SCENIHR PRE-CONSULTATION OPINION ON "ADDICTIVENESS AND ATTRACTIVENESS OF TOBACCO ADDITIVES"

JT INTERNATIONAL SA ("JTI") SUPPLEMENTARY COMMENTS ON ABSTRACT, EXECUTIVE SUMMARY, BACKGROUND, TERMS OF REFERENCE AND SCIENTIFIC RATIONALE

This paper sets out JTI's further comments on the SCENIHR pre-consultation opinion on "addictiveness and attractiveness of tobacco additives." It is intended to supplement our main response to the Working Group's draft Opinions, which we submitted online on 3 September 2010. We are happy for it to be shared with members of the Working Group and/or made publicly available.

Given the limited time available to us to produce these comments, we have focussed on what we consider to be the most important issues with the pre-consultation opinion. If we have not commented on other issues or wording, this should not be taken as signalling our agreement with the same.

Page	Para-graph	Statement / JTI's comments
4	2	Statement: "*… tobacco has a high addictive potential*" Comment: This is not supported by data presented elsewhere in the pre-consultation opinion.
4	3	Statement: "*In humans, the positive correlation between tobacco consumption and dependence suggests that individuals with high nicotine levels in their blood are more dependent*." Comment: This is a non-sequitur, given the acknowledgement in the previous paragraph that: "*The reinforcing potency of drugs is measured after intravenous injections and suggests that the addictive potential of pure nicotine is weak*". The conclusion that nicotine is only weakly reinforcing is also supported by other data in the pre-consultation opinion.

4	4	Statement: "*However, sugars, which are present in high quantities in most tobacco products, give rise to acetaldehyde in cigarette smoke. Acetaldehyde given intravenously is addictive and enhances the addictiveness of nicotine in experimental animals.*" Comment: The statement could give the inaccurate impression that sugars present in tobacco product and/or acetaldehyde in smoke have been shown to cause dependence. On the contrary, as the authors note elsewhere, "*there is no proof that acetaldehyde in smoke contributes significantly to blood levels of acetaldehyde*" (p.9) and "*one study showed that even during heavy smoking, acetaldehyde in breath rose six-fold in smokers although only minor amounts of the acetaldehyde in the smoke is absorbed into the blood stream (McLaughlin et al. 1990), suggesting no (indirect) addictive effect of sugars when used as a tobacco additive*" (p.41). This is consistent with other studies cited by the authors (at p.43), which suggest that acetaldehyde would have to be present in high concentrations in the blood in order to overcome aldehyde dehydrogenase and cross the blood brain barrier (Tabakof et al. 1976). Other reviews (e.g. van Andel I et al, 2002, The Health and Addiction Risk due to Exposure to Aldehydes of Cigarette Smoke. Part 1; Acetaldehyde, Formaldehyde, Acrolein and Propionaldehyde. RIVM Report 650270003/2002 - conducted by RIVM for the Dutch Directorate for Public Health) have concluded that it is highly unlikely that acetaldehyde in cigarette smoke has any pharmacological effect on the smoker. The major source of the brain acetaldehyde is from alcohol consumption, not smoking (see Eriksson, CJ, 2001, The Role of Acetaldehyde in the Actions of Alcohol (update 2000). Alcohol: Clinical and Experimental Research, 25, 15S-32S.).
4	4	Statement: "*Additives that facilitate deeper inhalation (e.g. menthol) or inhibit the metabolism of nicotine may enhance the addictiveness of nicotine indirectly.*" Comment: The statement that menthol facilitates deeper inhalation of cigarette smoke is incorrect: the authors acknowledge at p.54 of the pre-consultation opinion that "*current data are inconclusive*" in this regard. Further, in light of the conclusion that "*the addictive potential of pure nicotine is weak*" (p.4), it is unclear that, even if ingredients were to facilitate deeper inhalation and/or inhibit the metabolism of nicotine, this would be meaningful in terms of smoking behaviour.

4	4	Statement: "*Substances such as ammonia that increase the pH of the tobacco and the smoke, result in higher amounts of uncharged nicotine. However, it is uncertain if more nicotine is absorbed with higher smoke pH.*" Comment: This is inconsistent with the authors' conclusion at p.54 of the pre-consultation opinion that it is "*unlikely*" (rather than "*uncertain*") that ammonia compounds increase the absorption of nicotine by the lungs. Generally, the pre-consultation opinion quite correctly supports the conclusion that the use of ammonia compounds has not been shown to have any effect on nicotine absorption. Further, in light of the conclusion that "*the addictive potential of pure nicotine is weak*" (p.4), it is unclear that, even if the bioavailability or speed of delivery of nicotine were somehow enhanced by the use of ammonia or similar compounds, this would be meaningful in terms of smoking behaviour. JTI does not, in any event, add ammonia or ammonia compounds to the tobacco in its cigarettes.
4	8	Statement: "*The use of fruit and candy flavours seems to favour smoking initiation in young people.*" Comment: The authors cite no credible evidence, here or elsewhere, to support the proposition that the use of any particular flavour favours smoking initiation by minors. The wording used here ("*seems to favour…*") is an indication of the lack of evidential basis for this statement, which should be removed. The authors also appear uncertain whether the use of fruit or candy flavours generally, or only "*in high amounts*" (p.10, para. 7), have this effect. JTI does not design its products to appeal to minors or market them to minors.
4	8	Statement: "*Menthol also attracts a number of smokers (in particular African Americans).*" Comment: Statistical evidence concerning the smoking preferences of African Americans is by definition of limited utility in assessing preferences among EU consumers. As the authors note at p.10, menthol cigarettes command a relatively small market share in EU countries and there is currently a trend towards cigarettes that contain no ingredients. It is therefore potentially misleading to write that "*menthol… attracts a number of smokers*" (since the implication is that this is a high number, while the evidence suggests the contrary as far as the EU is concerned).
8	2	Statement: "*… tobacco has a high addictive potential*" Comment: This is not supported by data elsewhere in the pre-consultation opinion.

