation or use of any nicotine product. It is possible that nicotine oral pouches may attract youth and young adults. Research on preventing youth initiation and use of this category of products, should be a priority, including restrictions on marketing to children.

  Another important issue is the way in which studies measure current youth use of oral nicotine products. Exaggeration of use can easily occur if the definition of "any-past-30-day-use" is employed. It is vital to use more precise metrics to determine the frequency of use by youth and investigate the possibility of youth nicotine dependence. The same applies to the so-called "gateway theory" of oral nicotine use, which can supposedly lead to cigarette smoking. Neither of these hypotheses has been adequately researched or proven.

- ***Cessation:*** Smoking cessation remains the top priority for global public health. Article 14 of the FCTC states that all parties "shall take effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence."[25] Longitudinal research is necessary to assess the efficacy of ONDS to decrease tobacco consumption and cessation. It is also imperative that health professionals and researchers clearly specify quit rates, including with the use of ONDS.

- ***Consumer-based research:*** The behavioural sciences are usually a blind spot for public health, but where industry science excels. A deep consumer understanding can be developed by using the right methodology, to determine the reasons for use, frequency of use, methods of use and presence of dual use.

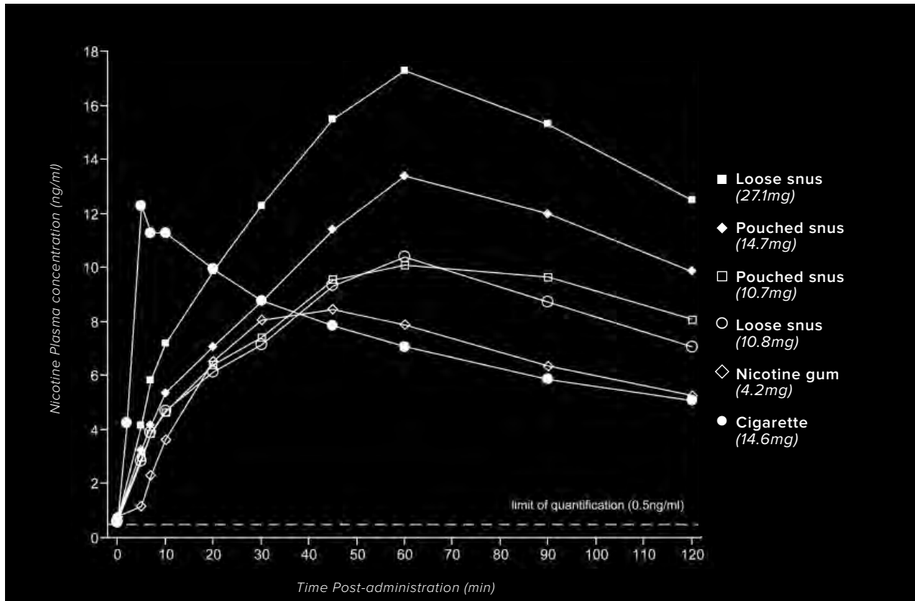
- ***Clinical Studies:*** Methodologically sound clinical studies are necessary for both short- and long-term use of ONDS, to verify their individual health impact. This way more definitive risk differentiation models can be established, and the category regulated accordingly.

- ***Population Studies:*** In most countries, several studies will be required for ONDS to be classified as a modified risk product, including:

  - The relative toxicity and risks of ONDS compared with cigarettes;
  - Concomitant use of ONDS and cigarettes with the potential for increased exposure to toxicants;
  - Increased prevalence of ONDS due to increased uptake among those who would otherwise never use tobacco or nicotine;
  - Maintenance of ONDS use in consumers who would have otherwise quit and/or relapse to tobacco use; and
  - Potential as a gateway product to or from cigarette smoking.

