

Tobacco Smoking: Harm Reduction Strategies An ERS Research Seminar*

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Abbreviations

APA	American Psychological Association
ASPECT	Analysis of the Science and Policy for European Control of Tobacco
BaP	Benzo(a)pyrene, a carcinogen
BAT	British American Tobacco
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular Disease
EMA	European Agency for the Evaluation of Medicinal Products
EHN	European Heart Network
ENSP	European Network for Smoking Prevention
FEV1	Forced expiratory volume in 1 second
GMASH	German Medical Association Action Group on Smoking or Health
HIV	Human Immunodeficiency Virus
ITS/FSI	Institute for Tobacco Studies, Stockholm / Research Group for Societal and Information Studies (FSI)
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
NGOs	Non-governmental Organisations
NHS	National Health Service (UK)
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, a metabolite of the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
NRT	Nicotine Replacement Therapy
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-counter
PREPs	Potential Reduced Exposure Products
SACTob	Scientific Advisory Committee on Tobacco Product Regulation
SCoRs	Selective Constituent Reduction
TSNA	Tobacco-Specific Nitrosamine
WHO ICD	World Health Organisation International Classification of Diseases

Protecting smokers: the big challenge for respiratory medicine

Lung cancer and COPD are major problems in respiratory medicine and are caused predominantly by smoking. Preventing smoking and promoting smoking cessation, are therefore important priorities for respiratory clinicians. But what about the smokers who just cannot quit? Are there ways in which we could reduce or prevent the harm caused by continued addiction to nicotine products?

To look into the possibilities of harm reduction the ERS organised a research seminar in October 3 and 4, 2005. Presentations to the meeting covered a range of topics, including the basic mechanisms of nicotine dependence, the toxicity of smoked and non-smoked tobacco and pure nicotine-containing products, and the policy aspects of various harm reduction approaches.

The meeting was conceived and planned by Yves Martinet (chair of the Smoking Prevention Committee), Karl Fagerström and Fiona Godfrey. The main outcome of the meeting was that the ERS needs to follow the harm reduction science carefully and work towards a regulatory system that encompasses all nicotine containing products. The opportunities presented for substantial harm reduction by the wider application of either medicinal nicotine products, or more controversially by smokeless tobacco, are of such potential benefit to patients with respiratory disease that they should not be ignored.

Please read the complete report of the meeting. If you have comments address them to either of us Yves Martinet (y.martinet@chu-nancy.fr), Karl Fagerström (karl.fagerstrom@swipnet.se) or Fiona Godfrey (fiona.godfrey@ersnet.org)

Executive Summary

The objective of the seminar was to evaluate the rationale for and feasibility of harm reduction in tobacco control through nicotine replacement therapy (NRT) and smokeless tobacco.

The role of nicotine

Nicotine exhibits all the principal properties of a drug of dependence but appears to contribute little to the overall disease burden of tobacco use. Improved health outcomes are observed when some non-combustible nicotine delivery devices are used compared with smoking. As a precautionary measure, it is argued that any toxic smoke constituents that could be reduced, should be reduced, but that alone is unlikely to make a significant reduction in harm.

Conditionary reinforcers, such as the irritation of the sensory receptors in the mouth, throat and bronchi of smokers by tobacco smoke, may also be driving smoking behaviour independently of the nicotine that is being delivered, for much of the day. If the role of nicotine in addiction to smoking is central, other pharmacologically active substances present in tobacco may play a significant role. The Swedish example, where more men now use snus than smoke, suggests that it may be easier for smokers to transfer their dependence to another form of tobacco than to pure nicotine.

Lessons from other drug addictions

The experience of harm reduction strategies in relation to other drug addictions, in particular heroin use where this has involved needle sharing programmes and methadone substitution, could be useful for offering help to dependent tobacco smokers. There is an urgent need to develop viable and professionally acceptable treatment regimens that give nicotine addicts the option of being able to continue to use nicotine in the medium to long term whilst avoiding the harmful effects of tobacco toxins.

Relevance to the tobacco industry

Tobacco companies have a real opportunity to compete for commercial advantage by marketing products that are acceptable and substantially less toxic alternatives to cigarettes. The industry is divided about harm reduction and should not be regarded as a homogeneous body on this issue. Genuine and substantial harm reduction initiatives should be encouraged.

A continuum of nicotine delivery

Nicotine products can be categorised along a continuum of risk with combustible products being at the most harmful end.

If a non-combustible nicotine-delivery product could successfully compete with cigarettes and other smoked products for the nicotine maintenance market, this would likely result in a vast reduction in tobacco-caused death and illness, via major reductions in lung cancer and chronic respiratory disorders.

Snus is a concrete example of a reduced harm product that has been demonstrated (from tobacco attributable mortality and oral cancer incidence rates in Sweden) to reduce net harm to health. There is disagreement on the extent to which snus has contributed to declining smoking prevalence in Sweden, and whether its experience could be replicated in other countries.

In order to increase accessibility and reach more smokers, barriers to NRTs use need to be removed and more effective NRTs need to be developed. Smoking reduction is an alternative option for the many smokers who are unwilling or unable to quit but who want to do something to reduce the harm.

A clean recreational addictive nicotine product does not yet exist. Pharmaceutical companies might be persuaded to produce and launch such a product but a social experiment is needed to test its effects. In order for this to happen, the tobacco control community needs to support the idea. The tobacco industry might be better placed to produce such a product, but this would increase the urgency of the need for an appropriate regulatory framework and regulatory authority.

The way forward

Assuming the current mix of tobacco control strategies and continuing declines in smoking prevalence it will take several decades to reduce smoking to zero, and much longer in certain populations. Without new approaches cigarettes will continue to dominate and the tobacco control movement will be failing to respond to the health burden.

Although there is a general acceptance of the need to regulate tobacco products and of the end goal of eliminating death and disease, there is little consensus on whether and how a harm reduction strategy should be developed. In the meantime however the tobacco industry is forging ahead focusing much of its research and development on Potential Reduced Exposure Products (PREPs) with some companies taking a particular interest in smokeless tobacco in response to consumer interest in less risky products.

The key question for product regulation is whether the focus should be on regulating conventional cigarettes, PREPs, smokeless tobacco or NRT, and whether the ultimate goal should be to remove combustible tobacco products from the market. Political interest in reduced ignition propensity cigarettes is growing in Europe as well as interest in reducing the yields of certain toxins from cigarette smoke. However, without a firm goal to end smoking, reduced toxicity cigarettes could be seen as reinforcing the continuance of smoking, instead of a precautionary protective measure for smokers until such time as cigarettes are no longer sold.

A regulatory framework is needed to move the harm reduction strategy forward. Although several organisations have advocated the urgent need for a nicotine and tobacco regulatory authority, it is unlikely that this will be achieved at international level in the near future. It may be more fruitful in the short term to advocate for similar bodies at national level.

Following a discussion a draft consensus statement of the meeting was agreed:

- Harm reduction is desirable as part of a comprehensive tobacco control programme
- Nicotine is not the problem
- Combustible products are the problem
- The status quo should not continue
- Snus is a lot less harmful than cigarettes
- Snus also has potential as a smoking cessation aid
- Lifting the EU ban on snus within a proper regulatory framework needs to be considered
- The playing field for “clean nicotine” should be levelled via deregulation and taxation and pricing measures
- Toxic ingredients should be removed from conventional cigarettes.

It is proposed that an ERS Task Force be set up to focus specifically on harm reduction in Europe.

Full Meeting Notes

Welcome and introduction

On 3 and 4 October 2005 the ERS Smoking Prevention Committee hosted a Research Seminar entitled 'Tobacco Smoking: Harm Reduction Strategies'. Professor Ronald Dahl (former president of the ERS) opened the meeting and welcomed participants. Professor Yves Martinet (Chair of the Smoking Prevention Committee and organiser of the meeting) explained that the objective of the seminar was to evaluate the rationale for and feasibility of harm reduction in tobacco control through nicotine replacement therapy and/or smokeless tobacco. He likened smoking to playing Russian Roulette with a half loaded gun and explained that harm reduction approaches were critically important for those who could not or did not want to give up smoking.

Session I: Cigarettes, nicotine and addiction

The first two speakers in this session outlined the role of nicotine and other components of cigarette smoke in mortality and morbidity: Dr Benowitz, University of California, began by explaining the role of nicotine, followed by Professor Wiebel, German Medical Association Action Group on Smoking or Health (GMASH), who discussed the role of other components of cigarette smoke. The second part of this session focused on the role of nicotine in addiction. Professor David Balfour, University of Dundee Medical School, discussed nicotine addiction in animals and then Professor Karl Fagerström, from the Smokers' Information Centre in Sweden, explained the role of nicotine in addiction to tobacco smoking. The session finished with further discussion.

Presentation I.1: The role of nicotine in cigarette related morbidity - Dr Neal L Benowitz

The aims of Benowitz's presentation were to assess the evidence on the safety of nicotine as a way to promote harm reduction and to discuss progressive reduction of the nicotine content as an approach to reducing the addictiveness of cigarettes.

Understanding the role of nicotine is important as many approaches to harm reduction involve maintaining or satisfying the need for nicotine intake whilst endeavouring to reduce the intake of other noxious substances in cigarette smoke. Such approaches include the use of smoke-free tobacco, novel tobacco products with lower exposures to combustion products, and maintenance with nicotine medications.

In general Benowitz believed that the Lung Health study in the US supported the safety of nicotine regarding respiratory disease. It is not yet clear whether nicotine plays a role in impaired wound healing or in peptic ulcer and gastro-oesophageal reflux. Benowitz therefore focused his talk on the role of nicotine in cardiovascular disease (CVD), cancer and pregnancy.

CVD is one of the main killers and nicotine has the potential to adversely affect some cardiovascular risk factors but there are also other chemicals in tobacco



smoke that may contribute including oxidizing gases (which probably play the most important role), carbon monoxide, polycyclic aromatic hydrocarbons and 1,3 Butadiene. Benowitz summarised by saying that the risk of CVD related to nicotine medications or smokeless tobacco use was unequivocally much less than that of cigarette smoking. This meant that nicotine medications to aid cessation are safe for patients with CVD and that these medications or Swedish type snus appeared to be safe (with respect to CVD) if used for nicotine maintenance in place of smoking. There were still some concerns with nicotine and diabetes.

Regarding cancers, the main areas of concern are that nicotine breakdown generates carcinogenic nitrosamines; that nicotine inhibits apoptosis resulting in possible impairment in killing cancer cells and that nicotine promotes angiogenesis resulting in possible promotion of tumour growth. Benowitz indicated that these concerns were theoretical and that the widespread experience with snus in Sweden indicated that there is little if any increased cancer risk associated with many years' exposure to high levels of nicotine.

The risks of smoking in pregnancy are well known. Concerns about nicotine in pregnancy include its role in low birth weight, sudden infant death and

behavioural and/or cognitive disturbances in children. However, other chemicals in cigarette smoke including carbon monoxide, anabasine and other minor alkaloids, oxidant gases, lead and cadmium are likely to be playing a more important role. The area of greatest concern around nicotine is on the neurological development of the foetus but if the mother is smoking, these risks are already present.

Benowitz discussed two trials which examined the relative risks of nicotine in pregnancy. The first, a randomised controlled trial of nicotine patches for pregnant women, found no effect on cessation rates. However, saliva cotinine levels were similar or lower than those on placebo patch suggesting these women were smoking less and birthweight was significantly higher in the patch group indicating a beneficial effect of the patch therapy.

The second trial by England and colleagues, a population based cohort study in Sweden, examined snus users compared with cigarette smokers and non nicotine users. There was a reduction in birth weight of babies born to mothers who used snus compared to non-users but the reduction was less than that observed with cigarette smokers. Snus also increased the odds of preterm delivery. Preeclampsia was the only risk factor which had a more negative outcome with snus use compared to cigarette smoking and this was likely to be due to the protective effect of carbon monoxide, a vasoconstrictor. Overall, these trials suggest improved outcomes with non-combustive nicotine use in pregnancy compared with smoking.

Recognising the key role of nicotine in addiction, Benowitz concluded by outlining a proposed policy to reduce the nicotine yields of cigarettes over a 10-15 year period whilst simultaneously making pharmaceutical nicotine more widely available. This policy would make cigarettes less addictive, with the potential benefit of making it less likely that adolescents who experiment with cigarettes become addicted adult smokers.

Benowitz's laboratory has conducted a pilot study on the feasibility of reducing the nicotine content of cigarettes. Research cigarettes were manufactured in five prototypes with progressively reduced nicotine content, ranging from 12 down to 1mg; tar yields remained the same. Twenty smokers smoked their own cigarettes and each of these research cigarettes for one week each. The study indicated that smokers can tolerate reductions in nicotine. There was no significant change in cigarette consumption and nicotine intake as indicated by

plasma cotinine declined progressively in proportion to nicotine content. No adverse effects on a number of biomarkers were observed. After 4 weeks some of the smokers reported quitting. Benowitz concluded that regulation of the nicotine content of cigarettes and the use of a nicotine reduction strategy to prevent or reduce the level of nicotine addiction appeared to be safe and feasible, at least in the short term. The study is now being replicated on a larger scale.

Presentation 1.2: The role of the other components of cigarette smoke in cigarette related morbidity - Professor Friedrich J Wiebel

The aim of Wiebel's presentation was to outline the toxicity of components other than nicotine in cigarette smoke. Wiebel believes that it is important to understand the role of these other components, not least because the European Commission will be addressing this under the European product regulation Directive 2001/37/EC.

Cigarette smoke is a complex array of over 4000 chemicals, some of which are reactive (predominantly in the gaseous phase), and others which have to be metabolised to become reactive (predominantly in the particulate phase). The metabolism of these chemicals is tissue-specific and species-specific so an active substance in rats cannot necessarily be assumed to be active in humans. Tobacco smoke constituents also interfere with each others' metabolism in an unpredictable manner. Given this complexity, it is difficult to isolate the impact of single chemicals.

