

Nicotine analogues: a review of tobacco industry research interests

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ABSTRACT

Aims To explore the tobacco industry's interest and intentions driving its nicotine analogue research.

Methods Review of internal tobacco industry documents regarding nicotine analogues released as part of the Master Settlement Agreement between the tobacco industry and US state governments in 1998.

Findings The tobacco industry investigated nicotine analogues extensively. Four principal areas of interest are evident. First, research on tobacco products was directed towards greater understanding of nicotine pharmacology, how to screen for potential analogues and how to separate the central and peripheral effects of nicotine. Secondly, interest lay in the potential for analogues to replace nicotine in order to create more 'desirable' products and to circumvent anticipated nicotine regulation. Thirdly, interest lay in potential pharmaceutical applications for analogues such as treatments for neurological disorders. Finally, there was interest in the public relations potential of the therapeutic potential of analogues to reduce the demonization of nicotine, by allowing the industry to point to its beneficial uses.

Conclusions With tobacco product and nicotine regulation being increasingly advocated in tobacco control it is important to understand the industry's interests in the potential role of nicotine analogues. Initial interest included using analogues as a means to circumvent regulation, but evidence suggests these plans were discarded due to fear that this may have instigated regulation of tobacco products. Nicotine analogue research has led to potential therapeutic uses for Alzheimer's and Parkinson's diseases and alarmingly for the industry, to a potential vaccine to prevent nicotine addiction.

Recommendations Tobacco manufacturers should be obliged to declare all additives being used in tobacco products. Regulatory bodies should be aware that there is a distinct possibility that the industry has discovered ways to circumvent future regulation of nicotine through the utilization of nicotine analogues. Any regulatory drafting should broaden the definition of nicotine in order to incorporate analogues into the scope of pharmacologically active substances being regulated.

KEYWORDS Analogue, nicotine, regulation, smoking, tobacco, tobacco industry.

INTRODUCTION

Part of the judgement handed down in the 1994 successful suit against the tobacco industry brought by the State

of Minnesota and the Blue Cross and Blue Shield health insurance companies [1] resulted in the public availability of millions of pages of the industry's internal documents which had been discovered in the legal proceedings

[2]. Following a spate of similar litigation, in 1998 the industry signed the Master Settlement Agreement (MSA) with US State Attorneys General [3]. Part of this agreement requires that until 30 June 2010 the US tobacco companies must provide public access to all industry documents produced in state and other smoking- and health-related lawsuits by maintaining these on a website collection [3–5].

The release of millions of previously private internal tobacco industry documents has stimulated numerous reports, including those revealing insights into the industry's knowledge of addiction and its chemical and pharmacological research including the manipulation of nicotine, additives and smoke treatments [6–13]. Glantz *et al.* [7] mentioned briefly the development of nicotine analogues, but industry activity and the potential significance of these compounds has not been explored further by tobacco industry document researchers. This paper considers insights obtained from the documents about the industry's nicotine analogue development programme.

The documents show that the tobacco industry has long held a fundamental interest in nicotine, as it has been long appreciated as 'the most important component of smoke' and 'the reason for smoking' [14]. Nicotine elicits many actions within the body including reinforcing effects. These are produced via activation of nicotinic receptors in the brain and can lead to addiction. Nicotine also affects the peripheral nervous system (PNS), mainly the cardiovascular and respiratory systems. Nicotine raises blood pressure and increases heart rate and in the 1980s it was speculated that nicotine was the primary cause of cardiovascular disease caused by smoking [15], a role now considered less important [16].

Because of the multitude of effects caused by nicotine it was natural for industry scientists to have a deep interest in understanding further the structure and functions of nicotine and its pharmacology and how it might be manipulated in the pursuit of the commercial goals of maximizing consumption and reducing harm. The industry sought to research every aspect of nicotine, including receptor research and nicotine pharmacology. This included research into nicotine analogues, compounds which are structurally similar or related to nicotine, including enantiomers, nicotine derivatives, metabolites and salts [17].

