

House of Commons Health Committee

Supplementary Memorandum by

BRITISH AMERICAN TOBACCO

**“The Tobacco Industry and the
Health Risks of Smoking”**

House of Commons Health Committee
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These are the views of British-American Tobacco (Holdings) Limited. References in this memorandum to British American Tobacco when denoting opinion refer to the company – British-American Tobacco (Holdings) Limited – and when denoting cigarette business activity refers collectively to its group of operating companies.

February, 2000

House of Commons Health Committee

Supplementary Memorandum by British American Tobacco

Executive summary

Introduction

1. British American Tobacco submitted a Memorandum to the House of Commons Health Committee on the 19th October 1999 (1). During the course of the inquiry, the Committee has raised several issues that were not covered in our initial Memorandum and has asked us for more information on a variety of topics. Throughout the inquiry we have been asked to respond to the Committee on specific questions, which we have done. This Supplementary Memorandum covers the remaining issues, and should be considered alongside our original Memorandum. It should also be read in conjunction to British American Tobacco's views on taking the issues surrounding smoking forward into the new Millennium (2).
2. To assist the Committee, we cover the additional issues in brief, putting together the key facts to be considered. Some of the matters are of significant scientific complexity, and this Memorandum should not be seen as a fully comprehensive review given our purpose was to provide evidence of relevance to the Committee's inquiry in a timely and concise manner.
3. The Executive Summary outlines the issues discussed in this Memorandum, and should be considered alongside the full Supplementary Memorandum.

Statistics on smoking-attributable deaths

4. This Memorandum considers, in response to the Committee's request for further information, the estimates of smoking-attributable deaths made both by the UK Health Education Authority (HEA) (3), used in the Government's White Paper on Tobacco (4), and the estimates produced by the World Health Organisation (WHO) (5). We also consider, in light of the WHO predictions, the current global health priorities as reported in the World Health Report of 1999 (5).
5. We conclude that, while it is acceptable for public health authorities to produce smoking-attributable death estimates in order to provide public information and to set funding priorities, the estimates given are extraordinarily broad and not scientifically verifiable. The UK estimate, for example, is not based on records of deaths in smokers, but rather from an extrapolation of an epidemiological study conducted in the 1980's on an affluent American population.

6. The HEA report (3) states that, “Deaths from smoking cannot be estimated directly. Individuals who die from their smoking cannot be identified. Even were smoking status included on the death certificate it would not be possible to identify which deaths were actually caused by smoking since a proportion of smokers, albeit small for some diseases, die from a disease that smoking can cause, not on account of their smoking but due to other causes of the disease.”
7. It is not possible to suggest an alternative estimate to that currently used by the Government, since any alternative would suffer from the same lack of a basic scientific foundation. The key problems with the UK estimates of smoking-attributed deaths are the lack of a fundamental scientific measure, the difficulty in extrapolating from one group to another, the fact that all the diseases associated with smoking have more than one cause and that it is not scientifically possible to determine at the level of an individual that a particular person died because they smoked. Given the emphasis given to this information by public health authorities, it would be useful to undertake additional research in the UK to provide a more sound scientific foundation for such estimates.
8. We suggest that it is important that those who use the UK’s smoking-attributable death estimate understand the basis of that estimate and accept that there are considerable uncertainties associated with the estimate. More useful, perhaps, is the consideration of mortality trends in the diseases strongly associated with smoking, since this may give an insight into the success of past public health policies and provide guidance for the future. The UK mortality trends show reductions in the incidence of lung cancer, chronic obstructive pulmonary disease and heart disease, suggesting that past policies, including the low tar programme, have provided benefits.
9. These considerations are important to appreciate before using such statements as “half of all who continue to smoke for most of their lives die of the habit.” (4) Such statements are not fairly supported by the evidence, are not scientifically verifiable, are unlikely to be accurate, take “rounding” and “approximation” to an unacceptable height, underestimate the importance of other risk factors, and provide incomplete health information to any adult who wishes to continue smoking. While the intention may be to inform people that smoking is very risky, the practical implications are that this estimate gives people no sense of how the risks associated with smoking vary dramatically by both the numbers of years smoking and by the numbers of cigarettes consumed per day.
10. The difficulties of extrapolating from an affluent American group of people to the UK population as a whole are considerably multiplied in attempts to produce global estimates of smoking-attributed deaths. Commenting on one of the methodologies used to produce such estimates, researchers from the US National Institute of Environmental Health Sciences stated that “This exercise is admirable in intent but flawed in execution. Peto et al disregard risk factors other than smoking; project from a selective sample of the upper middle class in the US to the entire socioeconomic stratum of other countries including

some, such as Romania and Bulgaria, which are much less developed and more polluted; and ignore evidence that non-smoking lung cancer is increased in some countries and time trends that implicate other causes of disease besides smoking.” (6)