Wiebel discussed the difficulties in assessing intermediate indicators of the harm caused by tobacco smoke. Tobacco smoke constituents play a role in each of the three main stages associated with the pathogenesis of tobacco smoke associated cancer (initiation, promotion and progression) and there are now well developed test systems and guidelines for measuring in vitro genotoxicity, mutagenicity and in vivo carcinogenicity. Although tobacco smoke is well known to contain radicals and cytotoxic constituents which activate proteases and inactivate anti-proteases causing oxidative stress and COPD, in vitro and in vivo tests are needed to assess this damage in the lung. In addition, while tobacco smoke damages the endothelial cells which are responsible for cardiovascular disease, the methods for examining this damage are available for exploratory use but need to be validated.

Wiebel discussed the regulation of toxic smoke constituents. He discussed the pros and cons of three options of regulation:

- the reduction of all toxic constituents in the particulate and gas phases;
- the reduction of single tobacco constituents e.g. carbon monoxide or nitrosamines; or
- the reduction of all constituents in, for example, the particulate phase e.g. tar.

While reducing all toxic constituents in both particulate and gas phases would be certain to reduce the total disease burden, it would be impossible to set limits to the many toxic constituents in these phases. The advantage of approaching constituents singly is that these is readily measurable but the disadvantage is that a significant reduction in total disease burden is unlikely.

Down-regulating all the constituents in the particulate phase would mean reduction of total disease burden but although it would reduce the risk of cancer, it might have little impact on respiratory or CVD risks. The difficulty with this latter approach is the measurement of the change in composition of the tar as one possible outcome is a variation in the chemical composition of tar such as that observed in Eclipse cigarettes.

Overall, Wiebel believed that any constituent that could be reduced should be reduced. However, he was keen that such policies should not produce the illusion of making a significant reduction in harm. They are precautionary measures. He discussed whether it might be preferable to regulate toxic constituents by setting limits to toxic effects. For example it is known that conventional cigarettes have a harmful effect on the lung. An initial goal of regulating constituents could be to reduce this overall burden by 25%. Meaningful regulation would require the setting of gradually decreasing toxic effect limits. Regulation of tobacco products should adhere to norms applied to other consumer products such as food, beverages or cosmetics i.e. the product should cause no, or only minimal, harm.

In summary Wiebel believed that what is needed over the next 30 years is a cigarette that is free of the effects of pyrolysis . To achieve this would require:

- mandatory reduction and elimination of all toxic tobacco smoke constituents;
- setting and gradually lowering limits of adverse effects associated with cancer, respiratory and CVD; and
- determination and perseverance.

Discussion

In the discussion that ensued the implementation of the nicotine reduction strategy proposed by Benowitz was explored further. There was a belief that while such a strategy might help some smokers it would not help those smokers currently affected by smoking-related diseases. Others believed that the drug-seeking behaviour underpinning most smoking would undermine such an approach as smokers would develop new strategies in order to achieve satisfactory doses of nicotine, such as breaking off filters.

Whether the toxicity of cigarettes could be reduced without increased compensatory behaviour was discussed. Some believed the role of taste was important and that consumers could adapt over time to changes in products. Wiebel mentioned that the process of reducing nitrosamines in Swedish snus took about 5 years and that during this time the manufacturers changed the taste of the product so that consumers could get used to it. In addition Benowitz indicated that cigarette manufacturers have in the past altered the products to facilitate compensatory behaviour. The increase in counterfeit cigarettes would also be a complicating factor. Parallels were drawn with the approach to alcohol in the US early in the last century where prohibition was attempted rather than phasing it out. Benowitz believed that it was difficult to make this analogy as most people enjoyed alcohol whereas most smokers want to stop smoking.

One participant highlighted that a preferable strategy would be to move away from combustible nicotine products to smokeless tobacco products which would immediately reduce the health risks caused by nicotine-seeking behaviour. Benowitz believed that taking combustible products off the market would be very difficult politically. Regulating nicotine would be more acceptable and feasible. Others stressed the need to differentiate among smokeless tobacco products, as some had been linked to oral cancer.

There was some debate over the importance of measuring the impact of reductions in tobacco smoke constituents. Whilst tests for carcinogenicity exist, they do not enable fine quantitative analysis of carcinogenic effects. Wiebel believed that a combination of tests could allow a reasonable estimate of the effects of constituent reductions on the carcinogenicity of tobacco smoke.

Presentation 1.3: Nicotine addiction in animals: mechanisms and models - Professor David JK Balfour

The aims of Balfour's presentation were to discuss the ways in which laboratory studies of experimental animals complement clinical studies of human smokers by providing insights into the mechanisms which may be implicated in nicotine and tobacco dependence.

In laboratory experiments, nicotine exhibits all the principal properties of a drug of dependence. It has reinforcing properties that can be measured using an intravenous self-administration paradigm (animals will not inhale smoke but they will press a lever to get intravenous doses). Additionally, abrupt withdrawal of the drug, following a period of continuous chronic administration, results in an abstinence syndrome that can be measured. Balfour explained that in his experience the reinforcing effect is the most important. It is likely that the avoidance of withdrawal also plays a role initially but this does not explain relapse in smokers who have abstained long enough for the principal withdrawal effects to have waned. Balfour felt it reasonable to conclude that addicted smokers may smoke both for the positive reinforcing properties of the nicotine present in tobacco smoke and to prevent the aversive consequences of abstinence. However, other results suggest that the psychobiology underlying addiction to tobacco involves a more complex interaction between the nicotine present in tobacco smoke and the tobacco smoke vehicle by which it is delivered.

The reinforcing and abstinence effects can be explained by the complementary effects of nicotine on the dopamine neurons that project to the core and medial shell of the nucleus accumbens. Biochemical studies have shown that nicotine stimulates dopamine overflow in these two principal subdivisions of the nucleus accumbens, although the effects in the core are only observed in animals treated repeatedly with the drug. The response in the medial shell of the accumbens is thought to mediate the “rewarding” properties of the drug and to facilitate acquisition behaviours, such as a lever-pressing response, which deliver the drug. Many of the neuronal nicotinic receptors, through which nicotine exerts its effects in the brain, are desensitised by sustained exposure to nicotine at concentrations that are commonly found in the plasma of habitual smokers. Thus, for significant periods of the day, it seems likely that the inhalation of nicotine in tobacco smoke does not elicit the increases in dopamine overflow in the nucleus accumbens that are thought central to its ability to cause dependence.

Microdialysis studies with experimental animals have shown that a single injection of nicotine elicits increases in dopamine overflow in the accumbens that persist for 90 to 120 minutes after the injection. Subsequent injections of the drug administered during this period have little or no further effect. Balfour's studies favour the hypothesis that the substantial and sustained increases in dopamine overflow, evoked by nicotine in the accumbal shell, confer rewarding or hedonic properties on behaviours that deliver nicotine such as lever-pressing in rats or smoking in humans. The increases in dopamine overflow in the accumbal core evoked by repeated nicotine doses confer reinforcing effects on conditioned stimuli associated with delivery of the drug.

These effects of nicotine on dopamine overflow are shared by other drugs of dependence and appear to play an essential role in nicotine dependence. However, in self-administration studies with experimental animals, when compared with other drugs of addiction, nicotine is a relatively weak reinforcer. These weak "rewarding" properties do not seem compatible with the hypothesis that the drug alone mediates the powerful addiction to tobacco smoke experienced by many habitual smokers.

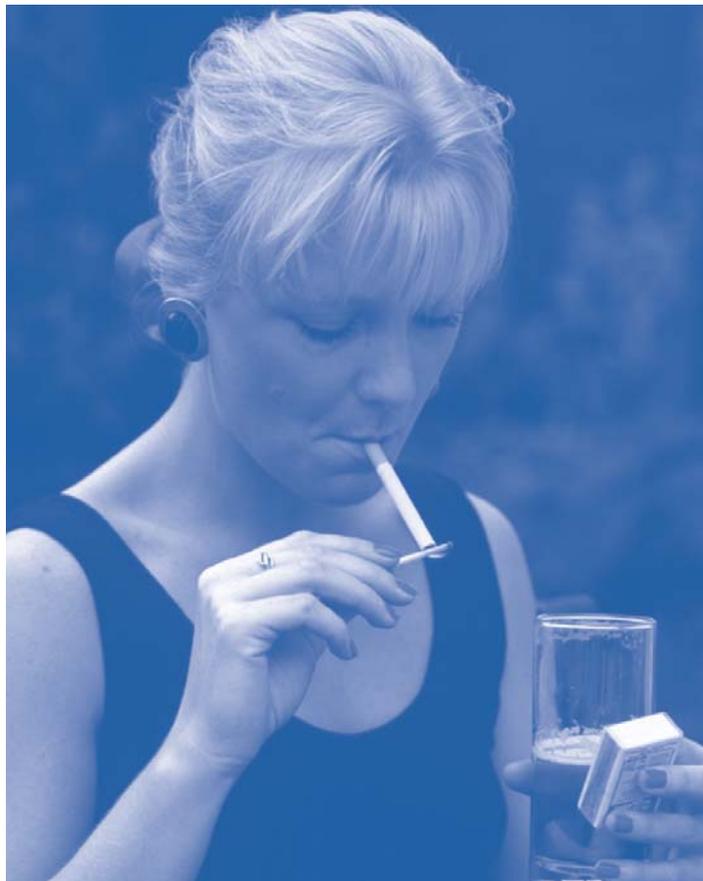
In order to address this apparent inconsistency between the relatively weak reinforcing properties of nicotine alone and the powerful addiction to tobacco smoke, researchers in a number of laboratories have explored the possibility that the tobacco smoke vehicle by which nicotine is commonly delivered may play a more important role in the addiction than was originally appreciated. Experiments suggest that if rats are trained to respond to nicotine which is paired with a conditioned stimulus, such as a light, removal of the stimulus reduces responding by approximately 50 percent. Furthermore, in abstinent animals, the re-establishment of drug-seeking behaviour seems to depend to a significant extent on the co-presentation of the conditioned stimulus. More recent studies have shown that non-contingent injections of nicotine, administered by the experimenter, also enhance responding for a stimulus that has not previously been paired with nicotine. The results suggest that nicotine can enhance the reinforcing properties of stimuli that otherwise have very little salience as reinforcers and that conditioned stimuli play a pivotal role in the expression of nicotine-seeking behaviour that can maintain the behaviour in the absence of nicotine itself.

Balfour commented that this conclusion is fundamental to our understanding of the psychobiology underlying tobacco dependence, because it suggests that

nicotine may also confer powerful reinforcing effects on stimuli, such as the irritation of the sensory receptors in the mouth, throat and bronchi of smokers by the tobacco smoke vehicle that delivers the nicotine. This idea is consistent with evidence that suggests that sensory stimuli within tobacco smoke contribute significantly to tobacco dependence, especially amongst the most highly dependent smokers.

Balfour proposed that although the effects of nicotine on dopamine overflow in the shell and the core of the nucleus accumbens are likely to play pivotal and complementary roles in the development of tobacco dependence, the sensory stimuli evoked by inhaling the tobacco smoke vehicle also play a central role. Thus, the powerful addiction to tobacco smoke reflects the ability of nicotine to confer potent reinforcing properties on sensory stimuli within the tobacco smoke vehicle. These stimuli both enhance the addictive properties of nicotine and maintain the habit during periods of the day when many nicotinic receptors in the brain are desensitised. It is this aspect of the dependence that is inadequately treated by NRT and needs to be addressed if more efficacious treatments are to evolve.

Balfour concluded with his working hypothesis about smoking behaviour as follows. When smokers smoke their first cigarette of the day this releases dopamine that has a hedonic effect in the nucleus accumbens shell. This promotes further nicotine seeking behaviour and smoking. In addition, conditional reinforcers promote Pavlovian responses in the accumbens core which further reinforces the behaviour. When smokers have abstained for a



period (when they are asleep for example) the receptors become resensitised and the addictive cycle starts again. The hypothesis predicts that for much of the day, conditioned reinforcers are driving smoking behaviour independently of the nicotine that is being delivered. This makes the first cigarette of the day much more important than the later ones.

*Presentation 1.4: Tobacco smoking as an addiction -
Professor Karl Olov Fagerström*

The aim of Fagerström's presentation was to discuss the extent to which cigarette smoking is an addiction to nicotine. Fagerström opened by saying that classification systems differ in whether they talk about nicotine dependence or tobacco dependence. WHO ICD refers to tobacco dependence, APA refers to nicotine dependence. Tobacco contains many more pharmacologically active substances in addition to nicotine and historically we have not seen addiction to pure nicotine. In this there may be parallels with the use of coffee, where the addiction is to coffee drinking rather than caffeine on its own. He also queried whether the dopaminergic mesolimbic system, although important for animals, is so important for humans. Fagerström commented that nicotine affects two structures, the cortex and the limbic system. These dual effects mirror the reasons smokers give for smoking, for stimulation and tranquillisation. He explained that the fact that nicotine has two major impacts may explain why it is the world's second most used drug after caffeine.

Fagerström explained that upregulation of nicotine receptors occurs with continued smoking, and tolerance develops. If nicotine is injected and brain patterns observed, more nicotine is found in the brain of a smoker than a non-smoker. When a smoker decides to give up nicotine, the body no longer gets the nicotine that it expects. As a result the body system is very sensitive to any nicotine intake, similar to the response to the first cigarette of the day. One cigarette can stimulate the system and this is very different from later cigarettes, which is why time to first cigarette is a very good indicator of dependence. There are therefore differences between short term and long term tolerance. Short term is related to the status of a receptor but long term tolerance is related to the number of receptors (the degree of up-regulation). It is not known whether this eventually returns to normal when someone stops smoking.

Withdrawal can occur after a few hours and usually peaks within two weeks. Only two withdrawal symptoms predict relapse with some reliability: craving and dysphoria. Fagerström listed the WHO ICD-10 criteria for tobacco dependence. He indicated that smoking is very difficult to give up as only 2-3% smokers succeed in the long term and three-quarters of those addicted to other drugs find it as least as difficult to give up smoking as they do to give up their other drugs.