Tobacco ingredients are universally unregulated. The industry has relied on a defence of 'commercial in confidence' to avoid being required to disclose all the ingredients it uses in addition to tobacco in the manufacture of cigarettes [18]. In a small number of nations, it has reached voluntary agreements with governments that have seen public disclosure of a limited range of additives such as flavourants. However, these agreements typically

allow the industry to maintain secrecy over any ingredients deemed commercially valuable or in some way sensitive. In Australia, for example, ingredients for all brands listed on the internet by three tobacco companies include ubiquitous use of unspecified 'processing aids' [19]. This category is not defined or otherwise specified, and so may well include additives such as nicotine analogues.

METHODS

This paper is based on internal tobacco industry documents released as part of the Master Settlement Agreement between the tobacco industry and US state governments and available on the Internet [20]. Preliminary research was conducted in February 2004 using terms and phrases representative of the concept 'nicotine analogue'. Documents containing the word nicotine coupled with various terms such as analog(s), analogue(s), program(me), derivatives, metabolites, and -like compounds were located with search wildcards used to anticipate variations in spelling and inconsistencies in the document description data (known as metadata).

To facilitate systematic document analysis, the 2547 documents and related metadata collected from the preliminary searches were incorporated into a database. The results were sorted by date and evaluated according to their degree of relevance. Relevance was determined if (i) the document provided any insight into nicotine analogue research and (ii) the document described reasons why this research was being undertaken. Follow-up research was conducted on the original websites searched as well as secondary tobacco document collections from March to May 2004 [21–23]. These searches were prompted by clues located in reviewed documents and included named researchers, specific programmes and chemical compound names. Three hundred and thirty documents were judged as most relevant; these were summarized and indexed using a ranking system from 1 (relevant to the subject, providing background knowledge) to 3 (highly significant evidence, strong supporting quotes). Most information concerning nicotine analogues was found in Philip Morris (PM) and R. J. Reynolds (RJR) documents.

British–American Tobacco (BAT) was exempt from providing website access to their documents [5], consequently secondary tobacco document collections making available small subsets of BAT documents were searched for any evidence concerning nicotine analogue research using a selection of the terms listed above [21,23]. A large selection of BAT documents were subsequently released by the University of California, San Francisco (UCSF) in August 2004 [24] and this collection was also searched. We were unable to access the hard-copy versions of

documents held at the Guildford depository in the United Kingdom and the problems of accessing these documents have been reported elsewhere [5].

RESULTS

The documents reveal many aspects of nicotine analogue research within the industry. Specific programmes were developed by PM and RJR to undertake this research. The tobacco industry directed research towards the understanding of the pharmacology of nicotine, how to screen for potential analogues and how to separate the central and peripheral effects of nicotine. Analogues were being investigated for their potential to increase the social acceptability of cigarettes and enhance the effects of nicotine. References were found concerning the potential of analogues to circumvent anticipated nicotine regulation. The industry also held interest in potential pharmaceutical applications for analogues such as treatments for neurological disorders. Finally, there was also interest in the public relations potential of the therapeutic potential of analogues to reduce the demonisation of nicotine, by allowing the industry to point to its beneficial uses.

Programme development

Although there are reports of earlier interest in nicotine analogues, this research began to be of particular importance to tobacco companies in the 1970s and 1980s. One PM programme, Project 2500 (also referred to as both the Nicotinoid Program [25] and the Synthesis of Tobacco Additives [26]), was active in the early 1970s. This was followed by PM's Nicotine Analogue Program which commenced in 1978 [14]. RJR established the Committee on Nicotine Analog Research (CONAR) in 1986 [27]. These programmes were extensive, incorporating research from chemical, pharmacological and bio-behavioural laboratories [15,28]. The main objective of these companies was identical: to synthesize compounds that exhibited positive central nervous system (CNS) nicotinic effects (e.g. reinforcing properties) without the negative PNS effects (e.g. tachycardia). Discovery of such compounds held immense commercial potential, as a compound with these properties might be substituted for or used in conjunction with nicotine, with the final product having the same or improved appeal as regular cigarettes while not carrying the same negative health risks for the cardiovascular system.