8	2	Statement: "*In addicted individuals a modified neural network exists, and the potential to induce such modifications should be the criteria used to define the addictive potency of a product.*" Comment: The pre-consultation opinion contains little evidence to suggest that nicotine exposure produces modifications to neural networks and/or that this is indicative of "*the addictive potency of a product*" (see our comments below regarding p.31, para. 2). Moreover, it is clearly premature to assert that the potential to induce modification of the regulation of neural networks can be used as criteria to define the addictive potency of a product, given the current, uncertain status of the science. The authors acknowledge this uncertainty at various points in the pre-consultation opinion: see e.g. p.32 ("*The brain regions underlying nicotine physical dependence have not yet been fully clarified, although an involvement of nAChRs located in the medial habenula and the interpeduncular nucleus has been recently reported (Salas et al. 2009)*") and p.36 ("*The action of nicotine on the CNS is multifaceted and the mechanisms of addiction are still poorly understood*").
8	6	Statement: "*… tobacco consumption (e.g. number of cigarettes smoked per day) is positively correlated with dependence. This suggests that individuals who maintain higher nicotine levels in their blood are more dependent than individuals who maintain low levels.*" Comment: It is not the case that number of cigarettes smoked per day is an indicator of dependence, as the authors go on to acknowledge at p.63 of the pre-consultation opinion ("*… the number of cigarettes smoked per day is often a poor measure of dependence*"). Moreover, even if such a correlation did exist, this would not suggest that smokers with high levels of nicotine in the blood would be "more dependent" than smokers with lower levels of blood nicotine. Correlation is not causation. On the contrary, the authors' conclusion that "*the addictive potential of pure nicotine is weak*" (p.4) would suggest that this is improbable, as would the observation (page 8, para. 9) that reinforcement is not directly linear with the dose of nicotine in animals.
8	10	Statement: "*However, sugars which are added in high quantities to most tobacco products, give rise to acetaldehyde in tobacco smoke and acetaldehyde given intravenously is self-administered by animals and may thus be considered addictive.*" Comment: This conclusion is not tenable in light of the current state of the science. See our comment re. page 4, para. 4, above. Moreover, the pre-consultation opinion does not support the statement that sugars are added "*in high quantities*" to "*most*" tobacco products. On the contrary, the authors observe elsewhere that, typically, only low levels of flavour ingredients are used (p.40) and that "additive-free" brands are increasingly popular in many markets (p.80).

9	2	Statement: "*Sugars or their derivatives produce numerous substances upon heating. One of these is acetaldehyde, which enhances the addictiveness of nicotine when injected into experimental animals, probably by inhibiting monoamine oxidase (MAO) in the brain. Smokers have decreased levels of MAO in the brain.*" Comment: This tentative conclusion about a possible mechanism relating to MAO inhibition is not tenable in light of the current state of the science, or indeed in light of the following sentence (which correctly states that "*there is no proof that acetaldehyde in the smoke contributes significantly to blood levels of acetaldehyde*"). In particular, the MAO/harman/norharman hypothesis that is raised at a number of points in the pre-consultation opinion is purely speculative. The emphasis given to this issue is disproportionate, given that the authors recognise that "*the relevance of this observation in the addiction of tobacco smoking is not clear*" (p.43) and "*[t]he mechanism of action of harman is not well established. For example, could coffee drinking also lead to inhibition of MAO?*" (p.44). To the extent that smokers do have decreased levels of MAO in the brain, it is not certain that this is a pharmacological effect of tobacco smoke or tobacco (rather than, for example, a biological characteristic of smokers or the result of confounding behaviours – e.g. if coffee drinking does lead to inhibition of MAO, perhaps smokers drink more coffee than non-smokers). The authors of the study which is later cited to support the suggestion that MAO inhibition contributes to dependence (Berlin and Anthenelli 2001; see p.14) acknowledge in that reference that it is a "*hypothesis*" that chronic habitual smoking can be understood in terms of reduced MAO activity. Berlin and Anthenelli also acknowledge in that paper that their conclusion that MAO inhibition by compounds found in tobacco smoke or tobacco can potentiate nicotine's effect is "*speculation*".
9	3	Statement: "*Additives that facilitate deeper inhalation (e.g. menthol) may enhance the addictiveness of nicotine indirectly.*" Comment: see our comment re. p.4, para. 4, above.
9	3	Statement: "*Substances such as ammonia that increase the pH of the tobacco (and the smoke) result in higher amounts of uncharged nicotine that is more easily absorbed by the cells. However, due to the high buffer capacity of the lining fluid in the lungs it is uncertain if more nicotine is absorbed with higher smoke pH.*" Comment: see our comment re. p.4, para. 4, above.