- ***Product-based research:*** Currently, most research on these products are industry-led, but should at least include:

  - Toxicological Assessment: Human-tissue based in-vitro assays of the pathogenesis of tobacco-attributable diseases. Bishop et al developed an approach for the extract generation and toxicological assessment of tobacco-free "modern" oral nicotine pouches. The study demonstrated the generation of extracts from these products and performing toxicological evaluation using in vitro approaches[26];
  - Pharmacokinetic studies to determine how quickly nicotine is delivered, in comparison to existing smokeless tobacco products. Lunell et al reported that nicotine, using ONDS products of 6 and 8 mg, was delivered as quickly and as to a similar extent as existing smokeless products, with no significant adverse effects[27]. Nicotine absorption into the blood from various tobacco and nicotine products should be measured, as Digard et al have done[28] and consumer perceptions studied.



Mean plasma nicotine concentrations at each time point following single use of the different tobacco products and nicotine gum. Products (nicotine content): ● Cigarette (14.6 mg); □ Pouched snus (10.7 mg); ○ Loose snus (10.8 mg); ◆ Pouched snus (14.7 mg); ■ Loose snus (27.1 mg); ◇ Nicotine gum (4.2 mg). The dashed line represents the limit of quantification (0.5 ng/ml).

Digard H, Proctor C et al, Nicotine Tobacco Research 2013

- Human biomarkers of exposure and effect and the relationship between these biomarkers with disease risk;
- Methods and measures for short-term clinical and epidemiological studies, including consumer perception testing;
- Post-marketing surveillance or long-term studies to determine the impact of THR products at a population level;
- Chemistry studies to characterise and establish the contents of ONDS, as compared to those in oral smokeless tobacco;
- Population studies to determine how the ONDS category might affect population health, normally by using simulation modelling.

BENEFITS OF ORAL NICOTINE DELIVERY SYSTEMS (ONDS) AS PART OF TOBACCO HARM REDUCTION (THR)

Why Oral Nicotine? The answer is clear: ONDS provides consumers with a safer way to consume nicotine because they contain no tobacco and significantly fewer chemicals than cigarettes and do not require combustion.

As Michael Russell, a pioneer in THR(and the inventor of the nicotine patch) noted back in 1974: *"People smoke for the nicotine but they die from the tar."*

They also offer other benefits, such as no second-hand smoke , no lingering unpleasant odours on clothing and hair, and maybe even mouths that dentists will find cleaner and healthier. Many adult consumers of snus - people already familiar with how oral nicotine products work – may be attracted to ONDS because of the lack of tobacco and as well as flavours and since they can get their nicotine delivered in the same way as with snus.

Harm reduction is a term used to denote the reduction of harmful consequences associated with a specific risky activity. Any behaviour that could damage the health of the individual involved or their community. Washing hands to avoid Covid transmission, car seatbelts, helmets, and condoms for safe sex are all examples of harm reduction.

This is exactly where ONDS fit into tobacco harm reduction. The WHO Framework Convention on Tobacco Control (Article 1) (FCTC) explicitly endorses harm reduction strategies as part of tobacco control:
(d) "Tobacco control" means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke[29]"

One need only look to various governments that ban snus and e-cigarettes while still allowing the sale of traditional cigarettes to understand that this approach has not been implemented worldwide. It is almost as if the fire exits have been blocked for smokers seeking a less risky, smoke-free alternative.

Precautionary Principle Misapplied. Governments, especially in the EU, who ban tobacco-free nicotine pouches, usually do so by invoking the so-called precautionary principle. For example, snus was banned in the same way - before adequate research had been done on this product category. Hereby, the unspecified possible risks of any new product, are positioned to carry undue weight in the predictably restrictive regulatory measures levied against it. The consequences of this, no matter if it is unintended or not, may be deadly.

Because the current lack of differentiation between the risks of various tobacco and nicotine products means that public health officials, doctors and others who could play key roles in the world of harm reduction cannot do so properly. Thus, consumers do not have the opportunity to understand the benefits unless they make an extraordinary effort to find out for themselves.

In other words, the precautionary principle represents a short-sighted approach to the issue at the very least – and one that possibly risks lives. If applied responsibly, for example as outlined by the European Commission, it would be preceded by measured assessment, taking account of:[30]

- Proportionality between the measures taken and the chosen level of protection;
- Non-discrimination in application of the measures;
- Consistency of the measures with similar measures already taken in similar situations or using similar approaches;
- Examination of the benefits and costs of action or lack of action;
- Review of the measures in the light of scientific developments.