While BAT appeared to be researching nicotine analogues in the early 1970s [29] we have found no evidence of a programme dedicated to this (although papers held in the Guildford Depository may be relevant here [5]). Perhaps anticipating later developments in the pharma-

ceutical industry with nicotine replacement therapy, BAT envisioned that cigarette-delivered nicotine could become less attractive if an alternative product was available ('Should nicotine become less attractive to smokers, the future of the tobacco industry would become less secure' [29]). It was also concerned with the possible development of nicotine antagonists which could 'negate the effect of nicotine and lead to the rejection of the smoking habit by some consumers' [29]. Research was performed in anticipation of external research in this area and may indicate motivation for the development of a nicotine analogue as a means to substitute nicotine in tobacco products or to find these alternative compounds before the pharmaceutical companies.

Understanding nicotine

Nicotine analogue research was undertaken initially as a means of better understanding nicotine chemistry [27]. The industry realized that it was important to understand the effects of nicotine and how these were produced as this could determine how these effects could be better controlled and optimized against considerations of consumer satisfaction and addiction. This knowledge could be used to develop a superior smoking product, as RJR noted in a 1990 pharmacology mission statement: '[s]cientific knowledge of nicotine's pharmacological effects and sensory properties is . . . essential in order to define the role of nicotine in smoker satisfaction and to optimize nicotine as a product design parameter' [30]. Also, assessments of the potential health hazards of nicotine on the cardiovascular system could be made [31]. A PM senior scientist saw the nicotine receptor programme being justified 'as a defensive response to the antismoking forces criticisms of nicotine and also as fundamental research into the nature of our product and how it affects our customers, the smokers' [32].

Screening analogues

Research was performed to determine the physical and chemical properties of different analogues. This area of research was carried out at INBIFO, a laboratory in Germany which a PM source noted was 'a locale where we might do some of the things which we are reluctant to do in this country [the USA]' [33]. PM conducted pharmacological screening of analogues, running different animal assays to determine particular aspects of nicotinic activity and to ascertain which compounds were most like nicotine [34]. Compounds were categorized as nicotine-like, partly nicotine-like or not nicotine-like depending on how consistent the results were between assays. The compounds' structure and activity were compared to nicotine to determine which components contributed to

receptor binding and physiological activity. Reports on properties such as the partition coefficients [35] and pKa [36] of each analogue were noted. These properties have implications for the ability of nicotine to cross biological membranes (such as the blood–brain barrier) and the amount of compound available to bind to receptors, respectively. Such research may have isolated compounds with increased addiction potential, as the kinetics (such as the speed and dose) of nicotine delivery play an important role in addiction [37,38].

Animal studies were used to screen analogues for CNS activity and nicotine-like action. PM used discrimination tests to evaluate whether compounds exhibited CNS effects similar to nicotine [39]. Self-administration tests were used to study reinforcing effects and prostration syndrome experiments demonstrated which compounds were acting centrally [40]. Similar tests were used at RJR [15]. The primary researchers named as working in this area were Leo Abood and Victor DeNoble. DeNoble subsequently testified against PM, arguing that self-administration tests were used to indicate whether a substance has abuse liability potential (i.e. whether it is addictive) and that his studies ‘showed that nicotine has reinforcing properties and therefore it could have abuse liability’ [41]. In this testimony DeNoble also indicated that analogues desired by the tobacco industry must retain nicotine’s reinforcing qualities, implying that the compound that PM was searching for would also have addictive potential [41].

Separation of central and peripheral effects

Although appearing structurally simple, nicotine is a complicated compound which triggers many actions in the body. During the 1980s the relationship between nicotine and cardiovascular disease was uncertain [42]; however, the industry considered it important to investigate this further and try to minimize the cardiovascular effects of nicotine. A goal of the nicotine programme—to separate the positive central effects from negative peripheral effects on the cardiovascular system—was intended to create a less harmful, more desirable cigarette. This was termed by PM as ‘offensive research’ to discover a substitute for nicotine which could lower the medical liability of cigarettes [43]. Attempts were made to study nicotine receptors as such knowledge should make it more possible to synthesize a compound to specifically activate that receptor. Different nicotinic receptors are located in the brain than are found in the PNS [44]. It was important to differentiate these nicotinic receptors as adverse effects occur via stimulation of PNS receptors. By targeting the brain (or central) nicotinic receptors, the ‘desirable’ characteristics of nicotine might be captured. Thus there was hope to develop a compound that would

activate these receptors specifically [31]. The record of the documents suggests that most CNS research was performed by PM.