9	5	Statement: "*Many smokers compensate for a lower dose of nicotine by increasing puff volume and frequency, and by deeper inhalation*". Comment: Such compensation refers to smokers who trade down from a tobacco product with higher machine-measured TN yields to one with lower machine measured TN yields. In other words, it is a product of changing smoking behaviour – smokers generally have not been shown to "compensate". Moreover, compensation does not occur in all smokers who switch. Indeed, the evidence suggests that, among smokers who do compensate, compensation is not complete and is temporary (see Scherer G (1999) Smoking Behaviour and Compensation – A Review of the Literature. Psychopharmacology, 145, 1-20). Finally, in Opinion 7, the authors state that smokers "*usually*" compensate, which is not supported here.
9	6	Statement: "*The criterion for attractiveness is the stimulation to use the product. Attractiveness of additives refers to factors such as taste, smell and other sensory attributes. In addition, a number of external factors (e.g. ease of use, flexibility of dosing system, cost etc.) contribute to the attractiveness of the product.*" Comment: This definition of "attractiveness" fails established criteria for issue definition and no scientific criteria have been developed to assess the "attractiveness" of tobacco products, let alone to regulate on that basis. JTI does not accept the suggestion that a policy objective of ingredient regulation should be to make smoking less pleasurable. The wide range of factors identified here indicates that the concept is inherently subjective, and the methods suggested at p.10 of the pre-consultation opinion for assessing the attractiveness of a particular ingredient (e.g. monitoring subjective response of smokers on test panels) reinforce this. The authors' definition of attractiveness also appears to vary throughout the pre-consultation opinion (e.g. sometimes it extends to cover non-ingredient factors such as packaging – which are, in any event, outside SCENIHR's terms of reference, as discussed below). Smokers use and enjoy tobacco products for many different reasons, and indeed (as the pre-consultation opinion acknowledges at p.10) many choose to consume cigarettes containing no or few ingredients.
9	6	Statement: "*The attractiveness of tobacco products may be increased by a number of additives that create a specific taste/flavour in order to attract certain target groups.*" Comment: The pre-consultation opinion presents no evidence that the purpose of the use of flavouring ingredients is to "*attract certain target groups*".

10	7, 11	Statements: "*The use of fruit and candy flavours in high amounts seems to favour smoking initiation by young people*" (para. 7); "*Cigarettes with certain flavours (e.g. fruit, candy) appear to be developed to target young people.*" (para. 11). Comment: The authors cite no credible evidence, here or elsewhere, to support the propositions that the use of any particular flavour is intended to, or does in fact, favour smoking initiation by minors. The wording used here ("*seems to favour*", "*appear to be developed…*") is an indication of the lack of evidential basis for these statements, which should be removed. JTI does not design its products to appeal to minors or market them to minors.
12	1	Statement: "*Some 72-92% of adult cigarette smokers meet the criteria for dependence.*" Comment: Various studies have suggested that a varying proportion of smokers are "dependent", but these studies do not involve clinical assessments as required under the various diagnostic instruments. In addition, the reference given to support this statement (Henningfield & Zeller 2002) is inappropriate. The reference is an opinion article, which itself makes (uncited) reference to FDA data on dependence among smokers in the USA.
12	2	Statement: "*By altering the taste and smell of cigarettes the product are made more attractive and the smoke more palatable, which leads to an increase in smoking initiation.*" Comment: These statements are unsupported. The pre-consultation opinion contains no credible evidence suggesting a link between ingredient use and smoking initiation (let alone "*an increase in smoking initiation*" – i.e. cases of people become smokers as a result of the use of ingredients, who would not otherwise have done so).
12	2	Statement: "*At present, the role of additives in enhancing the addictiveness of tobacco products is not clear.*" Comment: The statement presupposes that ingredients have such a role. In fact, it is not clear that ingredients play any role whatsoever in "*enhancing the addictiveness of tobacco products*".

12	3	Statement: "*In order to make tobacco products more attractive, design features are introduced, e.g. package design and cigarette form. In addition, these features are used to undermine the effect of the maximum limits set by the Tobacco Products Directive 2001/37/EC on tar, nicotine, and carbon monoxide yields in cigarettes.*" Comment: Consideration of the role of package design and cigarette form falls outside SCENIHR's terms of reference (p.13), which are confined to the impact – if any – of tobacco ingredients and certain technical characteristics of the product itself on addictiveness and attractiveness (see below).
13	1	SCENIHR's terms of reference are narrowly defined and do not include, among other things, the design of packaging of tobacco products, product design (except insofar as this concerns ingredients and certain technical characteristics of the product itself), advertising and promotion (unless on the basis of ingredients use) or smoking related disease. Areas of discussion in the pre-consultation opinion that fall outside these terms of reference should be deleted: see e.g. p.12, para. 3 (wording re package design and cigarette form); p.47, paras.8-9 (descriptors, pack colour); p.50, paras. 6-7 (alleged impact of mentholation on B[a]P content of smoke and on lung cancer incidence); p.65, para. 1 (pack design); p.70, para. 5 (advertising and promotion); p.71, paras. 4-6 (perceived brand preferences); p.79, para. 6 (alleged targeting of advertising and promotion to minors). SCENIHR was asked to consider the association between ingredients and tobacco consumption (term of reference 11), but a notable omission from the pre-consultation opinion is any discussion of epidemiological and ecological data comparing the use of cigarettes with added ingredients and those without (e.g. mentholated vs. unmentholated cigarettes, or Virginia vs. American blend cigarettes).
14	2	Statement: "*The addictiveness of nicotine is enforced by substances in tobacco leaves that inhibit the action of monoamine oxidase (MAO) in the body (Berlin and Anthenelli 2001).*" Comment: see our comments re. p.9, para. 2, above. In particular, this statement fails to acknowledge Berlin and Anthenelli's own recognition that the role of nicotine-induced MAO inhibition is hypothetical and speculative.

14	3	Statement: "*Certain flavours (e.g. candy and fruit) have been used largely to make tobacco products more appealing to children (called "young adults" by the tobacco industry).*" Comment: The authors cite no credible evidence, here or elsewhere, to support the proposition that the use of any particular flavour favours smoking initiation by minors or that they have been used in this way. This statement should be removed. JTI does not design its products to appeal to minors or market them to minors. It does not use "codewords" in its documents to refer to minors.
16	3	Statement: "*Cigarettes are highly engineered, exquisitely designed 'nicotine delivery devices'.*" Comment: The authors provide no evidence, here or elsewhere, to support this proposition. Further, in light of the conclusion that "*the addictive potential of pure nicotine is weak*" (p.4), it is unclear why cigarettes would have been engineered in this way.
16	3	Statement: "*Similarly, the physical and chemical characteristics of cigarettes interact to alter the size distribution of the aerosol particles that convey nicotine and other chemicals, and thus influence absorption (WHO 2007b).*" Comment: This statement should be deleted, as it conflicts with the authors' conclusion (at p.27) that, "*based on the limited publicly available information, it seems that exposure to nicotine cannot be substantially increased by altering the particle size of the smoke aerosol.*"
17	5	Statement: "*For the purpose of this report, we consider that the WHO definition [of ingredients] is the most useful, as some of the added ingredients (e.g. different forms of sugar) are already present in the tobacco leaves.*" Comment: This definition of "ingredients" is not consistent with that used in the current EU Directive 2001/37/EC.