Fagerström postulated that there are different types of smokers, in particular “trough maintainers” or negative reinforcer smokers, and “peak seekers” or positive reinforcement smokers. Trough maintainers smoke to avoid withdrawal: they seek a certain nicotine level that they reach after their first few cigarettes and maintain this level, which remains below a toxic level. Peak seekers smoke more for positive reinforcement and therefore smoke to achieve surges in nicotine, making them likely to smoke fewer cigarettes than trough maintainers. A key issue would appear to be whether or not withdrawal effects are different.

Fagerström questioned whether the role of nicotine in addiction to smoking had been over-emphasised. He argued that there has been no epidemic of pure nicotine use and no misuse of NRT. As Balfour had said, nicotine was not a strong reinforcer in animals. The evidence from human self-administration studies using intravenous nicotine was not very convincing although it is not clear how much can be generalised from these studies. Studies comparing denicotinised cigarettes with NRT products found that the former were liked more than the latter and that less harmful cigarette substitutes such as Premier, Eclipse and Accord are not liked by smokers.

Fagerström asked why smoking could be more difficult to stop than other drugs. He postulated one reason to be the presence of other pharmacologically active substances in tobacco smoke such as carbon monoxide; naphthoquinone, acetaldehyde, benzene, and styrene. Fagerström concluded that the Swedish experience in which more Swedish men now use snus (23%) than smoke (15%) is important. He argued that pure nicotine is not as addictive as tobacco and that cigarette smoking is a very addictive form of tobacco use. The implications is that it will be easier for smokers to transfer their dependence to another form of tobacco than it will be to pure nicotine.

Discussion

The main discussion focused around the role of nicotine in human addiction to smoking and whether evidence from animal studies is transferable to humans. One French study has shown that rats will self-administer nicotine faster and stronger under the influence of a nicotine inhibitor but this work has not been replicated due to a shortage of research resources. One difference between rats and human smokers is that new tobacco users take a few years to become addicted whereas rats learn to self-administer nicotine over a much shorter time period. Balfour commented that the rats may not necessarily be dependent and that there was also evidence that some young people became dependent on cigarette smoking very early on in their smoking careers. Defining dependence was thought to be critical, for example should daily smoking be a criterion of dependence? Do definitions of dependence distinguish between dependence on nicotine or dependence on other constituents or attributes of smoking?

The changing pattern of smoking in the US was also noted. In some states there had been a phenomenal increase in light smoking (in California about 25%). Although light smokers do not exhibit the same dependence and withdrawal patterns as heavier smokers, they do not quit. There may be parallels with adolescent smokers who exhibit some dependency even at much lower levels of cigarette consumption. There do appear to be smokers whose smoking is very situation-specific, e.g. smokers who only smoke in the evenings. The complexity of smoking was also demonstrated by the high prevalence of smoking found in certain psychiatric populations where smoking may be helping in some way to alleviate psychiatric symptoms or states. Clearly current theories of dependency are inadequate to explain these varying smoking patterns. Some smokers do not qualify as dependent using the usual criteria but nevertheless exhibit signs of dependence on their smoking.

The role of sensory cues was also discussed. If some smokers are smoking mainly for sensory cues, why do they regulate their nicotine levels so tightly during the day? Is it possible that although some nicotine receptors are desensitised, these are only the receptors that are mediated by dopamine. Other receptors could be acting differently. Some evidence of this has been found using brain imaging, showing that nicotine will continue to cause responses in some areas of the brain where tolerance does not appear to develop. It does appear to be the case that not all receptors desensitise at same rate.

The impact of the type of tobacco on dependence was also discussed. Fagerström commented that the cigarette was an ideal vehicle to create dependence. Pipes and cigars if not inhaled were likely to be less physically dependence-forming. Fagerström had calculated nicotine intake in Sweden from various forms of tobacco use. Snus users take in a little more nicotine than cigarette smokers but are equally dependent on their tobacco use. Whether some people self-selected to different types of tobacco was also discussed. Although snus use in women is currently only 4%, Fagerström believed that snus use could also become popular among women.

Given the role of sensory cues and Pavlovian reactions, the role of aversive therapy was discussed. Fagerström commented that rapid smoking had been tried and although it deterred smoking in the short term the effects usually wore off after a few days, requiring further aversive therapy. Electro-convulsive therapy had also been tried but had not been shown to be effective.

Session II: Scientific evidence backing harm reduction

In the second session three speakers focused on different aspects of the scientific evidence backing harm reduction. First, Dr Laurence Gruer, NHS Health Scotland, examined the experience of harm reduction from other drug addictions, followed by Professor David Sweanor, University of Ottawa, who looked at the potential for harm reduction within the tobacco industry drawing on experience from non-health fields. Finally Dr Jonathan Foulds, University of Medicine and Dentistry of New Jersey, examined one specific category of tobacco, low-nitrosamine smokeless tobacco and its potential as a harm reduction product compared with cigarettes.

Presentation 2.1: What is harm reduction? Principles and observations from outside tobacco smoking. Dr Laurence Gruer

The aims of Gruer's presentation were to explain the concept of harm reduction and discuss whether the experience from the illicit drugs field could be transferred to tobacco use. Gruer began by stating that the concept of harm reduction in the field of substance use is based on the idea that addiction, once established, is a chronic condition with attempts at recovery often ending in failure. The alternative is to help the addict avoid the worst consequences of the condition, by providing a pure form of the drug, administered in a safe and hygienic manner.

This was the thinking behind the conclusions of the UK's Rolleston Committee which considered the problem of heroin addiction in the 1920s. The Committee's report, published in 1926, provided a legal basis for doctors in the UK to prescribe morphine or heroin to the small number of people who were addicted to opium, morphine and heroin. This laid the foundation for what became known as the British system, in which addicts were treated as patients, as distinct from the American approach where they were regarded as criminals. The British system was manageable as long as there were relatively few addicts. Gruer stated that it was debatable whether the British system was responsible for restricting the number of addicts but it worked reasonably well until the 1970s.

Two American researchers, Dole and Nyswander, attempted to find a way of stabilising heroin addiction by using synthetic opiates. They found that oral

methadone in the right dose could stabilise a large proportion of addicts, enabling them to pursue a relatively normal life while still addicted. This led to the establishment of a system of tightly controlled methadone clinics in the US and to its use in some parts of Europe in the 1970s.

Gruer contended that the modern concept of harm reduction in relation to substance use came into being in the 1980s. It followed recognition that some of the indirect consequences of drug use were worse than those of the drug itself. The most important of these was HIV infection, spread between drug injectors by sharing used needles and syringes. Drug injectors infected with HIV could also transmit HIV to non-injectors via sexual intercourse and an infected woman could transmit it to her baby during pregnancy, birth or breast feeding.

The Netherlands became the pioneers in this respect with the development of a needle exchange programme in Amsterdam in the early 1980s, initially to help prevent the spread of Hepatitis B. Other countries reacted with amazement, believing that giving addicts needles would only encourage them. However, when it was discovered that HIV was also spreading by needle and syringe sharing, attitudes changed, as this was a fatal and incurable disease which threatened the whole of society.

It was discovered in late 1985 that HIV was spreading rapidly among drug injectors in Edinburgh. The British government reacted swiftly, setting up an expert committee to advise on what should be done. In its 1988 report on AIDS and Drug Misuse, the UK Advisory Council on the Misuse of Drugs famously stated that 'the threat of HIV is a greater threat to public and individual health than drug misuse'. This paved the way for a change in thinking. Whilst it continued to be accepted that people addicted to heroin would be better off if they stopped using it altogether, it was now recognised that for the great majority of heroin addicts, ceasing to take drugs was not a realistic short term aim. Instead the priority was staying alive and avoiding the worse consequences of their addiction. This idea was to have a major effect on practical policies. Harm reduction in this area became government policy. Needle exchange pilots began in the UK in 1987, from which an extensive government-funded network soon developed. It is believed that this played a major part in cutting short the epidemic of HIV in the UK.

Gruer outlined a hierarchy of goals for harm reduction in heroin:

- Stop sharing (needle exchange)
- Stop injecting
- Reduce consumption
- Stop taking.



The weakness of needle exchanges is that clients remain at risk from drug injecting, for example due to overdose or infections due to contaminated drugs. Another factor is the tendency of many injectors to commit frequent crimes such as shop-lifting, burglary and prostitution to finance their addiction, leading to arrest and imprisonment. It therefore makes sense to help the drug

user to avoid using street drugs altogether and ideally to stop injecting even if they continue to be addicted to opiates. Daily oral methadone offers that possibility, but supervision and support are necessary to ensure the user takes the right dose.

Over the past 15 years, there has been a massive increase in the prescription of methadone to heroin addicts, with a seven-fold increase in patients in Europe between 1993 and 2000. Methadone has also become one of the most extensively researched therapeutic drugs. Studies have consistently shown it achieves large reductions in injections, HIV transmission, mortality rates and crime. Long term use is compatible with holding down a job, driving a car and leading a fairly normal life. It can however result in fatal respiratory depression if too much is taken and is itself highly addictive. Most opiate users do not enjoy taking methadone. They miss the euphoric effect of heroin and some people even miss the act of injecting. Consequently, there has been a search for safer alternatives. Buprenorphine, another synthetic opiate (popular in France), and a slow release morphine have both proved to be equally successful as methadone. The Swiss population voted a few years ago to allow heroin itself to be prescribed to addicts after it was shown that doing so could stabilise the behaviour of the small proportion that could not otherwise control their addiction.

In contrast to its success with opiates, the harm reduction model has proved less successful with other common drugs of dependence such as alcohol, cocaine or

cannabis. The problem with each of these is that continuing use of the drug itself typically perpetuates physical and mental health problems caused by the drug and there is no suitable substitute analogous to methadone for these drugs.

Gruer believed that the experience of harm reduction and heroin could however be useful for offering help to dependent tobacco smokers. He believed that both heroin and nicotine are highly addictive drugs with a short duration of action, yet their use is compatible with physical and mental well being (nicotine more so than heroin) and it is the delivery system causing most of the harm (again with nicotine more so than heroin). Helping the continuing addicted smoker to avoid the thousands of chemicals in tobacco would seem on the face of it to be just as rational as helping heroin users to avoid injecting.

Gruer pointed out the differences in approach to treatment of nicotine and heroin addiction. With nicotine, the focus is on abstinence, but this approach largely ignores the majority of highly dependent smokers who cannot stop and for whom short term NRT has failed. Paradoxically it is these smokers who are most likely to develop serious tobacco related disease due to the duration and intensity of their smoking. With heroin, the harm reduction approach predominates, with the seriously addicted being prioritized. These differences in approach are perhaps understandable from a political point of view as the perceived harm to society is greater from heroin use.

Gruer believed that this situation is unsatisfactory and that there is an urgent need to develop therapeutic programmes based on long term maintenance with nicotine or an appropriate nicotine substitute. This would require a new acceptance in policy and practice that abstinence is not always possible and that the severely addicted in particular need help. He suggested that there is a need to develop this approach also for dependent smokers during pregnancy, given the accumulating evidence on the serious short, medium and long term health effects of maternal smoking during pregnancy on the child. Among heroin users, methadone is widely used in pregnancy with improved outcomes for baby and mother, and buprenorphine is also being used with good results. A recent randomised controlled study in Glasgow found that intensive motivational interviewing did not result in an increase in the quit rate of pregnant smokers, with the overall quit rate in both intervention and control groups being only 5%. Although further research is needed to establish the relative safety of NRT during pregnancy, he believed that use of nicotine alone must surely be less harmful than continued smoking.

Gruer concluded by stating that harm reduction had a long tradition in opiate addiction and was recognised as a rational and effective approach to helping chronic opiate addicts avoid the most damaging consequences of their behaviour. He believed that there are important parallels between heroin and nicotine addiction and that there is an urgent need to develop viable and professionally acceptable treatment regimens that give nicotine addicts the option of being able to continue to use nicotine in the medium to long term whilst avoiding the harmful effects of tobacco toxins.

Discussion

A question was raised whether smoking in pregnancy affected later uptake of smoking in adolescence, similar to the experience with heroin. Gruer commented that a systematic review has examined whether any drug use in pregnancy predisposes to use of that drug later in life. Although it is difficult to distinguish between drug use in pregnancy and drug use later in the mother's life, at least one study seems to support the hypothesis in smoking and pregnancy. This effect is also consistent with the biological or theoretical effect. The extent to which nicotine would have this effect is as yet unclear. Some people will continue to have ethical and moral objections to drug use in pregnancy, and this explains why some will not advocate the use of NRT in pregnancy even if it means that a pregnant woman continues to smoke.

It was noted that a key barrier to getting people off drugs is social deprivation. Gruer commented that services can be designed with this in mind to suit users, for example by making them accessible at appropriate times for the local community, and high compliance can result. One example is making condoms much more widely available and success has also been achieved with drug users in deprived areas with methadone provided through pharmacists. Success has been achieved with quite complex treatment protocols. However, it is difficult to understand fully the circumstances in which very deprived people live and it is therefore hard to help people off drugs. Tobacco comes quite a long way down their list of priorities. People often need to deal with the biggest threats first and help to manage their addiction with a process compatible with normal life.

Although in theory methadone and heroin seem like an appropriate parallel to nicotine and cigarettes, the NRT products on the market do not have high enough doses of nicotine. Gruer agreed that the situation with methadone was

fortuitous, but he believed that given the predictions of the size of the tobacco pandemic, pharmaceutical companies should be putting more resources into finding better nicotine delivery devices.

One problem noted with this was the cost. The cost of methadone maintenance per heroin user is about £1500 per year. Given the higher prevalence of tobacco use, such harm reduction approaches might be cost prohibitive for governments but nevertheless they are relatively cheap treatments, well below those for most medical conditions. However, governments are often keener to act to intervene with heroin users because of associated crime and the potential to reduce other damage to communities caused by such drug use. This may not be the case with smoking.

*Presentation 2.2: 'Less harmful' cigarettes and new cigarette substitutes.
Professor David Swenor*

The aims of Swenor's presentation were to explain the reasons why many tobacco companies were now introducing novel products to the market, to describe these products and to discuss their public health implications.