Analogue research was intended to ‘lead to the design of compounds with enhanced desirable properties (central nervous system effects) and minimal detrimental properties (peripheral nervous system effects). . . [which could create] many opportunities for acquiring proprietary compounds . . . [to] serve as a firm foundation for new and innovative products in the future’ [14]. The intent to ‘enhance’ desirable CNS properties indicates that PM was hoping to find a compound which gave more rewarding sensations (which might increase the addictive nature of the product) rather than just trying to make a less dangerous product. This is supported by the comment of a key researcher working on the nicotinoid programme who described the ultimate objective of this project as ‘the synthesis or isolation of a compound or compounds which equal or surpass nicotine in their ability to satisfy the habitual user without the added disadvantages of doing unrelated bodily harm’ [25].

In response to a DeNoble court hearing in 1994 the PM director of research, Cathy Ellis, pondered how to reply to a certain issue on cardiovascular effects ‘without saying [we were] working on [an] addicting compound’ [45].

Although compounds were found that were as active as nicotine, a 1995 report suggests that no compound had yet been synthesized that effectively created the desirable effects of nicotine while eliminating negative side effects [46], although 2'-methylnicotine was reported to have similar CNS activity to nicotine and be less active peripherally [47]. A confidential 1995 draft report states that ‘none of the basic scientific information associated with this study [the nicotine analogue programme] has been used by Philip Morris in the design or marketing of cigarettes’ [48]. However, PM researchers trialled experimental cigarettes that contained various analogues of nicotine (nornicotine, 3-isonicotine, homonicotine and nicotyrine) although of these, only the nornicotine cigarette was deemed acceptable by the researchers that smoked them [49]. Even if these cigarettes were never commercialized this work demonstrates intent to observe the acceptability of analogues with regard to consumer acceptability, hence the plausibility of developing a marketable cigarette.

Social acceptability

The odour and irritation of sidestream smoke are important contributing factors to the social unacceptability of smoking [50]. In efforts to rectify this problem the industry used additives to alter the odour and the irritation potential of sidestream smoke [11].

Nicotine can take the form of two enantiomers (mirror images of the same compound), L-nicotine and D-nicotine, with L-nicotine being the naturally occurring form. Sensory research was conducted on enantiomers of nicotine by both PM and RJR. PM performed experiments on humans (smokers and non-smokers) to evaluate the irritation (burning, stinging, etc.) qualities of nicotine enantiomers [51] likely to determine ways to decrease these negative sensations. In an RJR marketplace performance document CONAR was part of a strategy to provide 'product and process technologies to proactively diminish external marketplace issues' [52], with social acceptability referred to explicitly as an external influence. Both PM and RJR observed that sidestream smoke was not as offensive and irritating when D-nicotine was used rather than the natural isomer, L-nicotine [53,54], although PM reported that D-nicotine produced no physiological impact [53] and therefore would not be a suitable substitute for nicotine. Japan Tobacco has a patent on the use of D-nicotine in cigarettes as a method of providing tobacco flavour [15].

Enhancement

By substituting nicotine with an analogue, the industry thought it might alter nicotine activity. As an RJR scientist said of D-nicotine in 1974:

It can vary the apparant [sic] nicotine level while maintaining the same physiological activity of the smoke. Conversely, it may be used to vary the physiological activity while holding the same level of nicotine [55].

Brown & Williamson were interested in gem-dimethyl analogues of nicotine which were thought to potentially 'amplify and accelerate the physiological response' of nicotine and hoped to find a compound with 'hypernicotinic activity' which would be useful in ultra-low tar cigarettes (often lacking in flavour and impact) to retain physiological satisfaction [56].