17	9	Statement: "*Addiction is the commonly used term referring to what is technically known as 'dependence' and is widely employed to connote severe substance dependence, as has been demonstrated to occur in tobacco users. Dependence has been defined by the WHO Expert Committee on Drug Dependence (2003) and The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines (WHO 1992). Addictiveness refers to the pharmacological potential of a substance to cause addiction. Abuse liability of a drug is the likelihood that its use will result in addiction (dependence) and it can be assessed in laboratories by methods referred to as abuse liability testing. (Schuster and Henningfield 2003, Wayne and Henningfeld [sic] 2008b, WHO 2003). The terms 'dependence-causing' and 'dependence potential' have been used as synonyms for 'addictive' and 'addictiveness', respectively. In addition to the neurobiological characteristics of the substance itself, dependence potential is related to the dose, speed of absorption, metabolism and to physical and chemical features of the formulation.*" Comment: The mixing and inconsistent use of the terms "addiction", "dependence", "severe substance dependence", "addictiveness", "abuse liability", "dependence-causing", "dependence potential" leads to a potentially confusing series of semantic interrelationships, which could in turn lead to potentially unsupported conclusions being reached. This inappropriate and technically imprecise usage ignores the fact that these different terms may indicate different things. For example, the authors of a 2006 letter to the American Journal of Psychiatry noted that, in relation to opioid-related phenomena, The American Pain Society, The American Academy of Pain Medicine, and the American Society of Addiction Medicine had developed a consensus document that clearly distinguished between "addiction" and "physical dependence" – such a distinction being an important tool in the prevention of "opioid-phobia" and the unwarranted fear of addiction that might impede effective pain management in a patient population (Fainsinger, Thai et al 2006). See also Shaffer HJ (1997) The Most Important Unresolved Issue in the Addictions: Conceptual Chaos. Substance Use and Misuse, 32, 1573-1580. This lack of clarity in issue definition renders the findings of the remainder of the pre-consultation opinion problematic. We note that, whatever definition of addictiveness is used, this does not affect the fact that people can stop smoking if they are determined to do so. Based upon the available scientific evidence, our view is that tobacco products with added ingredients are no more difficult to quit than those that do not contain added ingredients.

18	3	Statement: "*According to the WHO, the terms "attractiveness" or "consumer appeal" refer to factors such as taste, smell and other sensory attributes, ease of use, flexibility of dosing system, cost, reputation or image, assumed risks and benefits, and other characteristics of a product designed to stimulate use (WHO 2007b).*" Comment: see our comments p.9, para. 6, above. We also note that it is wrong to attribute the views of the WHO Study Group on Tobacco Product Regulation to the WHO itself. The front cover of the document referenced here clearly states that: "*This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.*"
18	4	Statement: "*Although the risk of dependence on any substance is partially related to the attractiveness and/or ease of use of the delivery system, these features are not typically evaluated in dependence-potential testing but rather are generally described as factors affecting "consumer appeal" or "attractiveness". Addictiveness and attractiveness go hand in hand as the real world liability for abuse of and addiction to a tobacco product is to a large extent also related to the attractiveness of the tobacco product.*" Comment: An inappropriate attempt is made to mix the concept of "addictiveness" with "attractiveness" (as described in the preceding paragraph). Addictiveness is previously described at p.17, para. 9 in pharmacological terms. How would the authors consider addictiveness and attractiveness to be scientifically related, as asserted here ("*go hand in hand*"), if addictiveness is a pharmacological measure and attractiveness is a measure of smokers' subjective response to a product, its ingredients and even its packaging? It is important to ensure that these terms, which the authors treat as largely synonymous, are used properly, or at least that the interrelationship between them is clarified. We note also that the authors make no attempt to (or are unable to) distinguish between the relative contribution of "addictiveness" and "attractiveness" to tobacco use, which is itself probably the result of the weak definitions that are offered here.
18	5	Statement: "*Attractiveness is powerfully determined by imagery and cultural associations…*". Comment: This both reinforces the lack of clarity surrounding the concept of "attractiveness", as it is used in the pre-consultation opinion, and appears to lessen the potential importance of other factors, such as ingredients. The role of imagery and cultural associations in the "attractiveness" of a tobacco product are also well beyond the authors' terms of reference.

19	5	Statement: *"Reconstituted tobacco or homogenized tobacco sheet is a paper-like sheet approaching the thickness of tobacco laminae… The introduction of reconstituted tobacco or RECON is the primary means by which ammonia chemistry and other chemicals are introduced into the cigarette."* Comment: JTI does not add ammonia or ammonia compounds to the tobacco in its cigarettes.
19	6	Statement: "*Blending is carried out to achieve specific pH, taste, burning characteristics and nicotine content.*" Comment: JTI blends tobaccos in order to ensure product consistency (in light of seasonal and geographical variations in tobacco crops).
22	3	Statement: "*Over the years the tobacco industry has developed genetically modified (GM) tobacco plants with an aim, among others, to manipulate nicotine levels…*" Comment: JTI does not knowingly employ genetically modified tobaccos in its products. In any event, from the examples that follow (if correct), it appears that the principal use of GM tobaccos by other companies has been to reduce machine-measured nicotine yields from tobacco products.
22	5	Statement: "*Cigarettes… are highly engineered nicotine delivery devices…*" Comment: See our remarks on p.16, para. 3, above.
23	3	Statement: "*It appears, however, that smokers compensate for the lower dose of nicotine per puff (due to increased ventilation) by increasing their puff volume, puff frequency, and [through] deeper inhalation of the smoke (Jarvis et al. 2001, Scherer 1999).*" Comment: See our remarks on p.9, para. 5, above.