Swenor commented that traditionally anti-tobacco initiatives have concentrated on reducing the death, injury and disease caused by the use of tobacco products by pursuing strategies aimed at preventing smoking initiation, protecting non-smokers from environmental tobacco smoke and promoting complete cessation of any form of nicotine. Swenor argued that logically there was a necessary fourth leg of any tobacco control strategy, the pursuit of measures that reduce risks for continuing users. With current consumption trends and growing awareness of the nature of both addiction and self-medication amongst the world's 1.25 billion cigarette smokers, he argued that it is inconceivable that a nicotine-free world could be achieved anytime soon. At the same time, he argued that there was abundant evidence that the public health catastrophe associated with tobacco use is primarily due to the means of nicotine delivery rather than inherent risks of nicotine use.

Swenor acknowledged that in the harm reduction field, heroin provides a fascinating example. However, he felt there is a significant difference between heroin and tobacco, because tobacco is a licit business. The tobacco companies are therefore unlikely to be using the lessons from heroin, but

would seek to make analogies with other licit businesses. He gave the example of Philip Morris which a few years ago had reached a critical juncture in recognising that the company might not be permitted to exist in the future. The company recognised that it was inevitable that their products will be regulated more in the future and developed their future business strategy around this.

Sweanor commented that the main motivation driving the tobacco industry is, similar to other public companies, their legal obligation to protect the interests of shareholders. Litigation and regulation are key drivers to change. Tobacco is a huge business, roughly similar in size to the entire pharmaceutical business. In many countries, the tobacco industry is run by an oligarchy. However, he believed that their market place is changing, as with many other industries, and that there is a growing recognition within tobacco companies that the market for nicotine was becoming a very different entity. He argued that as with the transitions that fundamentally changed the pharmaceutical industry, the food processing business, car manufacturing and myriad other businesses, this transformation will be based on advancing scientific knowledge, marketplace competition and regulatory changes. Harm reduction is common in other non-health fields and Sweanor cited the example of automobiles: more people now drive and there are more cars on the road, but death rates are much lower. Cars have been made safer and motorists have changed their behaviour and wear seatbelts. Analogies can also be drawn with cyclists who now wear bicycle helmets.

Each tobacco company now has the opportunity to attain a great commercial advantage by succeeding at marketing a product that will be seen as an acceptable less toxic alternative to cigarettes, and each company faces the threat that it will be beaten by a competitor. Sweden presents a good example of people opting to use other tobacco products indicating that the demand for nicotine is not always for the most harmful product, cigarettes.

Within the constraints imposed by regulation and risks of litigation many tobacco companies are now introducing a range of novel products. Like many other products on the market, there is a continuum of risk associated with nicotine use. At one end are cigarettes, very risky products, with most of the damage coming from the smoke. Within the range of categories of reduced harm products, modified cigarettes are still at the very risky end whereas smokeless tobacco products were further down towards the less harmful end

of the continuum with nicotine replacement therapy products at the least risky end of the continuum. Tobacco companies are now producing products in all these categories.

- 1) **Cigarettes with apparent changes in the presence or level of some toxins.** These include efforts to reduce nitrosamines and other known cigarette toxins.
- 2) **Cigarettes with fundamental changes to a number of toxins.** This is a far more complicated approach as it is aimed at reduction in aggregate risk rather than simply reducing the presence of a small number of toxins found in the 4,000+ chemicals found in tobacco smoke. This approach is currently best exemplified by the SCoR project at Philip Morris.
- 3) **Cigarettes designed to heat rather than burn tobacco.** This approach goes back to the 1980s at RJ Reynolds (now Reynolds American) and is now pursued by other companies as well. It is based on a recognition that the harm caused by smoking is overwhelmingly as a result of smoke inhalation, so significant reductions in inhaled smoke should benefit the health of those who would otherwise be smoking.
- 4) **Replacing cigarettes with smokeless tobacco.** Since smokeless tobacco has only a tiny proportion of the risks associated with cigarette smoking smokeless tobacco companies have been engaged in various efforts to promote the relative risk of smokeless tobacco compared to cigarettes.
- 5) **Novel smokeless tobacco products.** There have been several new forms of smokeless tobacco brought on to test markets, and considerable interest in using the technology behind Swedish snus. These products have much lower levels of tobacco-specific nitrosamines and are usually designed to be more consumer-friendly than traditional smokeless tobacco products.
- 6) **Medicinal and quasi-medicinal nicotine products.** More consumers are able to access medicinal nicotine products over-the-counter and able to engage in 'off label' use, such as long term maintenance of a tobacco-free lifestyle. In addition the line between recreational and therapeutic nicotine products continues to blur due to new products and to greater understanding of optimum usage time for different people.

These new products are challenging a lot of the underlying assumptions in tobacco control. Among other things, these products, combined with increases in scientific understanding about tobacco/nicotine use, are making an abstinence-only approach to nicotine use increasingly indefensible. These products are also showing the market forces that come into play, and could potentially be used to the advantage of public health, in a global cigarette market of roughly US\$400 billion a year. In addition this proliferation of products probably gives the strongest possible basis for effective regulation of all tobacco products by allowing for product differentiation based on relative risks to users.

Nevertheless, it is important for those in public health to be cautious and see where gains could be greatest. Sweanor argued that as it will take at least 20 years to see the health impact of their changing products, this is a long term strategy for companies that will keep them in business in the short term. Sweanor feared that the largest reduction in mortality and morbidity from changes to combustion based delivery products would be 20%, and that this is not necessarily a good strategy for public health.

Sweanor argued that in other markets, new products and market disruption force change across all companies and he strongly believes that this will apply in tobacco. These new products should be played to the advantage of future public health.

Discussion

In the discussion that ensued, a comment was made that although understanding the industry diagnosed the problem well, it didn't necessarily make it easier to solve the problem. Sweanor called for a pragmatic approach to solving the problem involving harm reduction, as the abstinence-only policy was not going to work. A harm reduction policy was needed and had to be directed by governments before the industry owned it. He believed that a harm reduction approach should be relatively easy because nicotine was not the harmful substance, and the companies could adapt according to scientific developments..

Sweanor argued that the goal of tobacco companies is not to sell products but to be sustainable to shareholders. Companies are divided about harm reduction, they are not a homogeneous body, having on the one side those who

are happy to continue marketing and selling cigarettes and on the other side, reformers who are interested in finding less harmful nicotine delivery systems. The tobacco industry is diversifying. Concerns were raised about waterpipe use which some believe is a growing market, but there is as yet little evidence of its comparative harm compared with cigarettes and the extent to which the tobacco industry is driving this product category. Sweanor believed however, that as with other products, product change could be positive, and disruptive technology is an ally rather than an enemy. As the market develops and new products start to emerge, science must differentiate between the products' respective effects.

Presentation 2.3: Smokeless tobacco as one route towards tobacco harm reduction. Professor Jonathan Foulds

Foulds began by defining tobacco harm reduction as 'an intervention (policy, advice treatment etc) designed to reduce the harm to health from tobacco, without requiring complete abstinence from all tobacco constituents (including nicotine) within six months'. He believed that harm reduction strategies need to be considered in tobacco control because smoking rates are declining very slowly at best in most countries of the world and the harm to health remains enormous.

Foulds also maintained that many people are not ready to give up nicotine use and currently the most toxic form of nicotine delivery (cigarettes) is perceived as their only option. Less than 10% of daily smokers are preparing to quit in the next month, and around 60% are not planning to try in the next 6 months. These figures remained stable throughout the 1990s. He argued that cigarettes (the most harmful nicotine delivery products) have a near monopoly in the nicotine maintenance market in most countries and that we should be allowing or encouraging markedly less harmful forms of nicotine delivery to compete with cigarettes.

Foulds defined nicotine maintenance as the long term (more than 6 months) use of a nicotine delivery product that is markedly less harmful to health than a traditional cigarette. He outlined that 'markedly less harmful' would not include products that involved the inhalation of combustion products, because combustion created an unavoidably toxic cocktail. In other words, products such as Omni, Eclipse, Advance etc would not be 'markedly less harmful'. Markedly

less harmful products would be nicotine delivery products that do not require inhalation of combustion products or delivery concentrations of toxic chemicals likely to cause disease, such as NRT products or potentially low-nitrosamine smokeless tobacco products (e.g. Swedish snus, Ariva, and Interval).

Foulds contended that if a non-combustion nicotine-delivery product could successfully compete with cigarettes and other smoked products for the nicotine maintenance market, this would be likely to result in a vast reduction in tobacco-caused death and illness, via major reductions in lung cancer and chronic respiratory disorders. He argued that it is important to consider smokeless products as more tobacco companies are now producing them. It is also important to get the right policies in place in order to avoid repeating the 'lights' fiasco. Light cigarettes were a massive fraud on the public and have caused millions of people to continue smoking who may otherwise have quit.

Turning specifically to smokeless tobacco, Foulds outlined the regulatory situation in Europe. Oral snuff is banned across the European Union but other forms of smokeless tobacco are allowed. In the UK, chewing tobacco is popular within some cultures, but little is known about its content and health impact.

Foulds described Swedish snus as moist fine-ground oral tobacco, predominantly from air-cured dark tobacco. It is manufactured by a pasteurisation-like heating process, without any fermentation as used in most manufacturing procedures for American snuff. The manufacturers claim tobacco-specific nitrosamine content (TSNA, proven carcinogens) to be less than 5 mg/kg and BaP content less than 10 microgram per kilogram. He contrasted this with the TSNA content of American snuff which has been shown to be between 16 and 130 mg per kilogram.

The main characteristics of snus are that it is stored in refrigerators which reduces TSNA formation and it is manufactured to the manufacturers' Gothiatek Quality Standard for toxin content. The product can be 'loose' or 'portion-packed' (like tea-bags) and has a high pH (7.8-8.5) which facilitates nicotine absorption. This low TSNA content has been demonstrated to result in low mutagenic activity in the body of smokeless users (similar to non users) compared with smokers.

Research has demonstrated that smokeless tobacco products are not homogeneous and vary enormously. The American Health Foundation in 2001 analysed various smokeless tobacco products and found a very wide range of TSNA levels across the products, the lowest levels being found in the products manufactured by Swedish Match. This research also demonstrated that TSNA levels increased in the US products over a period of six months when left out at room temperature, but not in the products manufactured by Swedish Match, which suggests that refrigeration may not be necessary. McNeill and colleagues analysed 7 brands of smokeless tobacco commonly used in the UK (including a tooth cleaning powder) and 4 international brands of smokeless tobacco. The products were purchased using the same criteria and tested for nicotine content, certain toxins and carcinogens. Ten of the 11 brands tested had detectable levels of TSNA, and the levels of TSNA varied 130-fold. The highest level was found in two products purchased in England. One US highly manufactured smokeless tobacco product had non-detectable levels of TSNA.

Foulds argued that snus is not harmless. Snus causes nicotine dependence (similar to cigarettes), it causes some reversible and some permanent oral lesions but not oral, gastric or head/neck cancer. It may slightly increase some cardiovascular risks but the evidence is currently unclear on this. He believed that snus would almost certainly be harmful to the foetus when used during pregnancy, though less so than cigarettes, and that there were no effects on respiratory disease or lung cancer.

Foulds then examined whether the use of snus had an influence on smoking patterns in Sweden. A graph of sales of snus and cigarettes in Sweden from 1916 to 2002 showed that snus and cigarette sales moved in opposite directions but this does not equate with cause and effect. He therefore looked at tobacco consumption in Swedish adults (15 years and over) over time. In Sweden, snus is used primarily by men. The most recent prevalence data from Ramstrom 2003 based on ITS/FSI data 2001-2, show that daily smoking among males has fallen to 15% with a 20% prevalence of daily snus use. Female daily smoking prevalence is 19% alongside a 2% daily snus use prevalence. Both male and female smoking prevalence has been decreasing over the years which Foulds attributed to excellent tobacco control initiatives. However, Foulds argued that Sweden is the only country in the world in which male smoking prevalence has reduced significantly faster than female smoking such that male smoking rates are now markedly lower than female smoking rates. He argued that this is partly due to snus use in men.

Foulds commented that youth daily smoking prevalence has been very stable over the past 20 years, at around 11% for boys and 16% for girls at age 16 in Sweden. He believed that there is no evidence of snus acting as a gateway drug to smoking in Sweden, drawing on data from Kozlowski and colleagues that concluded that at least 83% of snus use did not lead to smoking. Indeed he believed that most of the available evidence suggested the gateway was acting in the opposite direction i.e. from smoking to snus use.

Sweden has the lowest total tobacco-attributable mortality in men across Europe, and one of the lowest oral cancer incidence rates per 100,000 (age standardised to world population) in Northern and Western Europe. As male tobacco use (smokeless and cigarettes combined) is higher than in most countries, if snus were a significant factor in causing other diseases, then total tobacco attributable mortality would be higher, not lower.

Foulds reported data from Gilljam and Galanti which found that 29% of male ex-smokers had used snus to quit smoking. Data from Rodu and colleagues from MONICA study participants supported this finding. They examined changes in tobacco use over time and found that reductions in smoking occurred alongside increased snus use. Ramstrom and Foulds examined 895 Swedish smokers who reported using a specific aid (e.g. NRT, Zyban, snus) at their latest quit attempt and found that around 26% of the male ex-smokers used snus to quit. More men used snus to quit smoking than used all other NRTs combined, but notably a significant number of women had also used snus in their last quit attempt. Among those who used snus as an aid in their last quit attempt, the success rates were higher (around 60%) in those who used snus, than in those using NRT (around 35%).

Foulds postulated that the advantages of snus for smoking cessation are twofold. First, it delivers a higher dose of nicotine than NRT products (the speed and dose of nicotine delivery with snus is between that of cigarettes and NRT). Secondly, it is typical for the user to continue using snus chronically rather than quitting use after a few weeks or months. In other words, snus is used as a nicotine maintenance product rather than a cessation product. Around three-quarters of the people in their study were still using snus at the time the data was collected, compared with only 12% of those who used NRT still using NRT at data collection.