The precautionary principle has greatest relevance where the risks are systemic, irreversible, accumulative and/or severe; this is why the principle initially gained prominence in environmental policy-making, where decisions affect whole populations. But those conditions don't apply to smoke-free products (that contain tobacco or not) because they pose individual risks that can be addressed through user behaviour or retrospective legislation.

It is encouraging that, during 2019, the U.S. the U.S. Food and Drug Administration announced that, for the first time, it had authorized the marketing of eight snus smokeless tobacco products through the modified risk tobacco product (MRTP) pathway[31]. Hereby the manufacturer, Swedish Match USA, was given the right to market these products with the claim: "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

The FDA came to this conclusion following an exhaustive scientific review, including long-term epidemiological studies. Latest data on causes of mortality in the EU, provides a sobering reminder of how Swedish Snus has prevented tobacco-related disease and premature death in that country.

DEATH RATES PER 100,000 ATTRIBUTABLE TO TOBACCO - SWEDEN AND THE REST OF THE EU IN 2017

		SWEDEN	EUROPEAN UNION MEMBER STATES (OTHER THAN SWEDEN)		
			LOWEST	WEIGHTED MEAN	HIGHEST
TOTAL ALL CAUSES	Men (total population, age standardized)	70	76	125	252
	Women (age 50-54)	38	61	130	412
	Women (total population, age standardized)	52	19	44	79
TRACHEAL, BRONCHUS AND LUNG CANCER	Men (total population, age standardized)	14	19	34	56
	Women (age 50-54)	6.0	9.5	36	88
	Women (total population, age standardized)	13	3.1	11	22
LIP AND ORAL CAVITY CANCER	Men (total population, age standardized)	0.45	0.52	1.4	4.1
	Women (age 50-54)	0.35	0.73	3.3	13
	Women (total population, age standardized)	0.27	0.17	0.27	0.63
LARYNX CANCER	Men (total population, age standardized)	0.39	0.43	2.0	4.9
	Women (age 50-54)	0.34	0.64	3.5	12
	Women (total population, age standardized)	0.07	0.04	0.15	0.38
PANCREATIC CANCER	Men (total population, age standardized)	1.8	1.8	2.6	3.9
	Women (age 50-54)	0.89	1.4	2.8	6.0
	Women (total population, age standardized)	2.8	0.9	2.1	3.5
ISCHEMIC HEART DISEASE	Men (total population, age standardized)	17	12	26	96
	Women (age 50-54)	16	20	40	180
	Women (total population, age standardized)	8.9	3.1	8.7	32
STROKE	Men (total population, age standardized)	3.7	3.8	7.5	40
	Women (age 50-54)	2.8	3.7	9.1	57
	Women (total population, age standardized)	3.2	1.7	3.8	17
COPD	Men (total population, age standardized)	8.1	7.3	15	25
	Women (age 50-54)	0.86	1.7	4.4	19
	Women (total population, age standardized)	7.4	1.0	5.0	16

If Swedish snus has been the proof of concept for tobacco harm reduction, then ONDS has the potential to take it one step further in the rest of the world.

The primary objective of public health is to prevent disease and premature death. Tobacco-free Oral Nicotine (ONDS) can potentially be the breakthrough tobacco control has been waiting for. It deserves a place at the harm reduction table. Because millions of lives are at stake.