Addition of other compounds, rather than substitution of nicotine, was also considered. A 1984 BAT document suggested: '[a]ddition of nicotine analogues to products is but one way . . . in which the essential pharmacological effects of nicotine might be enhanced' [57]. In the late 1980s RJR experimented with the use of nicotine levulinate in their cigarettes [58] as a way of potentiating the effects of nicotine. This compound appears to increase brain receptor binding as it 'enhances the affinity of nicotine for a receptor site that normally has a relatively low affinity for nicotine' [59]. RJR has a patent on cigarette additives which stated the use of nicotine levulinate in cigarettes as a nicotine salt used to increase nicotine content [60].

If the effects of nicotine could be enhanced with analogues, then lower amounts of nicotine could produce the same sensation in users as obtained from regular cigarettes. With some public health addiction specialists arguing that addiction was unlikely to occur below a threshold level of nicotine delivery [61], the addition of analogues may have been seen by the industry as one way of circumventing any future policy developments that set nicotine levels below such a threshold.

Regulation of nicotine

The tobacco industry was quick to see the potential threat posed by the earliest proposals emanating from the public health community about the regulation of nicotine. A 1972 RJR document spelt out their concerns:

If, as proposed above, nicotine is the *sine qua-non* of smoking, and if we meekly accept the allegations of our critics and move toward reduction or elimination of nicotine in our products, then we shall eventually liquidate our business. If we intend to remain in business and our business in the manufacture and sale of dosage forms of nicotine, then at some point we must make a stand [62] [emphasis in original].

The US National Cancer Report of 1974 by the National Cancer Advisory Board (NCAB) [63] was perhaps the first such report to raise the prospect of federal regulation of tar and nicotine content with a follow-up working draft recommendation from the board that: 'A Government agency should be empowered to set maximum cigarette levels of tar and nicotine that will become progressively lower than the 1973 averages' [64]. The industry became concerned that nicotine could eventually be subject to such regulation and required to be removed or substantially reduced. In anticipation of such developments, alternative compounds were to be sought to replace nicotine. In 1974, RJR foresaw the specific use of D-nicotine in cigarettes which may be used '[in] countries where legislation requires the reduction of nicotine in products, D-nicotine could possibly be substituted for the natural product to maintain desirable taste and flavor levels' [55]. BAT intended to investigate 'alternatives to nicotine against the possibility of nicotine being indicted' [65] and RJR speculated that PM research on nicotine analogues was 'for eventual use, if nicotine becomes prohibited' [66]. RJR noted that the understanding of nicotine action and sites and function of neuroreceptors for nicotine and how other substances affect these sites 'may be useful if nicotine is ever ban[ne]d by the Federal Government as a harmful substance. The possibility is real and our alternatives are minimal' [17]. A handwritten, partly illegible, RJR document alludes to use of analogues so a minimum level of nicotine was present to avoid

restrictions and possibly to claim 'nicotine-free' products even though some nicotine would be there [67].

Dangerous research

Research into nicotine analogues was seen by PM as highly sensitive and posing political dangers to the industry. In 1969 William Dunn, a principal scientist at PM, stated:

I would be more cautious in using the pharmonic-medical model—do we really want to tout cigarette smoking as a drug? It is, of course, but there are dangerous F.D.A. implications to having such conceptualization go beyond these walls [68].

PM lawyers were concerned that research on the psychopharmacology of nicotine could be 'viewed as a tacit acknowledgement that nicotine is a drug' and that this 'would be untimely. Therefore . . . we must not be visible about it' [69]. With the prospect of FDA regulation in the background it was thought that such research could trigger FDA action. A 1994 document from PM remarked cryptically that there was a 'strong undercurrent to not "know" everything we can about nicotine + nicotine analogues' [70]. Similarly, BAT acknowledged that use of analogues would be problematic due to 'legal constraints and the cost of registering a new active compound in tobacco products' and might lead to difficult 'public relations and ethical questions' [57]. In 1984, the nicotine programme at PM was terminated with the cessation of DeNoble and Abood research, possibly due to fear of litigation [28,71].