In the light of all the evidence presented, Foulds questioned the rationale for the EU banning snus in a marketplace dominated by a far more harmful addictive product that is freely available. He also argued that is irrational to exaggerate the dangers of smokeless products as has been done in the US, relative to cigarettes.

Foulds made the following concluding points:

- Snus delivers much smaller quantities of toxins than smoked tobacco, and smaller quantities than most other smokeless tobacco products.
- Snus is not harmless (particularly in pregnancy), but is markedly less harmful to health than smoked tobacco.
- Snus is almost as addictive as cigarettes, enabling significant proportions of male smokers to transfer from smoking to smokeless.
- Swedish men who have quit smoking using snus have enjoyed health gain.

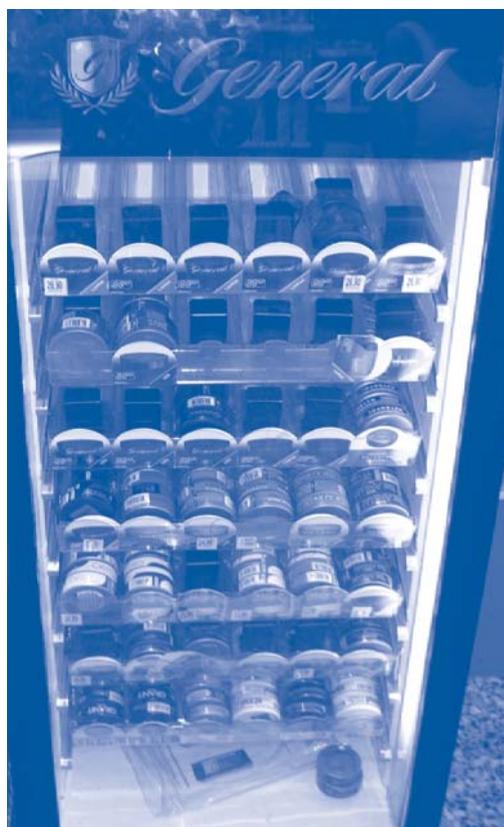
The improvement in smoking prevalence and health status has been greater in Swedish men than in Swedish women, or men in other countries. At least part of this is attributable to widespread snus availability, marketing and use by men in Sweden. Snus is therefore a concrete example of a reduced harm product that has been demonstrated to reduce net harm to health. It is possible (though not certain) that other similar products (e.g. NRT, Ariva) could have a similar beneficial effect, so long as they could compete with cigarettes on nicotine delivery, marketing, price etc.

Foulds believed that marketing of smokeless products is a key factor. He believed that in the US, the potential benefits of an evolving smokeless tobacco market are being constrained by the fact that the public health community in the US has not made a clear statement that the products are less harmful. He believed that the ERS needs to consider carefully what should be communicated about smokeless tobacco products. In Sweden, Osterdahl and colleagues have looked at nitrosamine levels in smokeless tobacco products produced by other manufacturers beyond those of Swedish Match and found they have similarly low levels to snus. He therefore believed that snus is not a highly technical product but could easily be produced by other manufacturers. Several studies that have found significant health risks of smokeless tobacco use (e.g. the recent Boffetta and colleagues' paper) have important errors, and he believed that it is incumbent on the public health community to get the science right in this critically important area of work.

Discussion

In the discussion that ensued, there was disagreement about the contribution snus had made to Sweden's favourably low smoking rates. Some believed that the availability of snus had only made a minor contribution to the reduction in smoking, and that it was unclear whether those smokers who used snus to quit would have done so in the absence of snus. Also there was a concern that concurrent smoking and snus use was more common than people quitting by using snus. Foulds responded that anything that reduces smoking was a good thing and tobacco control needs to use all the tools at its disposal. For this reason, he felt this is an important issue for the ERS to act upon. If nothing is done, thousands will continue to die of lung cancer and respiratory diseases. If only half of these could be saved, that would be a major public health benefit.

Questions were raised on the reasons for the rapid rise in snus use in Sweden, and whether this experience was unique or replicable. Fagerström believed that snus use was common in Sweden because the country was not involved in the world wars (which were associated with sharp rises in cigarette smoking). There was some snus use at the end of the 1960s and 70s, then the socialist movement developed and people emulated the workers, some of whom were using snus. At the same time, the tobacco companies highlighted that there were other ways to enjoy nicotine without annoying bystanders. Health messages were not used, as snus use was deemed to be at least as harmful as cigarette smoking at the time. Fagerström also argued that another important factor in Sweden was that snus use was not confined to certain social



classes, it was a mainstream phenomenon and even many physicians used snus. Although snus is not attractive to women, this is thought to be due to its traditional presentation as a loose tobacco product, but with newer manufactured smokeless tablets, this might change.

Others argued that heavy marketing was another important factor in the expansion of snus use, as was the fact that it was cheap and very accessible. NRT is only sold in government monopoly pharmacies. Sweanor reiterated the role of price, as economic influences are paramount. The government owned the monopoly of snus and made a policy that snus would be cheaper than cigarettes. He argued that the environment is very important. Swedish Match have recently withdrawn their products from India in the face of local opposition.

Some argued that public health messages are important. The US market is markedly different from Sweden as many leading cancer and health agencies have publicly stated in the US that smokeless tobacco is at least as dangerous as smoking cigarettes. Others argued that rescinding the EU ban on smokeless would mean that tobacco companies would market their products to adolescents and cited some evidence of this in the US.

Foulds argued that in Sweden there had been a tendency to look at the nicotine market in a unique way, with a belief that nicotine could be delivered in a less harmful way. Indeed NRT was invented by Swedes. He also believes that NRT products could, with the right marketing and pricing structure, have a similar effect to snus.

In relation to the EU, Foulds felt that the ban should be lifted and a standard introduced, such as the Gothiatek standard. Ideally there should be a simultaneous liberalisation of restrictions on NRT use, so that consumers may purchase NRT on the same basis as snus or cigarettes (i.e. OTC anywhere for as long as the consumer wants to use it, in whatever dose/quantity the consumer desires). Public health campaigns should emphasise that tobacco smoke is extremely dangerous, smokeless is tobacco much less harmful and NRT has minimal risks, thereby allowing consumers to make their choice based on accurate information. He doubted it would have a huge initial effect but believed that smokers deserve to be given a choice about which nicotine products they use. He also believed that in this scenario more consideration should be given to examining tobacco manufacturers' legal liability for selling extremely harmful products when they could relatively easily switch to selling markedly less harmful forms of tobacco (e.g. snus).

Session III: Break out sessions

This session consisted of three break-out sessions examining different aspects of harm reduction: Group 1, led by Professor Lynn Kozlowski, examined public health research needed in the harm reduction field; Group 2, led by Professor Karl Fagerström, focused on what characteristics harm reduction products would need to have to be accepted by smokers; and Group 3, led by Professor Dave Burns, examined biological research needs in this field. The break out sessions fed back to the plenary in Session 5 and a synthesis of the sessions and the ensuing discussion is provided in Appendix 2.



Session IV: Nicotine as a medicine

There were two speakers in this session, Dr Jacques Le Houezec, Consultant in Public Health, who examined the potential of current NRT products, followed by Dr Nigel Gray, International Agency for Research on Cancer, who discussed the potential of clean addictive nicotine products of the future.

Presentation 4.1: Nicotine replacement therapy - Dr Jacques Le Houezec

The aim of Le Houezec's presentation was to discuss a possible role for NRT beyond that of cessation, in particular a role in smoking reduction. Overall, he believed that in order to increase accessibility and reach more smokers, barriers to NRT use needs to be removed and more innovation is needed to bring more effective NRTs to the market.

Le Houezec commented that although only a minority of smokers are ready to quit in the next 30 days, many more smokers are concerned about the deleterious health effects of their smoking and want to do something to reduce the harm. He proposed that smoking reduction is an alternative therapeutic option for smokers unwilling or unable to quit, commenting that it is generally the case in medicine that if the optimal solution cannot be immediately attained, other alternatives need to be explored. Smoking reduction is unlikely to have a major health impact so should be recommended only to those who cannot quit, and be positioned as a first step towards quitting.

Le Houezec said that smokers should not be advised to switch to 'light' or herbal cigarettes or to simply reduce cigarette consumption as this will result in their over-smoking the remaining fewer cigarettes in an attempt to maintain their 'normal' nicotine intake (compensation). The goal of smoking reduction with NRT is to smoke fewer cigarettes with little or no compensation as using NRT will enable smokers to maintain their nicotine dose whilst reducing their intake of toxic combustion products. Smokers forego the reinforcement ensuing from peaks of nicotine reaching the brain which may help to move them towards the ultimate goal of cessation.

Le Houezec commented that there are four placebo-controlled clinical trials that have been published which demonstrate that NRT effectively reduces

smoking and that this reduction can be maintained. These studies recruited smokers who were smoking at least 15 cigarettes per day, who had failed to quit at least once, and who did not feel able or ready to quit smoking but were motivated to reduce their smoking. The primary efficacy parameter was a reduction in daily cigarette consumption by at least 50% compared to baseline, sustained from week 6 to month 4, biochemically verified by a sustained decrease in expired carbon monoxide levels. Secondary objectives were to investigate whether smoking reduction affected intention to quit smoking or led to smoking cessation, even if this was not the intention of the smokers at study inclusion.

In all four studies, active NRT was statistically significantly superior to placebo in achieving a sustained reduction in smoking. Moreover, data from these clinical trials show smoking reduction to be a positive first step toward cessation. Although all studies enrolled smokers who felt unable or unwilling to quit, a number of subjects in each study did stop smoking. Around 10% of the smokers in the active group, twice as many as in the placebo group, were abstinent at 12 or 24 months. (The outcome measure used to assess smoking cessation in smoking reduction studies is point prevalence abstinence. As participants are permitted to smoke while using NRT, sustained abstinence is not an appropriate measure).

Other studies also indicate that smoking reduction promotes cessation. One study, where subjects did not use NRT, showed that moderate to heavy smokers who reduced consumption to below 15 cigarettes per day had significantly higher quit rates than non-reducers (24.9% versus 5.8%). Another study showed that among smokers not interested in quitting, 18% of those using NRT ultimately quit smoking entirely versus 4% from the placebo group. This study reported 7-day point prevalence rates, but these were self-reported, and not biochemically verified. Another study by Etter and colleagues showed a significant difference between active and placebo at 6 months (at the end of treatment), but not at 2 years. However, this study was implemented through the internet, and so was very different from classical clinical trials.

In the 4 placebo-controlled clinical trials reported above, smoking reduction clearly increased smokers' intention ultimately to quit; when questioned at 4 months, 50-87% of study subjects responded that participation in the smoking reduction study had increased their interest in quitting. Other studies also suggest that achieving the goal of reduction may increase smokers' intention to

quit. One study found that moderate-to-heavy smokers who reduced their consumption to below 15 cigarettes per day were more likely to quit in the near future. Another study of smokers not interested in quitting found that 43% of those who reduced their cigarette consumption made a quit attempt compared to 16% in the placebo group. This was also confirmed by a study using the internet to contact smokers.

The safety of NRT used concomitantly with cigarette smoking was assessed in all clinical studies. No unexpected adverse events occurred whilst those events that were observed did not substantially differ from those seen in smoking cessation studies.

Smoking reduction has been approved as an indication for NRT in many European countries including France. The advantage of this new smoking reduction indication is to obtain a rapid risk reduction in smokers who need to quit smoking but are unable or unwilling to do so. Le Houezec believed that it may add around 10% more ex-smokers than if only the classical smoking cessation indication is used because smokers not interested in quitting are being targeted. In terms of public health this is a gain that should not be overlooked.

Discussion

It was noted that there were differences across the studies in both the duration of NRT use and whether the treatment was reimbursed. There was a discussion about whether the experience of clinical studies would translate to the real world and whether, for example, smokers would continue to use NRT for prolonged periods of time if they were paying for the products themselves. Some thought it unlikely that governments would subsidise such long term use of NRT. Others thought that as NRT products were not more expensive than cigarettes, smokers could be encouraged to purchase NRT.

The magnitude of the public health benefit of smokers reducing their cigarette consumption while using NRT was questioned and whether there was a linear relationship between benefit and reductions in cigarette consumption. However, if there was a 10% increase in quitting among those not willing or ready to stop, this was believed to be a real benefit. Le Houezec believed that this outcome could be improved with better NRT products.



There was also a concern that motivation to quit might only increase in smokers who successfully reduced their cigarette consumption. However, a reduction indication for NRT could bring more smokers into the quitting process or at least into contact with people who could ultimately help them to stop. An analogy with heroin addicts was drawn. In the early 1980s when abstinence was the only approach being advocated, very few addicts were coming forward, but once methadone clinics opened, a much broader range of addicts came forward for treatment. Using a combination of cessation and smoking reduction approaches, treatment clinics would have something to offer all smokers.

The use of NRT for temporary abstinence was also discussed. Some European countries have had this indication for some time but it is not known what proportions of smokers use NRT for this purpose, although it was acknowledged that using NRT for this purpose might increase as more countries adopt smoke free policies in public places.

Presentation 4.2: The concept of 'Recreational clean addictive nicotine' - Dr Nigel Gray

Gray's presentation aimed to discuss the role that recreational clean addictive nicotine products could play in tobacco control. He emphasised that such products did not yet exist.

Gray opened by defining 'clean' nicotine as something that would be acceptable to regulators, and 'addictive' as something that would be very hard to give up, but also capable of giving a tobacco-like 'fix'. He defined 'recreational' as an enjoyable leisure activity, a word associated with use of other drugs, but not heroin. In 1991, Professor Michael Russell, stated that 'there is no compelling objection to the recreational or even addictive use of nicotine provided it is not...harmful... to the user or others'. Gray believed it might be hard to reconcile an 'enjoyable leisure activity' with an addictive one, which is by definition compulsive, but felt it was hard to come up with a suitable alternative to the word 'recreational'.

Gray commented that harm reduction is often about alternatives. In believing that harm reduction is a viable strategy for tobacco control, one needed to make the following assumptions:

1. Nicotine addiction is here to stay
2. The cigarette is a disaster
3. Smokeless tobacco is a lesser disaster
4. But nothing that includes tobacco is acceptable - Gray believed that the inclusion of tobacco would incur too much risk.