Compiled from The Burden of Disease Study https://vizhub.healthdata.org/gbd-compare/# by Lars M. Ramström, Institute for Tobacco Studies, Sweden lr@tobaccostudies.com

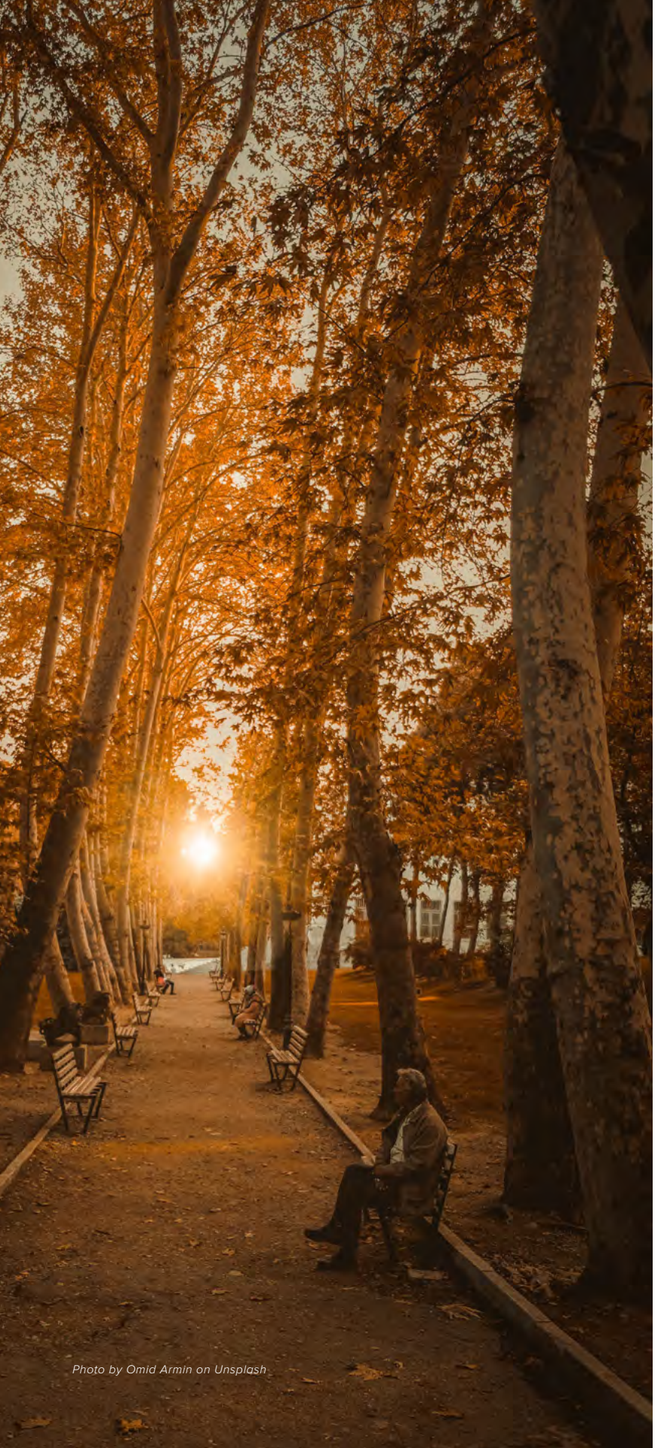


Photo by Omid Armin on Unsplash

CURRENT CONCERNS RELATED TO ORAL NICOTINE

As with other THR products, there is opposition to the very existence of ONDS. In Kenya, for example, advocacy groups have expressed worry that the contents of oral nicotine pouches may raise the risk of cancer and heart disease, and reproductive and other developmental problems. Indeed, the Kenya Tobacco Control Alliance has stated that foetal nicotine exposure may lead to post-natal health problems and that nicotine has been linked to the development of insulin resistance and irregularities in the metabolism of glucose, among other health problems.

Clearly, as with any consumer product, safety and quality are primary concerns. So, what would a responsible approach be to identify and regulate the material risks linked to ONDS? Because ONDS are tobacco-free, it is sometimes called 'clean white snus.' It is based almost entirely on cellulose, with pure nicotine and flavours added afterwards. This means that the product contains NO tobacco-specific nitrosamines, or TSNAs, which occur when tobacco leaves are grown, cured, aged and then processed. This is important, as TSNAs are the carcinogenic agents in tobacco smoke[32]. Despite the obvious advantages, there are areas of concern:

Safety of Ingredients: All efforts need to be made to ensure that ingredients are of a purity grade suitable for use in food, and the nicotine of pharmaceutical grade purity. No toxic or carcinogenic ingredients should be allowed.