The available documentation of PM's patent registrations for nicotine analogues does not seem to reflect the research they conducted in this area, possibly reflecting its sensitive nature. Patents from the late 1970s and early 1980s state the use of analogues as potential insecticides [72–75], with no mention being made of other uses or the PM research being performed with analogues at this time. A PM patent from 1991 entitled 'Nicotine Analogs' covered compounds which 'exhibit tranquilizing and muscle relaxing activities in mammals, without inducing nicotine-like effects such as hypertension and tachycardia' [76]. This appears to be more linked with the PM research discussed in this paper, although in this patent the compounds are stated as being intended for pharmacotherapeutic uses. This patent was issued 2 years after a consultant alerted PM to the potential use of nicotine analogues in the treatment of Alzheimer's disease [77].

Pharmaceutical interest

The industry was concerned that incorporation of analogues into cigarettes would be prohibited by regulatory

authorities such as the Food and Drug Administration (FDA) because such compounds were pharmacologically active ('unlikely that pharmacologically active novel materials, such as nicotine analogues, would be acceptable either to the Group or regulatory bodies') [78]. This realization led to an expansion into the pharmaceutical market. At PM '[m]anagement concluded that the probability of getting FDA approval for use of these analogues in cigarettes was zero—therefore there was no business value relative to the cigarette industry and the work was patented to cover potential use in the pharmaceutical industry' [79]. Nicotine is thought to have beneficial effects in areas such as the treatment and prevention of Parkinson's and Alzheimer's diseases and Tourette's syndrome [80]. Nicotine is thought to produce its beneficial effects via stimulation of nicotinic cholinergic receptors in the CNS. It was reasoned that nicotine analogues may display similar positive effects.

As early as 1980, a BAT scientist suggested the company should 'look at itself as a drug company rather than as a tobacco company' [81] and recognized the potential to diversify into use of nicotine analogues, and even cannabis, as tranquillizers. This scientist noted that for the market to thrive the 'social acceptability' of use of these drugs would need to be increased.

At present, the taking of many of these drugs is either medically prescribed or regarded as deviant behaviour, but could be socialised; like alcoholic drinking and tobacco smoking [81].

Research on nicotine benefits led RJR to develop the Nicotine Pharmacology and Neurodegenerative Disease Program [82] and in 1997 RJR established Targacept [83], a pharmaceutical company dedicated to the discovery of nicotinic compounds for therapeutic uses. RJR claims that this company is completely separate from its cigarette company [84]. RJR has patents on nicotine analogues which describe uses as pharmacological treatments for hypertension [85] and neurodegenerative diseases [86].

Public relations benefits

While the diversification into pharmaceuticals was motivated primarily by the prospect of increasing revenue, this development was also seen as a way to improve the industry's corporate image. PM decided that supplying research on analogues to Warner-Lambert, a pharmaceutical company, for investigation of nootropic agents may be 'an opportunity for some positive public relations' [87]. In 1989, RJR saw the research into neurological benefits of nicotine as bringing secondary public relations gain to the industry by

'improv[ing] public perception of nicotine/smoking' [88]. RJR also saw that information on these benefits would 'ultimately improve the acceptance of RJRT products and positively impact smokers' preference for these products' [88]. In 1994, RJR continued to seek positive perceptions of these benefits: '[d]evelopment of therapeutics from nicotine derivatives may be valuable RJRT goodwill; e.g. perceived positive product from Company know-how' [89].

Nicotine analogue research outside of the tobacco industry

There is continued interest in the pharmaceutical applications of nicotine analogues in the treatment of CNS disorders [90]. Analogues may also have potential as smoking cessation devices as seen by the use of cytisine, a nicotine-like compound found in certain leguminous plants [91]. Cytisine is the principal ingredient of Tabex, a smoking cessation medication which has been used since the 1970s.