Gray offered a possible alternative to tobacco as: 'A tobacco-competitive nicotine fix, available easily including vending machines, cheap, easy to use, promoted at Grand Prix and in buses, socially acceptable, full flavour, made by Wrigleys or big Pharma, would carry a health warning'.

Gray believed that there is a spectrum of harmfulness in nicotine sources as follows:

- Wartime cigarette (as smoked during World War II)
- Today's cigarette (recognising that there is a range within this)
- Cigars and bidis
- Chewing tobacco and like products (also a range within these)
- Potential Reduced Exposure Products (PREPs)
- Snus

- Addictive clean nicotine (does not yet exist)
- NRT.

Within this spectrum he outlined the opportunities for harm reduction as:

- Regulate (carcinogen/toxin) cigarettes (not being discussed in this seminar)
- Legalise/regulate snus (could be viewed as a tobacco-based NRT)
- Allow tobacco PLUS NRT (dose reduction)
- Introduce new (tobacco-based) delivery devices (PREPs)
- Regulate ALL tobacco products
- Screening
- Addictive pharmaceutical nicotine.

Gray defined regulation as setting upper limits for toxicants. He believed that regulation of cigarettes was a top priority as was the production of addictive pharmaceutical nicotine. He believed that less priority should be given to legalising or regulating snus. Although snus gives a competitive nicotine fix and is considerably less harmful than smoking, he still had some concerns about possible health impacts such as pancreatic cancer. In addition, the range of smokeless products available would mean that regulations would have to be developed very cautiously to avoid other more harmful smokeless products entering the market. Although Gray was persuaded that snus had contributed to the low male smoking rates in Sweden, snus had not been popular with women and he believed that something better than snus was therefore needed.

Gray queried why pharmaceutical addictive nicotine was not yet available and concluded that it would be disliked by the temperance movement, the tobacco control community would be divided about it and the pharmaceutical companies had not yet made it (and indeed lacked incentive to do so as they prefer their current range of low risk products). In addition, such a product would present difficulties for regulators who currently have no mandate for allowing addictive products onto the market, and to do so might not be a politically popular move.

Gray speculated as to the likely effects of bringing a much more efficient NRT product onto the market. He postulated that it might result in a significant increase in quitting among those who want to stop, but that it might also be used as a bridge when smoking is impossible, which could result in reduced quitting among those less committed to stopping. He believed it unlikely that it would be

used as a gateway drug, but did not rule out the possibility. Overall he argued that these ideas could only really be tested by a social experiment where such a product is introduced and monitored like a new cigarette brand.

Gray concluded that as long as we face a relatively unfettered tobacco industry the nicotine market will continue and that there would be a better chance of beating the industry's products through competition with them. He acknowledged difficulties with his approach in that the outcomes are speculative and unlikely to be easily tested. Gray believed it would better to regard such an approach as a social experiment and its effects measured as it progresses. He believed snus was an example but not the answer. The approach most likely to be successful is to persuade a pharmaceutical company to produce a recreational clean addictive nicotine product and agree to have it tested in a social experiment with Sweden being the most appropriate country for the experiment to take place. However, he also believed that nothing would happen unless the tobacco control community embraced the idea and worked for it.

Discussion

Some in the audience believed that there were such nicotine delivery devices now in development whereas others suspected that it might be very difficult to create such products. Smoking creates a peak of nicotine in arterial blood very rapidly and although this may not be necessary, many believe it is important in maintaining dependence. In order to emulate this we will need to better understand the psychopharmacology behind smoking and why it is so addictive. A huge investment would be needed for pharmaceutical companies to go down this route. The potential for failure was also enormous.

Some believed that such a product should be available on the open market for all consumers to buy, as it would be inappropriate to regulate it for access through health professionals only. Others believed it should be introduced through restricted access treatment sites first, and then access broadened as demand increased. Gray believed that to compete with cigarettes, such a product would need to be cheap, and the only way to achieve this would be to have it subsidised. Although many products are subsidised in the EU, European regulators would currently be unlikely to be prepared to subsidise a recreational clean addictive nicotine product. The difficulties of subsidising such a product when the income from tax on cigarettes was so large were also discussed. Gray believed that tobacco taxation was so popular it could be increased and by earmarking it you could apportion funds for subsidising an alternative product.

The question was raised as to why only pharmaceutical companies should be encouraged to produce such a product, and not the tobacco companies who may be more likely to have the relevant knowledge, technology and resources. Tobacco companies could be innovative and frequently introduced new cigarette brands onto the market. Gray had reflected on this a great deal and although he would prefer the new nicotine product not to be produced by a tobacco company, he would support it whatever its source. Some thought that it would be necessary to direct the industry to go down such a route and encourage them to do so. Others believed that if that was to happen it would be crucial to have a proper regulatory framework in place. In France and the UK, national Tobacco and Nicotine regulatory authorities have been advocated. Although a similar authority has been proposed at EU level, this is unlikely to happen for some time and it seems more likely that national bodies will be developed. Precedents exist such as medicines regulatory bodies, offering a model that could be adapted for a regulatory authority.

Session V: Harm Reduction: practical issues

The final session focused on moving the harm reduction agenda forward. Professor Murray Laugesen, Health New Zealand Ltd, assessed the benefits and risks of promoting harm reduction; Professor Gerard Hastings, University of Stirling focused on the role of marketing; Fiona Godfrey, European Respiratory Society, examined the preferred regulatory framework; and the session closed with Professor Yves Martinet leading a discussion around concrete next steps.

Presentation 5.1: What is at stake? What are the possible gains and risks? Dr Murray Laugesen

The aim of Laugesen's presentation is to elucidate the benefits and risks of adopting harm reduction policies for tobacco control. Laugesen believed that a plan to end combustible tobacco products is needed alongside traditional forms of tobacco control, such as advertising bans, taxation increases, smoke-free policies etc. He believed that, as many other speakers have outlined, there is a clear continuum of risk across nicotine-containing products. Cigarette smoking has killed millions in Europe, more than in the two world wars combined, making cigarettes such a dangerous product that they should be phased out. He believed that the tobacco control movement had to state very clearly this end goal, whilst acknowledging that the means to this end could vary.

Although huge gains in tobacco control are being made, Laugesen contended that progress is too slow without developing an additional harm reduction strategy. The average reduction in adult smoking across 22 OECD countries over the last ten years when projected forward (with trends remaining constant) means that it will take around 70 years to reduce smoking prevalence to zero. Even slower reductions in prevalence are currently being observed among those groups where prevalence is highest, for example, more deprived groups or indigenous populations in Australia and New Zealand.

The risk of doing nothing is that the status quo remains and cigarettes will continue to dominate in all countries, except Sweden. Laugesen noted that in Sweden, where oral tobacco has been a culturally and legally approved alternative to smoking at least for men, the lung cancer epidemic has never reached great heights and remains lower than for any other developed country.

The other major problem with the status quo is that health groups are out of line with the science. Health groups largely approve the continued sales of cigarettes and bans on smokeless tobacco sales, whereas the mortality risk of smokeless is far less than that of cigarettes.

Laugesen proposed a plan to end the sale of combustible tobacco as follows:

- Stage 1 - Promote smokeless alternatives. Reduce nicotine in cigarettes
- Stage 2 - Ban combustibles. Retain smokeless products
- Stage 3 - Watch tobacco mortality wane to 5% over next 15 years.

Laugesen clarified that the law would not ban smoking, just the sale of cigarettes, in other words a reverse of the laws currently banning smokeless tobacco in the EU, Australia and New Zealand.

Laugesen posed a number of urgent research questions concerning smokeless forms of nicotine:

- What are smokers' views about snus? Is snus acceptable in non-user countries?
- Should snus carry a 'causes heart disease' warning?
- Can NRT be changed to give a more rapid hit? Does this make it more addictive?
- Is snus addictive only because of its nicotine, or because of other substances in tobacco?
- Can nicotine products without tobacco be just as satisfying as snus?
- Does snus have market advantage because it is sold as a lifestyle drug, has an attached ritual, and is not a treatment?
- Which is better - upper lip absorption of nicotine versus lower mouth?

He suggested that key questions for policy development are the extent to which the different smokeless forms of nicotine (current NRT products, faster acting NRT products and smokeless tobacco products) rank as substitutes for cigarette smoking, and the extent of their addictiveness. If a faster acting nicotine product was almost as good as snus then a country with a snus ban in place would have little incentive to lift the ban.



BAT has tried to develop a “safer cigarette” but had found this too difficult, opting instead to enter the smokeless market in South Africa and Sweden. BAT aims to develop rituals around snus use to replace the former smoking rituals, package the smokeless products attractively, price them just below cigarettes and use well-known cigarette brand names for the snus products. BAT also encourages the government to tax the snus product to bring the price in line with that of cigarettes, when in fact the health risks are very different. As a low-toxicity smokeless manufacturer, BAT wants regulations to keep out high-toxicity products. On the other hand, BAT needs a breathing space from public health groups' criticisms, so that smokeless products can become established as an alternative to cigarettes.

Laugesen then examined possible gains from ending the sale of combustibles. Laugesen believed that a clear policy to end the sale of combustibles could unite the tobacco control community. He believed that such a goal is feasible, if alternative products providing smokers with pure nicotine or oral tobacco nicotine could be provided. The smoker would have to give up smoking, but not addiction to nicotine.

He believed that by creating alternatives to smoking tobacco there is the potential to accelerate current rates of prevalence reduction. This would depend on the market share of clean nicotine products, which would be affected by their legal status and the relative prices of cigarettes versus non-combustible nicotine products. Laugesen noted that the price of NRT is about the same as cigarettes in New Zealand, whereas in the US it is some three times more expensive than

cigarettes. In a comparison of consumption reductions in men in New Zealand and Sweden, Laugesen noted that between 1990 and 2000 Sweden had reduced cigarette consumption to a greater extent than New Zealand, without raising the costliness of cigarettes as in New Zealand.

He thought the greater reduction in male cigarette consumption in Sweden was due to the rising male consumption of snus in Sweden. Laugesen commented that a risk-based tobacco excise could be implemented such that excise taxes were levied proportional to the risk of each tobacco product.

Finally, he commented that the use of smokeless forms of nicotine would have the following effects on mortality rates: help to end indoor second-hand smoke exposure which would impact on mortality within around three years; aid smokers to quit smoking and reduce relapse which would impact on mortality rates within a period of around 15 years; and be an alternative to smoking for teenagers which would have an impact on mortality over a longer period from about 20 to 50 years.

Laugesen went on to outline the risks of adopting such an approach. In particular, he was concerned that it could blur the quit message. The current simple quit message is clear and unequivocal, whereas refining this to say 'quit smoking but you don't have to quit nicotine or tobacco' means educating smokers that nicotine is not necessarily bad. To counter this, more emphasis has to be placed on the dangers of smoking. Lack of policies and research to support reducing combustible sales to zero could mean that this end-goal is seen as unattainable. In addition, if there is no firm goal to end smoking, reduced toxicity cigarettes could be seen as cementing the continuance of smoking, instead of a precautionary protective measure for smokers until such time as cigarettes are no longer sold.

Laugesen believed that the health community, in its zeal to oppose the tobacco industry, often failed to differentiate between the cigarette manufacturers and the smokeless companies and the risks of their respective products, encouraged members not to communicate with any part of the industry, and failed to address cigarette research and science, leaving the field of regulation to the expertise of the cigarette makers. In particular he felt it important that funding be found for the research needed to replace cigarettes as a nicotine source. He believed that the simplest way was a tax levy per cigarette, or unrestricted donations by industry.

Laugesen summarised by saying that comprehensive tobacco control programmes, even with the help of subsidised NRT, are slow in reducing smoking prevalence. Nicotine products and snus are far safer than any modified cigarette. The ERS needs to convey this message. Cigarettes are the most dangerous of all tobacco products and public health groups need to adopt the overarching goal of phasing out cigarettes. Research is needed to clarify whether fast-acting nicotine will match the effects of snus, be safer than snus and superior to current NRT products. He believed that multi-centre research on alternatives to smoking is required.

Presentation 5.2: Dangerous Liaisons? Professor Gerard Hastings

Hastings defined marketing as a way of influencing human behaviour. The tobacco industry has been hugely successful at marketing. Marketers influence different groups of people, namely consumers, allies, stakeholders and competitors, to do things voluntarily. Hastings urged caution about working with our competitors, the tobacco industry.

Hastings believed that the tobacco control movement needs to define what business it is in and clarify whether its goal is harm reduction or harm avoidance. Harm reduction means becoming involved in the recreational drug market, and he believed only two industries could help with this: pharmaceutical companies and the tobacco industry. Hastings believed that the pharmaceutical industry is in the health and drugs business and that they do not have the networks, business processes, or marketing expertise for recreational products. He believed that they would not risk their corporate reputations by stepping into the recreational drugs business and if they were cautious about doing so, then probably the tobacco control movement should be as well. On the other hand the tobacco industry is already in the recreational drug business.

Hastings could envisage benefits for the tobacco industry if the tobacco control movement adopted a harm reduction approach. In the illicit drugs business, there is not a corporate interest. In the alcohol field, there is an industry and he believed that some had come unstuck working with alcohol interests.

Nevertheless, Hastings acknowledged that events have already moved ahead. Several cigarette companies are now investing in the smokeless tobacco

market. He argued that this must be because they see a benefit to their companies, such as enhancing their brands or improving distribution networks. Above all he was convinced that tobacco companies would not undermine the cigarette business - this was an incredibly valuable commodity to them.

Hastings commented that previous presenters had talked about empowering consumers. He questioned whether despite our growing understanding of consumers' needs, we are really able to influence what they do and whether we might lose control by giving consumers a choice to avoid cigarettes but maintain their addiction. He questioned whether we understand the tobacco market place sufficiently to be able to influence it.