Nicotine: The World Health Organization (WHO) has included Nicotine Replacement Therapy (NRT) on its Model List of Essential Medicines[33]. ONDS also contains nicotine, which is part of its attraction for consumers, as it is addictive[34] – much like other "social drugs" such as caffeine and alcohol. Because of its addictive nature and toxicity in high concentrations, the threshold dose of nicotine per pouch has been widely debated, and a maximum should be scientifically determined and advocated.

Nicotine overdose: The total amount of nicotine in an oral pouch greatly exceeds the amount actually absorbed into the bloodstream of a consumer. Overdosing can still be possible, and could lead to vomiting, nausea, extreme fatigue, increased blood pressure and even cardiovascular arrest.

Flavours: Although these form an important part of the appeal of these products, the two concerns are safety and its potential role in attracting underage users. Consumer safety should be assured based on food purity requirements and marketing should be directed to adults only.

Preventing Youth Use: Responsible marketing practices and age verification systems need to be put in place to ensure that children younger than 18 years don't have access to ONDS.

Getting key critics/opinion leaders on board – the health professionals

This is actually a key concern in the development of tobacco-free oral nicotine as mainstream harm reduction tools. Tobacco control provided the insight that health professionals and in particular, medical doctors have tremendous influence in consumer choices. They can play a highly influential role in curbing tobacco use in any community. ***In fact, during the early part of the last century, doctors were the first to start smoking, but also the first social grouping to quit smoking***. This was mostly due to the research of Dr Richard Doll, whose 1950 article[35] in the British Medical Journal (BMJ) essentially started the tobacco control movement.

In this article, he powerfully established the link between cigarette smoking in medical doctors and lung cancer. Likewise, it is clear that where medical doctors take the lead and stop smoking themselves, advise patients to quit and advocate for policy change, sustained action follows.

Dr Derek Yach, former Executive Director at the World Health Organization (WHO), states that[36] "physicians were, in fact, key to progress in the USA and OECD countries, where smoking rates have dropped steadily over the decades. In these countries, doctors' smoking rates dropped and, within a decade, smoking rates fell in the general population. In many major LMICs, physician smoking rates remain extremely high. Correspondingly, doctors' voices and advocacy are weak. Until this changes, progress will be slow."

It is clear that future physicians and health professionals will depend on this generation to have made wise judgments on the science and value of oral nicotine to break the deadlock of tobacco on their patients' health. For the practicing physician today, the evidence is clear – they should include THR into their practices and consider to advise oral nicotine as a harm reduction tool to their smoking patients!

ONDS represent an exciting new chapter in the world of tobacco harm reduction. It is a chapter in which tobacco and inhalation have been eliminated, so has tremendous potential for optimising harm reduction.

REGULATORY CONSIDERATIONS

Governments around the world have different approaches to regulate this new category. Some consider ONDS as consumer goods, other as tobacco products, food products and even medicine. Ultimately, the goal of regulation is to ensure consumer safety, product quality and responsible use.

For this, proper risk assessment frameworks, stringent peer reviews and quality controls are needed. Consumers demand transparency, and need to be assured exactly what the pouches contain, and how their contents affect human tissues in a laboratory setting and users in the real world.

For public health, the most important regulatory consideration is whether ONDS can reduce smoking prevalence and tobacco smoking -related harm. Compared to cigarettes, ONDS can be regarded as reduced risk products, capable of helping adult smokers switch from dangerous cigarettes to a lower-risk product.

PRINCIPLES in the development of a proportionate regulatory framework:

- THR products should be regulated according to their relative risk potential and specific attributes;
- Most restrictive regulations applied to the most harmful products;
- Least restrictive regulations for the least harmful products; and
- Protect youth from initiation or use of any tobacco or nicotine product
- Non-tobacco nicotine products should be classified and regulated differently from tobacco products;
- Product quality and safety standards must be established and enforced in order to assure both regulatory bodies and consumers that THR products placed on the market meet the appropriate rigid criteria for quality and safety;
- A balance needs to be found between access, innovation and net public health benefits. If this category of products is medicalised, it will impede access for adult smokers, who are willing to switch. If access is completely liberalized, it can make it too easy for underaged consumers to experiment and initiate use of this type of product.