26	1	Statement: "*Light cigarettes have been marketed as products with a lower health risk as they should deliver less tar and other toxic compounds in the smoke inhaled.*" Comment: JTI does not present (via marketing or otherwise) products with lowered machine-measured TNCO yields as being less hazardous than any other product. In any event, the hypothesis that tobacco products yielding lower machine-measured TNCO may be less hazardous for health, on a population level, than those with higher TNCO yields was widely accepted by the international public health community for many decades and indeed finds expression in Directive 2001/37/EC's setting of maximum machine-measured TNCO levels for tobacco products sold in the EU.
27	1	Statement: "*Data obtained in animal studies suggest that cigarettes with high ventilation (often described as 'light' or 'low tar') may favour addiction to nicotine in the smokers of these products, because of an increased smoking frequency.*" Comment: No reference is given for this statement, and no explanation is given as to how highly ventilated cigarettes might favour addiction (particularly given that the authors' conclusion, shortly thereafter, is that "*based on the limited publicly available information, it seems that exposure to nicotine cannot be substantially increased by altering the particle size of the smoke aerosol*", by means of ventilation or otherwise). There is no credible evidence to suggest that regular smokers of lower tar and nicotine products find it more difficult to quit than those who smoke full-flavour products, or that they smoke more cigarettes.

29	8	Statement: "*After inhalation [nicotine] reaches high levels in the brain within 10-20 seconds, thus being equivalent to, or even faster than, an intravenous administration (Gourlay and Benowitz 1997, Hukkanen et al. 2005).*" Comment: Recent studies suggest that speed of delivery of nicotine to the brain during smoking is slower than previously thought. A recent study (Rose JE et al (2010) Proceedings of the National Academy of Sciences, 107, 5190-5195) using positron emission tomography showed that the time for inhaled nicotine to reach the brain was, on average, 126 seconds (to reach 90% of peak brain nicotine levels). Another recent study (Rose JE et al (2010) Psychopharmacology 210, 1-12) compared arterial nicotine levels after smoking or intravenous nicotine injections. Samples were collected every 5 seconds and the author found the concentrations of nicotine in arterial blood in both conditions to be 10 times lower than expected, were the entire pharmacologic dose of nicotine to be completely absorbed directly via the lung into the pulmonary circulation. The author concluded that "*the delivery of nicotine into arterial blood is substantially slower than would be predicted if nicotine were absorbed as rapidly as has generally been assumed*". In another study (Rose JE (2000) Pharmacology, Biochemistry and Behavior 67, 71-81), subjective human responses (in terms of "satisfaction" and "psychological reward") were found to be similar for continuous I.V. infusion of nicotine compared to pulse nicotine boli intended to simulate puff-inhalation. The author stated that: "*we found that arterial nicotine concentrations produced by nicotine inhalation or injection often show a gradual rise over 30-60 s, not dissimilar from what would be produced by a continuous infusion*". In any event, even if nicotine in cigarette smoke did reach the brain as rapidly as has been suggested in the pre-consultation opinion, this would not explain smoking behaviour. The suggested time period of 10-20 seconds for inhaled nicotine to reach the brain is not significantly different from the estimated 13 seconds that it takes I.V. nicotine to do so. Moreover, other studies suggest that, among NRT options, the fastest route to delivery (nasal spray) was the least preferred by smokers. So far as we are aware, no study shows a correlation to exist between the speed of delivery of nicotine and subjective reward.

31	2	Statement: *"Nicotine exposure produces adaptive changes in the central nervous system (CNS) leading to an addictive process characterised by compulsive tobacco use, loss of control over tobacco consumption despite the harmful effects, the appearance of withdrawal symptoms upon the cessation of tobacco smoking, and relapse after periods of abstinence (McLellan et al 2000).*" Comment: This finding is inconsistent with evidence elsewhere in the pre-consultation opinion to the effect that "*the addictive potential of pure nicotine is weak*". No further evidence is presented in the pre-consultation opinion as to the presence of adaptive changes in the CNS, despite this being one of the authors' major findings and their suggested basis for determining the presence of addiction (see remarks re. p.8, para. 2, above). Further, it is not accepted that tobacco use can be characterised as involving a loss of control.
31	2	Statement: "*… all the valuable information currently available about drug addiction, including nicotine addiction, is based on the results obtained in experimental models that evaluate drug rewarding/reinforcing effects (see section 3.9 for details about significance of the models.*" Comment: The experimental models referred to in section 3.9 of the pre-consultation opinion are experimental animal models. This should be mentioned here.
32	1	Statement: "*… repeated exposure to nicotine leads to up-regulation and desensitisation of nAChRs (Quick and Lester 2002), which are involved in the development of nicotine tolerance and the appearance of a withdrawal syndrome following smoking cessation.*" Comment: The statement that nAChR upregulation and/or desensitization are "*involved in the development of nicotine tolerance and the appearance of a withdrawal syndrome following smoking cessation*" is not supported by Quick and Lester (2002). In fact, nicotine-induced upregulation of the absolute number of nAChR receptors is of uncertain significance for smoking behaviour. There is controversy as to whether the functions of the receptors affected by up-regulation change and/or whether they become desensitized or not. Even if one assumes no change in the receptors' affinity for nicotine, the occurrence of nicotine receptor up-regulation does not dictate that the brain has become dependent on nicotine. This would run contrary to the accepted pharmacodynamic understanding of the mechanisms that produce tolerance in the case of drugs of abuse, which are associated with down- rather than with up-regulation.