PM discovered in the early 1990s that certain compounds could stimulate an immune response and trigger the production of nicotine-specific antibodies [92]. Although PM used this information to develop an enzyme-linked immunosorbant assay (ELISA) to determine nicotine concentration in samples, similar technology has been used by researchers outside the tobacco industry in the attempt to develop a vaccine which could prevent nicotine addiction [93]. The rationale behind the vaccine is that by inducing nicotine-specific antibodies which bind the free nicotine, the resultant complex cannot cross the blood-brain barrier, thus preventing nicotine having central effects so no positive reinforcement would be experienced when smoking. Without this positive reinforcement it would be expected that many heavy smokers will be more inclined to quit and new smokers will not become addicted. The vaccine has not been trialled in humans but has been shown to be effective in rats [94]. Work continues to make this vaccine compatible with humans [95]. Any eventual development and release of such a vaccine could have catastrophic implications for the future of tobacco products. If a compound was found to have the same actions as nicotine but was not affected by antibodies which work specifically to bind nicotine, tobacco industry interest in their development would be obvious as they may be able to use this to evade the actions of the vaccine. No evidence was located regarding the industry's reaction to the potential development of a vaccine; however, this is a very recent issue and it is likely that the industry is now much more careful with their documents, knowing the potential for them to be discovered in legal proceedings since the MSA.

DISCUSSION

The international tobacco industry has destroyed an unknown but extremely large number of internal documents for purposes that include the avoidance of litigation [96–100]. Given the extreme sensitivity within the industry to the threat of meaningful ingredient regulation, and increasing calls for the addictiveness and toxicity of tobacco products to be subject to such regulation [101], it is plausible that the industry may have destroyed or kept private many more documents on nicotine analogue research than we have been able to locate. Indeed, a 1992 fax from BAT's London lawyers detailing document destruction noted 'The documents now destroyed include . . . [some on] the properties of nicotine and the toxicity of certain additives' [96]. Therefore the evidence presented here represents an unknown cross-section of all research ever conducted by the companies in this area.

Despite many calls for nicotine and tobacco regulation by health advocates [38,102–105], there are currently no real limitations placed on the tobacco industry with regard to cigarette contents in any nation. Voluntary ingredient disclosure does not provide critical information on the true contents of tobacco products [13].

In October 2004 a bill was passed by US Congress for a \$10 billion buyout for tobacco farmers; however, an amendment that would have allowed FDA the authority to regulate tobacco products was omitted [106]. The FDA bill would have allowed the FDA to require disclosure of contents and changes to products to make them less harmful as well as to address other public health concerns such as youth smoking [107]. Within this bill nicotine was defined as 'the chemical substance named 3-(1-methyl-2-pyrrolidinyl) pyridine or C[10]H[14]N[2], including any salt or complex of nicotine' [107]. This wording does not incorporate nicotine analogues other than nicotine enantiomers (such as D-nicotine) and nicotine salts (such as nicotine levulinate).

Advocates of tobacco product regulation and regulatory agency staff should be aware that if nicotine is ever regulated that there is a distinct possibility that the industry has already discovered ways to circumvent less than comprehensive requirements through the utilization of nicotine analogues. Any regulatory drafting would need to anticipate such a possibility and broaden the definition of nicotine in order to incorporate analogues into the scope of those pharmacologically active substances being regulated. For this to happen, governments would need first to demand that tobacco manufacturers declare all additives being used in tobacco products, and not allow them to hide analogues and any other pharmacologically active ingredients in commercial-in-confidence 'catch-alls' such as 'processing aids' which are not revealed to either regulators or consumers [13].

The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) is a legally binding public health treaty designed to reduce the negative health and economic impacts caused by tobacco [108]. The FCTC provides a mechanism for regulation of nicotine and pharmacologically active products under articles 9 and 10, regulation of the contents of tobacco products and regulation of tobacco product disclosures, respectively [109]. The FCTC is becoming closer to legally binding implementation, needing 40 countries to ratify the Convention, with 34 having already done so (as at the end of October 2004) [108].

CONCLUSION

With the regulation of tobacco products including nicotine being advocated increasingly in international tobacco control circles [110,111], it is important to understand the industry's interests in this issue. Nicotine analogues have been considered by the industry as a means to escape regulation, although these plans later appeared to have been discarded due to fear that this may have triggered regulation of tobacco products. However, given the intensely secret nature of tobacco industry product engineering and its almost total lack of public transparency, it is not possible to reject the possibility that this research has continued or even been integrated into products already on sale. We would encourage governments to investigate explicitly the possibility that this is occurring and its implications for future regulatory developments.

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