Abrams et al.[37] call for regulation that will “save smokers” lives now while simultaneously protecting youth. The key challenge is to implement policies that maximise the net flow away from smoking and toward the use of safer products, or to no use. A balance can and must be found to protect youth without discouraging cleaner nicotine use by smokers unable or not wishing to quit their nicotine use.

In tobacco control, it is difficult to achieve this balance. This is because the public and consumers need to receive clear risk differentiation and risk communication about various product categories. At the same time, companies need to be incentivised to create new, less harmful products.

The case of Swedish snus again shows which pitfalls Oral Nicotine products will have to avoid. Governments rely on evidence-based policy guidance, and the World Health Organization (WHO) is regarded as the premier technical health policy advisory body in the world. Hopefully, it will be more circumspect about this category, than it has been regarding Swedish Snus.

Even with decades long of sound epidemiological evidence, WHO still publicly describes Swedish snus as “not a safe alternative to smoking”, even though there is ample evidence to the contrary.[38,39] Based on this advice, many countries still ban Swedish snus.

Key Regulatory Areas vital to address by those governments, which are in the process of developing regulatory frameworks for ONDS:

Product Classification: It would be preferable to classify ONDS in a separate category for tobacco-free oral nicotine products. In the European Union Tobacco Products Directive (Dir 2014/40/EU), other tobacco-free products, such as electronic nicotine delivery systems (ENDS) are regulated as “tobacco-related products”. Despite the absence of tobacco in ONDS and ENDS, this could be considered as a potential sustainable regulatory pathway. Based on relative risk potential and specific attributes, clear regulatory differentiation should be made from tobacco products.

Nicotine purity: Pharmaceutical grade should be the standard

Nicotine Thresholds: There seems to be growing consensus amongst stakeholders, that a threshold is advisable, and the EU Tobacco Product Directive guidance is that nicotine concentration should be limited[40];

Quality and Safety Requirements: No Ingredients that are deemed carcinogenic, mutagenic or toxic for reproduction;

Adults-Only Consumer Communications: Clear regulation to prohibit the sale of these products to anyone under the age of 18;

Flavours: Important tool to help adult smokers switch to a less harmful product, but important to safeguard children from inadvertently being attracted to this product category, based on flavours directed at children.

In conclusion, ONDS represent an exciting new chapter in tobacco harm reduction. It is a chapter in which tobacco and inhalation have been edited out, thus creating an exciting opportunity for smokers to change their health status. In a world where consumers make innumerable judgment calls every day, they deserve fair, proportionate and risk-based regulations to facilitate the most responsible and informed choices for their health.

The fact is, they deserve to have informed choices, period.

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RECOMMENDATIONS ON ORAL NICOTINE (ONDS) POLICY, SCIENCE, CONSUMER CARE AND PRODUCT STANDARDS

In this evolving product category, there are key considerations all stakeholders need to take into account. If the product category can prove itself as a net benefit to public health, it has the makings to become a gamechanger in tobacco control and harm reduction.

ORAL NICOTINE 2020 RECOMMENDATIONS

FCTC: *Recognition of THR and ONDS as one of the least harmful nicotine-based products*

- The harm reduction concept is endorsed in Article 1 of the World Health Organization Framework Convention on Tobacco Control (FCTC). This concept should be expanded and amplified to include recognition of and support for proportionate, risk-based regulation of ONDS;
- Tobacco and nicotine products should be placed on a continuum of harm, from the most harmful of combusted tobacco to much lower harms of smoke-free nicotine delivery with or without tobacco, including ONDS and NRT;
- For net public health benefit, the trend towards switching from high-risk smoking tobacco products such as cigarettes to low-risk smoke-free products such NONDS should be accelerated;
- Accurate risk communication: Consumers and the public, as part of their basic human rights, must be accurately educated about the relative harms of nicotine- containing products relative to smoking.