33	3	Statement: "*The efficacy of naltrexone on smoking cessation in humans supports the involvement of opioid receptors in nicotine reward (Rukstalis et al. 2005)*". Comment: The majority of studies suggests that naltrexone is not effective in combating smoking cessation (see David SP et al, 2006. Opioid Antagonists for Smoking Cessation. Cochrane Database of Systematic Reviews. Art.No.: CD003086).
33	2	Statement: "*Multiple neurotransmitter pathways are activated by nicotine, including dopaminergic, GABAergic and opioid pathways. The complexity of the mechanisms of addiction is further underlined by the involvement of the endocannabinoid system, and the serotonergic system also seems to be involved.*" Comment: However many different neurotransmitter systems are activated by nicotine, the overall "*addictive potential of pure nicotine is weak*" (p.4), and it is therefore inappropriate in this context to refer to these pharmacological processes as constituting "*the mechanisms of addiction*".
35	3	Statement: "*Addiction to nicotine is difficult to measure directly and is usually assessed experimentally with reference to reinforcement assessed in self-administration paradigms.*" Comment: It would be appropriate to note here that nicotine self-administration experiments of the sort described here demonstrate that nicotine is only weakly reinforcing.
35	4	Statement: "*Tobacco products are manipulated by tobacco companies by the addition of chemical compounds, most of which are flavours.*" Comment: The term "*manipulated*" has a loaded meaning and its use is thus inappropriate.
35	4	Statement: "*Obviously, the flavours are added to the natural tobacco to give the product a better taste thereby increasing the attractiveness.*" Comment: See our comments p.9, para. 6, above. JTI does not accept the suggestion that a policy objective of ingredient regulation should be to make smoking less pleasurable.

36-37	2 et seq.	Comment: Section 3.7.2 of the pre-consultation opinion addresses five approaches by which the "*addictive potency of tobacco products may in theory be increased*". In other words, these are theoretical mechanisms, the role of which in enhancing "addictiveness" (if any) will be examined in section 3.8 of the pre-consultation opinion. However, although the words "*in theory*" appear in the introductory paragraphs to this section, the more detailed wording describing the five approaches are not couched in such terms. They more closely resemble statements of fact and/or conclusions (e.g. "*The combination of acetaldehyde and nicotine appears to be more addictive than nicotine alone*", p.37, para. 1). There is a risk that readers might be misled and/or that these paragraphs could be quoted selectively in future. This problem could be easily remedied by making clear in the heading of each description at pages 36-37 that the discussion is theoretical (e.g. "Theory 1: Direct enhancement of the nicotine content"; "Theory 2: Addition of substances which increase the bioavailability of nicotine"; etc.) and by including more words signifying conditionality ("*alleged*", "*may*" etc.) in the paragraphs under those headings.
38	1	The "*Conclusions on addictive and attractive additives*" should be deleted. It is inappropriate to draw conclusions before the substantive analysis (which is set out in the pages that follow) has been undertaken.
40	2	Statement: "*Examples of additives causing addictiveness indirectly are provided in section 3.8.1.3*". Comment: Section 3.8.1.3 describes various ingredients that have been implicated in this regard, but the authors' ultimate conclusion is <u>not</u> that all of these ingredients "*cause addiction indirectly*". It is later concluded that: "*There is no proof that any of the additives are by themselves contributing to addictive potential, either directly or indirectly.*" (p.58). This wording is therefore potentially misleading.
40	5	Statement: "*Although several articles point put that some of the above mentioned additives may create dependence, it is probably more likely that they are acting by attractiveness, as they induce a more pleasant experience of smoking and therefore reduce the barrier in relation to smoking initiation.*" Comment: The statement that the listed ingredients encourage smoking initiation is entirely unsupported. In any event, see our comments p.9, para. 6, above. JTI does not accept the suggestion that a policy objective of ingredient regulation should be to make smoking less pleasurable.

40	6	Statement: *"Additives which increase the absorption of nicotine or potentiate in whatever way the effect of nicotine on the nervous system implicitly increase the addictiveness of tobacco products."* Comment: The examples that follow do not support this statement. The statement is also inconsistent with the finding elsewhere that *"the addictive potential of pure nicotine is weak"* (p.4).
40	7	Statement: *"Ammonium salts are used as additives to increase the pH of tobacco."* Comment: This statement is not referenced. JTI does not use ingredients to increase the pH of its cigarettes. In any event, even if this were correct, this would have no relevance to any overall finding in relation to the "addictiveness" of ammonium salts, since the authors conclude later that: *"It has been proposed that the addition of ammonium compounds increases the absorption of nicotine in the lungs by raising the pH in smoke, but this seems unlikely because of the high buffering capacity of the lung lining fluid."* (p.54).
43	3	Comment: The harman/norharman hypothesis described here is speculative: see our comments re. p.2, para. 9, above.
45	2	Statement: *"In conclusion, besides nicotine, a mixture of other factors probably plays an important role in craving and reinforcement. Although these unknown factors do not have pharmacological effects similar to nicotine and are probably not addictive, they definitely play a role in smoking behaviour."* Comment: If the factors are "*unknown*", we would question how the authors are able to say that they do or do not have pharmacological effects (whether similar to nicotine or not). In any event, the authors appear to accept here (correctly, in our view) that people smoke for many reasons that are unrelated to nicotine or to the effects, pharmacological or otherwise, of tobacco ingredients. More generally, the draft consultation opinion as a whole fails to support the conclusion reached here, particularly as regards the relative importance of nicotine and non-nicotine factors in smoking behaviour.