Hastings also had concerns about allies. He believed that there is a danger that the tobacco control community would fracture rather than unite, and that this could be dangerous unless our allies share our primary strategic goal of



reducing death and morbidity. However, there may be aspects of harm reduction that are more acceptable, such as more flexible and consumer oriented cessation.

Finally, Hastings considered the stakeholders. Politicians need to be kept onsite and 'on message'. The Commission has just reinforced the ban on snus, and is unlikely to acknowledge making a mistake.

Hastings believed that snus is a great marketing opportunity. He agreed that it is much safer than cigarettes and consumers might want to use it to avoid cigarettes, regardless of our stance on the issue. He proposed that the tobacco control community move forward cautiously, investigate snus as a cessation aid (which might be politically acceptable as it would avoid unregulated snus release) and progress the goal of a more consumer-oriented response to cessation. This would keep the tobacco control movement together and above all, he believed, avoid a potentially disastrous collaboration with the tobacco industry.

Presentation 5.3: What regulatory framework is preferable for successful harm reduction? - Fiona Godfrey

The aim of Godfrey's presentation was to outline the optimum regulatory framework to enable the harm reduction agenda to be progressed.

Godfrey began by offering two definitions of harm reduction. The first was from Robert Wallace, from the Institute of Medicine in 2003: *'Tobacco harm reduction refers to decreasing the burden of death and disease, without completely eliminating nicotine and tobacco use.'* The second was from Nigel Gray and Jack Henningfield from 2004: *'Attempts to reduce exposure in persisting tobacco users - either by reducing amounts of toxins/carcinogens in smoke or reducing amounts of smoke inhaled'*. Godfrey emphasised that harm reduction should always be implemented within a comprehensive tobacco control strategy which would include high taxation of tobacco products, smoke free policies, advertising bans and other comprehensive tobacco control policies.

Godfrey described a continuum of harm of tobacco and nicotine products with conventional cigarettes as the most dangerous through to NRT as the least dangerous. She positioned modified cigarettes as likely to be close to cigarettes on the continuum whereas snus would be close to NRT with other smokeless tobacco products also positioned within the less harmful end of the continuum. She described the current regulatory situation in the EU with the most dangerous products, cigarettes, being widely available while other less harmful products such as snus are banned from the market. She commented on the need to be clear about which products we were trying to regulate: conventional cigarettes, potentially reduced exposure products (PREPs), modified cigarettes with selective constituent reduction (SCORs), Swedish snus-style smokeless tobacco products, other smokeless tobacco products, or NRT products.

Godfrey then discussed who should regulate. The ASPECT project, which involved an extensive collaborative effort across Europe, advocates that a European nicotine and tobacco regulatory agency should be established. Its remit would include all aspects of tobacco and nicotine product design and marketing, as well as risk assessment and analysis, and ultimately all market authorisations. Philip Morris International has also advocated that the EU should establish a European agency for tobacco. However, she believed that this is unlikely to be achieved in the short term as within the current political

climate the tendency is to reduce the number of regulatory agencies. Godfrey suggested that if such an agency is not set up at European level then Member States should set them up at national level, but it was doubtful that this would happen. In countries that have lobbied for such agencies, politicians believe that they should be set up at European level.

Many views have been expressed over the last few years concerning tobacco product regulation. ASPECT suggests abandoning a piecemeal approach to regulation, advocates comprehensive disclosure adopting the SACTOB definition on ingredients, and requests a more comprehensive programme of regulation. As the ASPECT report is a consensus document it does not make recommendations on smokeless tobacco, as this would not have reflected views across Europe.

Gray, Benowitz, Dressler and colleagues in 2005 suggested a three phase policy to regulation, but the phases could be implemented simultaneously:

Phase 1 Short term

- Capture all nicotine into a regulatory system either by giving pharmaceutical regulators regulatory powers over all tobacco products or set up a specialist agency
- Define 'dose' for measurement purposes
- Develop marketing rules
- Set standards for toxicants
- Monitor the market.

Phase 2

- Diminish the tobacco nicotine market
- Make non-tobacco nicotine products more competitive through tax and other measures
- Eradicate additives to reduce attractiveness
- Once a wide range of 'clean' nicotine products are available, move towards reducing nicotine availability in cigarettes.

Phase 3

- Most toxic products would be most regulated
- Demand for nicotine would be met by wide range of 'clean' nicotine products
- Could lead to virtual elimination of tobacco use in its present form.

Godfrey asked whether regulation should start with conventional cigarettes or with PREPs. She believed that smokeless tobacco and NRT have a good evidence base, and are a low cost option to progress. She believed that these other products could be regulated to give them a competitive advantage over cigarettes.

Godfrey then outlined what pressures might influence where we start. Acceptance within the public health community would be a factor. Godfrey reported that a study led by Ken Warner in 2003 outlined that there was general agreement within the tobacco control movement within the US that tobacco products should be regulated, although there were many concerns voiced about the impact of harm reduction strategies.

Being clear on the ultimate aim of tobacco control is important. Godfrey reported the findings from a Department of Health tobacco control conference in London in November 2004 where 78% of the audience agreed that the main aim of tobacco control was to eliminate death and disease, with only a small minority believing the main aim was to eliminate addiction to tobacco, or to eliminate the tobacco industry. This was somewhat unexpected but could perhaps be explained by the fact that the audience was predominantly made up of people from the smoking cessation field and who therefore understood addiction and the difficulties involved in helping smokers to quit.

There is also some evidence of consumer acceptance. Smokers are willing to give PREPS a try, as suggested by a JP Morgan survey which showed that 91% would be willing to try a lower risk cigarette if it was available.

Politically, given that the last European products directive was adopted in 2001 and drafting began in 1998, it has been some time since there has been any action within Europe to develop new regulations. Godfrey commented that meetings with European civil servants and politicians indicated that there is some appreciation of the issues and the need for action but they appear unwilling to advocate new regulations. There seems to be some consensus on the need to bring reduced ignition propensity cigarettes onto the market, possibly because children's lives were likely to be saved by such a measure. Campaigners across Europe are now building broad support for this and Godfrey was optimistic that reduced ignition propensity cigarettes would be mandated, which might open the door to further regulations around the product. However, she questioned whether there is consensus on other matters.

In the meantime the tobacco industry is forging ahead with PREPs. JP Morgan's recent report indicates that it is very likely that proprietary PREP technology will be rolled out by Philip Morris International and BAT into several regions in the next few years. According to JP Morgan research, the tobacco industry has spent \$3 billion on research and development over the last five years, much of it on PREPs which are likely to be integrated into existing brands. FDA regulation is seen as critical to the success and acceptance of PREPs. The industry is also taking an increasing interest in smokeless tobacco. BAT and Imperial both entered the Swedish smokeless tobacco market in 2005, and RJR and PM are reported to be bringing out smokeless tobacco products. Godfrey questioned the impact these commercial developments would have on the EU ban on oral snuff, and she queried whether the possible referral of the Finnish government to the European Court of Justice would lead to a reassessment of the December 2004 decision to uphold the ban.

Godfrey believed that there is little pressure coming from elsewhere. Product research is currently completely underfunded across Member States and Europe and she believed that the scientific community should be providing a lead in this area.

Godfrey then outlined interim steps that could be taken. She believed it is critically important to work towards leveling the regulatory 'playing field' between NRT products and cigarettes. In the absence of a dedicated agency, the EMEA and national medicines agencies could deregulate NRT as has begun to happen in the UK. Pricing structures, reimbursement and taxation policies on NRT could be reassessed. She believed that the tobacco industry should be left to work on PREPS but that scarce national and EU resources should probably not be devoted to regulating, evaluating and approving them. She believed that a firm decision is needed on the International Standards Organisation's emission standards and that a replacement is urgently needed, but she cautioned about how the regulation of cigarettes could proceed. In some European countries there is less than one full time equivalent member of staff dedicated to tobacco control within the government and therefore there is little capacity to dedicate to tobacco product regulation. In addition there is little funding and research on these issues. At the European level, Godfrey believed that there is an urgent need for a regulatory agency. She recommended that resources be pooled across the EU and Member States to draw up standards, and to set up an independent laboratory to test cigarettes. Finally, she felt it important to consider the position of snus.

Godfrey finished by drawing up a consensus statement from the meeting. She highlighted the following key statements for the consideration of the participants:

- Nicotine is not the problem
- Combustible products are the problem
- Status quo should not continue
- Snus is a lot safer than cigarettes
- Snus has potential as a cessation aid
- Lifting the ban on snus needs to be considered.

Discussion

There was some discussion as to the likelihood of a regulatory framework being set up in the near future for smokeless tobacco products, and acknowledgment that it was a little bizarre to set up such a framework in advance of a regulatory framework for cigarettes. Some felt it more urgent to set up a regulatory framework for cigarettes first. Godfrey believed that there is a consensus to remove toxic constituents from cigarette smoke which was a helpful first step. Others thought that the markedly less harmful profile of smokeless tobacco products made setting up a regulatory framework for non-combustible nicotine products a more pressing priority.

There is some discussion around the wording of the meeting consensus statements. It is believed important to use the context of the Framework Convention on Tobacco Control which would give the power to move forward in this area. There was also an acknowledgement needed that a network is being set up in Europe for those involved in research and policy around cigarette smoke yields and toxicology. It was also suggested that a general point should be made at the beginning of the consensus statements that harm reduction is appropriate as a part of comprehensive tobacco control policy. Some believed that the discussions around smoke-free policies paved the way for the debate on harm reduction as smoke-free policies themselves are a harm reduction strategy.

There was a discussion as to how smokeless products should be marketed. There was some feeling that it would be better to position smokeless as a cessation aid rather than as a nicotine maintenance product which would substitute for cigarettes, as this would not antagonise the tobacco control

movement. Others believed that the evidence from Sweden is stronger for snus being a maintenance product rather than a cessation aid, and this was where the public health impact could be greatest. Some felt that it was extremely important that whenever references to smokeless products are made, it should be clear that the reference is to snus-like products, ie those with low nitrosamine delivery, rather than all smokeless tobacco products. Others thought that a focus on the Swedish snus would be a mistake. They believed that it was very unlikely that the EU ban on snus would be lifted in the next decade and that it would be better to start with the smokeless tobacco products that are allowed on the market, such as chewing tobacco products. For some, there was a clear distinction between cigarettes and any smokeless tobacco product: all smokeless tobacco products offered a clear reduction in harm compared with cigarettes.

Some believed that the proposal to ban cigarettes would not work. Drawing an analogy with pollution from cars, it could be proposed that over time, cars ought to be banned and only bicycles allowed. As this proposal would clearly not be feasible, it was no more likely that a ban on cigarettes would work. Laugesen answered that the end goal of banning cigarettes need not be immediate and also need not happen in our lifetime, but that a start needed to be made. Some countries already contemplate the feasibility of a zero prevalence of smoking, such as Australia. Having such a goal will help clarify thinking in this area, and make tackling the issue of smokeless tobacco products more urgent. He believed that it would be possible to get fast declines in smoking prevalence with the availability of non-combustible nicotine products. Current population declines in smoking were questioned, as comparisons between any current smoking and daily smoking suggest that there are no significant reductions in overall smoking prevalence. It was also suggested that reductions in smoking prevalence already achieved might be lost if alternative tobacco products were brought to the market. Smoking is now a minority, and in some countries a deviant, behaviour but this might change with the introduction of non-combustible nicotine products on a large scale. The importance of denormalising tobacco use might be lost if this strategy was adopted.

Working with the tobacco and pharmaceutical industries was also discussed. Some believed that pharmaceutical companies are already moving to present more competitive nicotine products to the market. Others cautioned against working with the tobacco industry. The ERS has now adopted a policy

prohibiting direct employees and industry-funded consultants from being members of the Society. The European Respiratory Journal has also revised its conflict of interest statement and is working with other respiratory medical journals to develop a joint position on acceptance of tobacco industry-funded research studies for publication.

The lack of funding for research was also highlighted, although some believed that waiting for the science base to be complete would take too long. Nevertheless, it was acknowledged that there is very little funding for research in Europe compared with the US. It was suggested that the tobacco industry ought to be considered as a source of funding through unrestricted grants, although in practice this was difficult to police. It was felt that the tobacco industry is only likely to fund research in areas which will not harm its core business and profits.

Following the discussion, Godfrey amended the meeting consensus statement to reflect the comments made as follows:

- Harm reduction is desirable as part of a comprehensive tobacco control programme
- Nicotine is not the problem
- Combustible products are the problem
- The status quo should not continue
- Snus is a lot less harmful than cigarettes
- Snus also has potential as a smoking cessation aid
- Lifting the EU ban on snus within a proper regulatory framework needs to be considered
- The playing field for “clean nicotine” should be levelled via deregulation and taxation and pricing measures
- Toxic ingredients should be removed from conventional cigarettes.

Presentation 5.4: Proposals for the future - Professor Yves Martinet

Martinet thanked all those present for a very interesting meeting. He also thanked those within the ERS Scientific and Educational Department for organising this research seminar.

He commented that the ERS has a strong commitment to tobacco-related issues and its impact on lung health as a result of the active promotion of tobacco control by several Presidents and by its Executive Manager. The ERS is one of the leading non-governmental organisations (NGOs) involved in tobacco control in Europe; it works with several other NGOs, including the European Network for Smoking Prevention (ENSP), the European Heart Network (EHN), Cancer Research UK, and the French Ligue Nationale contre le Cancer. The ERS contribution to tobacco control has been central in several major areas such as the Framework Convention on Tobacco Control, the ASPECT Report and the Smokefree Europe 2005 conference in Luxembourg.

Martinet commented that the ERS must be a leader and not a follower in scientific opinion. Those organising this seminar were of the opinion that it should be followed by the establishment of an ERS Task Force to focus specifically on harm reduction in Europe. ERS Task Forces are supported financially by the ERS and produce position papers, statements or guidelines that subsequently become official ERS documents on issues related to respiratory medicine. Martinet commented that guidelines are particularly important as they enhance general scientific understanding, especially in areas where controversy exists or procedures are unclear. They also establish consensus and are effective tools when combating disease on an international basis. The outputs of the Task Force could be the subject of special meetings and seminars or on the agenda at annual ERS meetings.