No marketing to Children (M2K): *Priority should be that the marketing and promotion of smoke-free oral nicotine products should not target youth. If this principle is not respected, the category is unlikely to be allowed to grow*

- ONDS advertising, packaging, flavour names, promotional gifts, activities and events should be directed only to adults;
- Age verification needs to be put in place.

Preferred Regulatory Framework: *Regulation that is risk-based, proportionate and recognises the harm reduction potential of smoke-free oral nicotine products compared to smoking tobacco products*

- Differentiation should be made between smoking tobacco products and smoke-free products such as Oral Nicotine (ONDS);
- Recognise that flavours are integral to the appeal of smoke-free alternatives, such as ONDS, and an essential part of the proposition to smokers to try switching and remain smoke-free.
- The policy for use of smoke-free nicotine and tobacco products in public spaces: In the absence of evidence of a plausible material risk to bystanders arising from ONDS, smoke-free ONDS should be allowed for use;
- Labelling should convey accurate but not exaggerated information, to explain relative risk.
- Products should meet specific safety standards for packaging and ingredients. There are established and recommended standards for smoke-free ONDS to draw on.

Risk Communication: *All state and non-state actors should be encouraged to employ Accurate Risk Communication of the ONDS category*

- Risk Communication: All state and non-state actors should be encouraged to employ Accurate Risk Communication of the ONDS category

Research: *Development of a comprehensive research agenda for the ONDS category, in order to grow the evidence base with regard to the safety, efficacy (for tobacco cessation) and quality*

NICOTINE

- Nicotine research should be central to establishment of an evidence base for this category, including safety, pharmacokinetics and possible side effects in ONDS
- Post-marketing surveillance should be in place to monitor potential nicotine overdoses.

NICOTINE UPTAKE BETWEEN DIFFERENT PRODUCTS

- Comparisons between smoke-free oral nicotine products and other tobacco products (e.g. cigarettes);
- When comparing smoke-free oral nicotine products to cigarettes, the mistake should not be made to compare the total amount of nicotine in the pouch, with the amount of nicotine measured in the emissions from a cigarettes

TOXICANTS

- Whereas the toxicants in cigarette smoke are responsible for most of the harm related to smoking, it is imperative for the ONDS research agenda to take a balanced approach in seeking to ensure product safety while enabling and encouraging adult smokers to switch to potentially reduced risk nicotine alternatives. This would include the measurement of:
  - Toxicant release: Amount of certain potentially harmful chemicals that are released when product use is simulated.
  - Toxicant exposure: Amount consumers are exposed to when they use the product
  - Toxicant risk: Effect these exposures have on the chances of developing a related disease.

BIOMARKERS

- A very important area of research in tobacco and nicotine. Biomarkers help measure the biological impact of an exposure to a product and its ingredients. Various biomarkers need to be studied, including:
  - Biomarkers of Biological Effect (BoBE): The effects that chemicals in ONDS have when inside the body, should be measured – e.g. blood pressure.
  - Biomarkers of Exposure (BoE): Determined by measuring the metabolic by-products of ONDS in blood, breath, saliva or urine.

EPIDEMIOLOGY

- Epidemiology is considered the most reliable method for assessing the long term risk. As this is a new category, epidemiological data need to be collected from the onset.

SOCIAL SCIENCES & CONSUMER UNDERSTANDING

- Market research on the preferences of various consumer groups, including young people and current smokers; risk/benefit analysis of the product, its expected effects on cessation of tobacco consumption, its expected effects on initiation of tobacco consumption and predicted consumer perception

Product Standards

- Products should meet specific safety standards for manufacturing, mixing, processing, packaging, labelling and ingredients. In addition, product standards for novel smoke-free alternatives such as ONDS should provide assurance to regulators and consumers on scientific studies on toxicity, addictiveness and attractiveness, in particular as regards its ingredients analysis of the product, its expected effects on cessation of tobacco consumption, its expected effects on initiation of tobacco consumption and predicted consumer perception.

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