45	4	Statement: "*Some additives increase the pH of smoke, thereby increasing the quantity of nicotine delivered to the smoker.*" Comment: This conflicts with the authors' later conclusions in relation to ammoniation ("*It has been proposed that the addition of ammonium compounds increases the absorption of nicotine in the lungs by raising the pH in smoke, but this seems unlikely because of the high buffering capacity of the lung lining fluid.*" (p.54)).
47	6	Statement: "*The irritating effect of nicotine on the lungs and the bad experience at too large amounts of nicotine in relation to the amount of tar may be remedied by additives that drown or reduce the harshness of the smoke, or nicotine salts may be added that do not cause the same irritation.*" Comment: JTI does not add nicotine or nicotine salts to its products. JTI does not use ingredients in order to "*drown or reduce the harshness of the smoke*".
47	8	Statement: "*A central feature of tobacco marketing has been to promote the perception that some cigarettes are less hazardous than others, so that smokers worried about their health risks are encouraged to switch brands rather than quit.*" Comment: No evidence is provided to support this assertion. JTI does not present its products in this manner (by marketing or otherwise). In any event, the hypothesis that tobacco products yielding lower machine-measured TNCO may be less hazardous for health, on a population level, than those with higher TNCO yields was widely accepted by the international public health community for many decades and indeed finds expression in Directive 2001/37/EC's setting of maximum machine-measured TNCO levels for tobacco products sold in the EU.
47	8-9	Statement: "*Products bearing the word "smooth" or using lighter coloured branding mislead people into thinking that these products are less harmful to their health… Plain packs significantly reduced false beliefs about health risk and ease of quitting and were rated by children as less attractive and appealing (Hammond et al. 2009a).*" Comment: The issue of the packaging of tobacco products is outside SCENIHR's terms of reference (see remarks on p.13, para. 1, above). The final two paragraphs on this page should be deleted.

48	2	Statement: "*Based on the information submitted by the tobacco industry to the competent authorities of the EU Member States, [levulinic acid and levulinates] have in many case not been included in reports, but have been used and mentioned several times in the internal documents of the tobacco industry.*" Comment: JTI does not use nicotine levulinate or levulinates in tobacco products. This is why references to such compounds "*have… not been included in reports*" by it to the Member States. JTI discloses the ingredients that it adds to its tobacco products in accordance with its regulatory obligations. The language here lacks objectivity and should be amended.
48	3	Statement: "*In a study of the published literature up to 2004, Keithly has also shown that the primary purpose of levulinic acid as an additive in tobacco is to make the smoke sweeter and softer and at the same time increase the nicotine absorption and the effect of nicotine in the brain. Keithly also describes the use of nicotine levulinate and levulinic acid to cause less harshness (Keithly et al. 2005)*". Comment: Keithly et al. 2005 is not a "*study of the published literature*"; it is a review of selected documents disclosed by the US tobacco companies.
48	4	Statement: "*Tobacco products may also be designed in such a way that they are easier to start smoking with*". Comment: None of the studies cited provides any evidence that this occurs. JTI does not use flavourings for the purpose of facilitating inhalation or to encourage initiation.
49	4	Statement: "*The tobacco producers have used additives that create sweetness and taste in the smoke to make it easier for new smokers to start smoking, since these tobacco products do not have the same harshness and bad experience at the first inhalations (Cummings et a. 2002, Wayne and Connolly 2002)*". Comment: as above.

49	6	Statement: "*In order to make the smoke less aversive and permit deeper inhalation, additives such as liquorice and menthol are used.*" Comment: The statement is unclear (it is alleged that liquorice is added to "*permit deeper inhalation*", or only menthol?). In any event, no evidence is cited to support this assertion. JTI does not use flavourings for the purpose of facilitating inhalation or to encourage initiation.
50	6-7	The discussion of the alleged impact of mentholation on benzo[a]pyrene content of smoke and on lung cancer incidence is outside SCENIHR's terms of reference and irrelevant to the question of the "addictiveness" or "attractiveness" of ingredients. These paragraphs should be deleted. In any event, only four of the eight available menthol/lung cancer studies are cited, and of those one (Sidney et al. 1995) is quoted selectively (the authors do not identify that there was no statistically significant increase in lung cancer incidence among female smokers of mentholated cigarettes). Furthermore, the results presented from the paper by Rustemaier et al (2002) all fall within the range of method variability described in ISO standard 22634 – Determination of benzo[a]pyrene in mainstream smoke – and cannot be viewed in isolation as indicative of an effect of menthol on mainstream smoke composition.
52	4	Statement: "*Menthol may increase the degree of dependence, or promote maintenance of smoking behaviour… Some investigators have found that menthol cigarette use increases cotinine levels…*" Comment: No evidence cited in support of the proposition that mentholated cigarettes may be harder to quit than unmentholated products. The authors omit to cite relevant epidemiological data, which in fact shows that no difference in quit rates between smokers of mentholated and unmentholated cigarettes. Furthermore, recent clinical studies (Heck JD (2009) Cancer, Epidemiology, Biomarkers and Prevention 18, 622-929; Wang J et al (2010) Regulatory Toxicology and Pharmacology, 57, 24-39) show no differences in cotinine levels between smokers of menthol and non-menthol cigarettes.
53	1-4	Speculation about effects of ammoniation is disingenuous, given that the authors go on to write that: "*[i]t has been proposed that the addition of ammonia compounds increases the absorption of nicotine in the lungs by raising the pH in smoke, but this seems unlikely because of the high buffering capacity of the lung lining fluid*" (p.54). JTI does not, in any event, add ammonia or ammonia compounds to its cigarettes.