Professor Giovanni Viegi, current President of the ERS, then organised a small round table with Dr Philip Tonnesen, Chair of the ERS Task Force on Smoking Cessation in Respiratory Patients, Dr Paul Van Spiegel, Secretary of ERS Group 6.3 (Scientific group on tobacco) and Professor John Britton, Chair of the ERS Tobacco Control Committee to discuss how best to take this work forward. Each explained his current work in the ERS and how the area of harm reduction and the Task Force might relate to this.

Discussion

It was agreed that the importance of this issue required the establishment of a Task Force with a closely defined remit and following the ERS's formal requirements for Task Force objectives and outputs.

Martinet concluded the session by saying the goal of a Task Force on harm reduction would be to define and describe what is known, unknown, knowable and unknowable on this issue and how any harm reduction policy could contribute to the denormalisation of tobacco use while complementing 'mainstream' tobacco/nicotine control policy.

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Session III: Break out sessions

Session 3 consisted of three break-out sessions examining different aspects of harm reduction: Group 1, led by Professor Lynn Kozlowski examined public health research needed in the harm reduction field; Group 2, led by Professor Karl Fagerström focused on the characteristics harm reduction products would need to have in order to be accepted by smokers; and Group 3, led by Professor Dave Burns, examined biological research needs in this field. The break out sessions fed back to the plenary in Session 5 and what follows is a synthesis of the sessions and the ensuing discussion.

Group 1 feedback: Harm Reduction: planning public health research. Led by Professor Lynn Kozlowski

Public health research in Europe on harm reduction needs to be carried out in the context of what is already being done by developing priorities for research that will help to move the harm reduction agenda forward.

Research on harm reduction policies must endeavour to take into account the impact on other tobacco control policies, notably prevention and cessation. Many were concerned that harm reduction would undermine other tobacco control efforts and so believed that harm reduction strategy needs to emphasise the prioritisation of proven tobacco control measures such as smokefree places and taxation increases. The impact of harm reduction measures (such as reducing smoking alongside NRT use) would need to be measured within this broader context, to ensure that smokers appreciate that quitting is of key importance.

Research is also needed on the harm reduction strategy itself, such as the standards that should be set for reducing cigarette smoke toxins and how they should be measured. The optimum structure of the regulatory framework and the systems required to regulate tobacco products also needs to be researched. The impact of setting differential costs for the various nicotine products and the impact of reimbursement practices on uptake and usage of the products also need to be examined.

The significant and unique case study of snus in Sweden should be the focus of more detailed and interdisciplinary research. There was a great desire to understand the situation in Sweden much better.

Turning specifically to NRT, research is needed into any health effects of nicotine, although such research always ought to be analysed and presented in the context of the much greater harm of cigarettes, so as not to deter smokers from using NRT products. The addiction potential of NRT and factors influencing this need to be understood. It was felt that ERS has an important role in encouraging the professional application of best practices in the use of NRT. Research is also needed to encourage the development of a medicinal NRT product that could compete with snus, which requires consideration of how NRT could be made more consumer-friendly and acceptable. There may be specific attributes needed to make alternative nicotine products attractive to women.

The need to address health disparities is believed to be a key public health issue. Factors relating to smoking in more deprived groups and cessation strategies for these groups should be researched, in particular the issue of how cost and the availability of alternative nicotine products could impact on health inequalities.

The ensuing discussion focused on how comparative risks can be effectively communicated and participants believed that much greater understanding is needed on how best to communicate quantitative risk differences. Some participants felt that it is no longer acceptable or appropriate to continue to distinguish risks by saying 'safe' or 'not safe' as this does not adequately reflect the continuum of risk related to the range of nicotine and tobacco products currently available. Others felt that there are many organisations and groups using the media, which would make it difficult to ensure risk is communicated in any rational way. Perhaps therefore it would be more important to focus on countering inaccurate communications.

The need for short term indicators on health impacts was also raised. Epidemiological effects would take too long to gather so the scientific community needs to agree which were the best short term indicators to use and implement them. The relative merits of implementing long term cohort studies against case control studies for picking up adverse effects were also discussed.

Some participants also believed that it would be beneficial to consider the timing of the introduction of harm reduction strategies. The benefits and harms might differ depending on the stage of the tobacco epidemic in different

countries. For example, harm reduction approaches might be more beneficial when a certain reduction in smoking prevalence has been achieved, or when smoking levels are very high.

On the specific issue of snus use in Sweden, participants agreed that more research is needed. Contradictory data had been presented on concurrent use of snus and occasional smoking, and participants were keen to see these data and analyses discussed in peer reviewed journals. Other questions included further research on the gateway affect, the causal connection between the decline in smoking and increase in snus use, the likely uptake and acceptability of snus and therefore public health impact in other countries, and an analysis of the current marketing strategies of tobacco companies launching smokeless tobacco products. Research is also needed to model the impact of different scenarios resulting from reversing the ban on oral snuff in Europe, including the extent to which uptake of snus might counter the benefits of switching.

Group 2 feedback: What characteristics would harm reduction products need to have to be accepted by smokers? Led by Professor Karl Fagerström, feedback by Fiona Godfrey

A broad range of characteristics were discussed in Group 2, with their conclusions summarised as follows:

- Recreational harm reduction nicotine product acceptable to smokers
- Appearance should be non-medical
- Faster nicotine uptake and higher nicotine concentrations than current NRT
- Spectrum of products
- Sensory stimulation was an important factor
- Taxation issues to be considered
- Product should have a competitive price compared with cigarettes
- Product should be pleasant and have ritualistic characteristics of use
- Broad availability
- Inhaled nicotine would be unattractive
- Product should be reimbursed in hospitals
- Product image should be modern, fun, and enjoyable
- No contraindications on the packaging
- Be promoted by health community
- Reasonable lower age limit.

The ensuing discussion focused on the need to better understand smokers' need for nicotine. Research is needed on whether compensation for nicotine is 100% or whether smokers could adapt to lower doses. This will be very important for deciding what alternative nicotine products people might use. In relation to this, there was a discussion around smoking patterns and the validity of reports of increases in occasional smoking in some countries. If people could move from daily to occasional smoking this implied they were regulating their nicotine yields at a lower level as 100% compensation was unlikely. Smokers therefore appeared to be moving from more dependent to less dependent patterns of smoking. This related to discussions the previous day on nicotine dependence and whether people smoke for positive or negative reinforcement, an area for further research.

Although the medical profession focused on treating withdrawal, this was only one measure of dependence and other measures were also felt to be important. Some believed that it was possible that other tobacco control measures could be starting to constrain how people could smoke which might be playing a role in increased reports of occasional smoking. Analogies were drawn with other drug use, as people can limit cocaine and heroin use to certain times or situations. Although there is an element of compulsion, it is controlled, and it may be that smokers' use of nicotine can be shifted from the most addictive forms.

In discussing the format of new nicotine devices, the link between the nicotine and the delivery device was important. In this sense, some were surprised that the NRT inhalator had not been more successful, as it closely mimicked the hand to mouth action of smoking, although the nicotine intake would be less reinforcing from the inhalator in comparison with the cigarette. Some believed that current NRT products were actually quite successful and more research was needed into longer term and off-label use of these products. In addition there was support for the view that not all smokers are the same and their preferences with respect to, for example, speed of nicotine delivery might vary. The solution is therefore unlikely to be just one form of delivery but a range, so that individual smokers could choose the most appropriate delivery device for them. Although there had been much talk about improving the delivery of the products, some participants felt that intake of nicotine would be somewhat limited by the buccal membrane, so there was a concern that nicotine intake via this route in snus type products may already have been maximised.

Again the issue of communicating relative risk of any new nicotine product compared with cigarettes was raised. Factors influencing consumer acceptability were also discussed, such as accessibility and marketing.

Group 3 feedback: Harm Reduction: planning biological research. Led by Professor Dave Burns

Biological research to assess the harm from tobacco needs to focus on all aspects of tobacco products, from communication (marketing, product and health claims), behaviour, emissions (quantitative measures as well as measures of toxicity), exposure (mouth level through to what is absorbed by the body and biologically effective exposure), to injury and disease.

Assessments can currently be made of the product, emissions, and some aspects of exposure such as carbon monoxide, cotinine, NNAL etc. However, there are currently no measures for smokers' injury. The measures that can be used are often are not directly validated by disease outcomes i.e. if a reduction in NNAL is found, it is unknown what impact would this have on lung cancer etc. FEV1 is probably the best measure that can be used currently as it indicates COPD.

Measuring impact on disease risk will take years - decades for some outcomes - so potential indicators of disease risk are urgently needed. This is challenging as we do not yet fully understand the biological mechanisms that underlie tobacco-related illness, but a set of measures are needed to cover the major disease categories. Measures of oxidative stress offer promise as potential biomarkers for CVD and COPD.

An important research question was thought to be the extent of change in exposure required for there to be a meaningful change in risk. Study of this question is complicated by the variation in human biomarkers due to a variety of host characteristics which adds to the variation due to differences in exposure to cigarette smoke. A further important question is the extent of change in measures of injury or risk required to predict a change in disease outcomes.

Given the long term nature of research into disease risks, there is an urgency to begin these types of studies now, preferably building on existing studies so that costs would be lower. Short term needs include developing biomarkers

which can be established as valid measures of injury (oxidation inflammation, genetic damage, addiction etc). Once these measures are developed, there is a need to demonstrate that differences in the biomarker predict a difference in disease outcome.

There is a need to understand better how changes to different product characteristics alter the toxicity of the product and subsequent injury and disease in smokers. Burns commented that there are no measures currently accepted that defined toxicity although potentially there are a set of measures that could be developed to define risks of certain diseases.

This complexity has led people to focus on harm reduction through noncombustible nicotine delivery products. The group also raised the need to understand better why people prefer snus to NRT, and whether these preferences are due to differences in delivery, presentation, biology, sociology etc? In particular, they felt it important to examine the role played by speed of absorption and dose and the relationship between these two factors. The group also asked whether the Swedish experience could be replicated. Could new nicotine products be developed which would allow availability of a continuum of products from medicines to recreational nicotine products in particular more rapidly inhaled nicotine delivery products?

Practical limitations to research need to be discussed, in particular the reality that differences in existing machine-generated smoke measurements do not measure differences in human exposures, and the difficulty and expense involved in acquiring sufficient sample sizes in population surveys when use of novel products is quite limited. There are also differences in results when exposures are measured in self-selected groups compared with experimental switching studies, and these differences need to be examined further.

The ensuing discussion emphasised the need for a consensus to be developed quickly on which biomarkers should be used, given that potential harm reduction products were already on the market. Randomised controlled trials could be carried out now with a variety of indicators such as expired-air carbon monoxide, cotinine, frequency and intensity of use, and presence and intensity of withdrawal effects when not used, all of which would provide information which could then be compared with other epidemiological data. However, it was recognised that this information would still not indicate relative harmfulness across different products.

Some were concerned that the complexity and cost of all the research needs set out by the break-out groups would divert attention from acting on our knowledge that active and passive smoking are dangerous. Others acknowledged that such research would not drive harm reduction in the short term, but it would have long term effects, but that meanwhile the tobacco control movement could no longer afford to ignore the issue particularly as different tobacco products are now being launched onto the market. There was also a concern that developing this research agenda is a global need that had been outlined in the Institute of Medicine 2001 report and that Europe should not duplicate this work.

On the whole participants agreed with the various research needs outlined by the groups but disagreement remained on two issues. The first was what should be done to the cigarette, and the second claims about benefits of using new products. In terms of lowering the toxins in products, there was a belief that indicative methods could be used and that disease outcomes were not necessary, so the use of bioassays should move forward quickly. In doing this it was acknowledged that such changes should be made mandatory and without communications to consumers.

The second issue was based on the concern that although there are products on the market which have a high probability of less harm compared with conventional cigarettes, they cannot be tested in the absence of biomarkers directly related to harm. What is the risk of using these products before we have definitive evidence of their relative harm compared with cigarettes? There was some agreement that measures of toxicity would be valuable for product modification, and that tobacco companies should be encouraged to develop these products and bring them to market. However, they should not be able to make claims about relative harms until there was a proper scientific evaluation. Some believed that the ERS task force that is looking at biomarkers for respiratory diseases might help to throw some light on which biomarkers to choose, with chronic mucous secretion, lung function and respiratory capacity being proposed as potentially useful measures.

The need for a regulatory body was also emphasised. Clearly no single structure currently exists that could make the required evaluations and decisions concerning relative harms. Parallels were drawn with the FDA in the US and other medicines regulatory bodies which follow a comprehensive approval process for new drugs.

Some believed that there is a danger that advocating for regulatory bodies or solid advance evidence of outcomes will result in inertia and that there is a need for a little less caution. We must not be led into believing that the area is so complex that nothing can be done. The relationship between science and policy was discussed, some feeling it was important to keep the science and policy separate. Scientifically the evidence is incomplete, but this does not necessarily mean that policies cannot be implemented, based on existing knowledge. The relationship between policy and communication was also further explored.

There was also concern that there should not be different criteria used to judge new products and conventional cigarettes. As new products are launched onto the market, we have to be careful not to create barriers against those that have the potential for less harm. Others questioned why the industry was launching so many products. As most new products are being launched in the US where tobacco advertising is still allowed, perhaps the industry is using them to keep tobacco in the public eye and overall promote their business. This also raised the question of how communications about new products could and would be delivered in the context of a tobacco advertising ban and a ban on health claims on packaging. Some thought that the industry would continue to use its branding in subtle ways to communicate messages.

Concerns were raised about the extraordinary regulations of tobacco products and it was felt worthwhile to examine how international policies have developed thus far. The irony of the contrasted situations in the US and Europe was noted: the US has less harmful products which tobacco control advocates feel that they have to be very careful to acknowledge, whereas in Europe some types of more harmful smokeless tobacco products are available, whilst snus is banned. Even without the science, it is easy to see that this situation is unacceptable. Some believed this was a clear case for invoking the precautionary principle. The challenge of changing policies back if new evidence emerged that did not support them, was also discussed.