56	4	Statement: "*More than 250 additives are found in snus…*" Comment: No reference is provided for this statement.
58	2	Statement: "*For most tobacco additives, information about possible effects on addictiveness and attractiveness do not exist. A number of studies have been conducted by the tobacco industry, and there are indications that some additives have effects in relation to addictiveness and attractiveness.*" Comment: It is correct that there is little evidence that tobacco ingredients play any role in "addictiveness". JTI has already made its position in relation to the concept of "attractiveness" clear. However, the statement that "*[a] number of studies have been conducted by the tobacco industry*" is unreferenced and clearly designed to be prejudicial. It should be deleted. The assertion that "*there are indications that some additives have effects…*" is so weak that it likewise warrants deletion. It also conflicts with the important conclusion that appears higher on this page, that "*There is no proof that any of the additives are by themselves contributing to addictive potential, either directly or indirectly.*"
63	2	Statement: "*Tobacco addiction is maintained by nicotine, and tobacco products that do not deliver nicotine do not sustain addiction.*" Comment: The statement that tobacco addiction is maintained by nicotine is not supported by the finding that "*that the addictive potential of pure nicotine is weak*" (p.4) or by the Rose study referred to at p.65 (denicotinized cigarettes continue to be smoked in the absence of nicotine reward).
63	3	Statement: "*Smoking and inhalation into the lungs, in particular, is a highly efficient form of nicotine administration, as the drug enters the circulation rapidly through the lung and moves into the brain within seconds.*" Comment: This is not supported by recent studies. See further our remarks on p.29, para. 8, above.
64	3	Statement: "*There is good evidence, for example, that cigarette smokers partially compensate for the low nicotine delivery by low tar cigarettes, possibly by inhaling more deeply, taking more puffs per cigarettes, and so on…*". Comment: See our remarks on p.9, para. 5, above.

65	1	Statement: "*It is also possible that extended product characteristics (e.g. pack designs) may acquire reinforcing properties…*" Comment: This is outside the terms of reference of this pre-consultation opinion and should be deleted.
65	4	Statement: "*There is evidence from tobacco industry documents that flavourings have been used to target younger smokers.*" Comment: JTI does not design its products to appeal to minors or market them to minors.
65	5	Statement: "*A survey in the US showed that 17 year old smokers are three times as likely to use flavoured cigarettes as are smokers over the age of 25 (Klein et al 2008). Therefore the addition of exotic flavours may be used to increase the appeal of tobacco products (including smokeless products), and in particular their appeal to naïve users and younger age groups.*" Comment: This conclusion is not supported by the paper by Klein et al (2008) which explicitly states "*we cannot address the important question of whether these products are attractive to adolescents or adults who have never smoked or are former smokers.*" Furthermore the paper does not examine smokeless products.
66	4, 5	Comment: The term "*impact*" is inconsistently described as "*an industry term for smokers' subjective awareness of the drug effects of nicotine*" (para. 4) and "*an industry term denoting the organoleptic sensation caused by nicotine*" (para. 5).
66	6	Statement: "*Unregulated botanical and chemical additives might have 'multiple use' purposes, such as enhancing flavour and producing 'smoother' cigarette smoke, as well as potentially preventing or masking symptoms associated with smoking related illnesses (Rabinoff et al 2007)*". Comment: This is pure speculation and should be deleted.
68-69	Various	Comment: See our remarks on p.9, para. 2, above, in relation to the MAO/harman/norharman hypothesis.

69	4	Statement: *"The factors influencing attractiveness can be broadly divided into: extrinsic factors (e.g. marketing, packaging, pricing); and intrinsic factors (e.g. taste, smell, sensory attributes, and pharmacological factors)."* Comment: See our remarks on p.9, para. 6 in relation to the concept of attractiveness. The problems with the authors' issue definition in this regard are evident from the fact that attractiveness is here (re)defined to include "*pharmacological factors*", which are elsewhere defined as being the basis for "addictiveness" (p.18: "addictiveness" is defined as "*pharmacological potential of a substance to cause addiction*"). We also note that the "*extrinsic factors*" referred to here fall outside the authors' terms of reference – see above.
69	4	Statement: "*Given the subtle interactions between different factors… identifying and measuring the influence of individual additives on attractiveness of products is difficult.*" Comment: This is an important conclusion. We note that, at p.72, the identification of the role of individual ingredients in enhancing "attractiveness" is stated to be "*very difficult*".
70	5-6	Comment: The issue of brand choice, and the impact (if any) of ingredients on such choice, can only properly be dealt with via consideration of epidemiological and ecological studies within and between populations who consume tobacco products containing different levels of ingredients. However, the authors omit to cite any such studies.
70	5	Statement: "*… the popularity of Marlboro worldwide is likely due to the substantial funding spent on its advertising and promotion. A further complication with interpreting brand preference data over time is that the tobacco industry has been expanding the number of variants of existing brands; since 1998 brand families have increased by more than 50%. For example, Benson & Hedges increased the number of brands from four in 1998 to 12 by 2008 (ASH 2010).*" Comment: Issues such as the impact of advertising and the number of variants of existing brands are outside the terms of reference of this pre-consultation opinion, and should be deleted.
71	4-6	Comment: The contents of the paragraphs under the heading "Perceived brand preferences" are outside the terms of reference of this pre-consultation opinion, and should be deleted.

72	4	Statement: "*It is very difficult to identify the role of individual additives in enhancing <u>addictiveness</u>…*" (underline added). Comment: Should this be "attractiveness"?
76	1-4	Comment: The role of information on smoking prevalence in this pre-consultation opinion is unclear. The authors do not attempt to relate this information to matters which are within their terms of reference. Statements concerning the possible impact of price and packaging on brand choice should be deleted, as these issues clearly fall outside the authors' terms of reference – see above.
77	6	Comment: The role of information on smoking prevalence among minors in this pre-consultation opinion is unclear. The authors do not attempt to relate smoking prevalence among minors to issues which are actually within their terms of reference.
79	6	Statement: "*Referring to section 3.12 it is clear that the tobacco industry not only has aimed to target different groups of users through advertising and promotion. They have also manipulated the cigarettes themselves.*" Comment: Section 3.12 of the pre-consultation opinion provides no support for these statements, and issues of advertising and promotion are in any event outside the terms of reference of this pre-consultation opinion. JTI does not design its products to appeal to minors or market them to minors.