11. The WHO estimates that by the end of the 2020's the annual smoking-attributed number of deaths will be 10 million (5). Their estimate for the late 1990's is 4 million smoking-attributed deaths per year (5). Neither of these estimates is fairly-based, let alone scientifically verifiable. For the WHO's estimate for the 2030's to be even plausible, the global incidence of smoking would have to increase considerably between 1980 and 2030, and the circumstances of world-wide smokers would have to mimic those of affluent Americans in the 1980s. Trends do not suggest that this will be the case.
12. Analysis of the global health statistics, as reported in 1999 by the WHO, illustrate that in many countries, particularly in the developing world, the diseases most strongly associated with smoking are currently not the main causes of death (5, 7).
13. Globally, lung cancer accounted for around 2.3% of all deaths in 1998. In Africa, HIV/AIDS ranked as the number one cause of death, and was estimated to cause the death of 19% of the total. In the WHO's Africa region, cancer of the trachea, lung and bronchus was ranked 38th at 0.3% of all deaths. Road traffic accidents were ranked higher as a cause of death than lung cancer in Africa, the Eastern Mediterranean and South East Asia, and similar in the Americas. The WHO has also stated that “Infectious diseases are now the world's biggest killer of children and young adults. They account for more than 13 million deaths a year – one in two deaths in developing countries.” (8)
14. None of this is to suggest that there are not real risks of serious diseases associated with smoking. Clearly there are, and smoking should be, and is, an issue addressed by public health authorities around the world. However, there are many serious public health problems, and sometimes Western dominated interests seem to underestimate some of the issues facing developing countries.

Comparisons between smoking and 'hard drugs'

15. Several witnesses to the Committee during its current inquiry have suggested that tobacco smoking is comparable to the taking of drugs such as heroin and cocaine. Mr. Hesford referred to a study that compared nicotine and cocaine by Jones et al (9), and there has been reference to the recently published study by the Royal College of Physicians, “Nicotine Addiction in Britain” (10). In order to assist the Committee, this Supplementary Memorandum addresses these two studies.
16. The Jones study investigated intravenous injections of nicotine and cocaine into ten cocaine dependent volunteers. The study found that, “At doses that produced comparable ratings of drug effect (40mg/70 kg cocaine versus 1.5mg/70kg nicotine), cocaine produced significantly greater good effects,

whereas nicotine produced greater bad effects.” The study concluded, “The drug versus money measure showed that the highest cocaine dose was worth twice as much [to the test subjects] as the highest nicotine dose. Thus, intravenous cocaine and nicotine can be differentiated by their subjective and reinforcing effects.” (9)

17. In the discussion section the paper states, “Nicotine and cocaine produced qualitatively different subjective effects. Nicotine, but not cocaine, produced dose- and time-dependent increases in “bad effects” and “jittery”. In contrast to the negative subjective effects produced by nicotine, the high dose of cocaine produced maximal ratings of liking that tended to be greater than those produced by the high doses of nicotine.” Hence, the study reported clear substantive differences between cocaine and nicotine and expressly stated that point.
18. The Royal College of Physician’s report, “Nicotine Addiction in Britain” concluded “Nicotine is highly addictive, to a degree similar or in some respects exceeding addiction to ‘hard’ drugs such as heroin and cocaine.” (10) Mr. Bates of Action on Smoking and Health (ASH), who, as far as we are aware has no scientific qualifications but was, somewhat surprisingly, a co-author of the report, stated in a press release, “The fact that they are legal is irrelevant – cigarettes are hard drugs by any physical or medical definition.” (11) In our view, the report does not provide a scientific basis for this conclusion.
19. For example, the report describes possible mechanisms related to the pharmacology of nicotine. Cocaine is thought to act by enhancing neurotransmission at dopamine synapses in the mesolimbic system of the brain. It has been hypothesised that nicotine acts in the same manner. The report, however, considers the science on this issue and rejects this hypothesis, concluding that, certainly for regular smokers “nicotine is unlikely to stimulate the mesolimbic dopamine neurons.”
20. In attempting to compare nicotine with heroin and cocaine, the report considers a variety of areas. Certainly there is some commonality among drinking coffee, smoking cigarettes, injecting heroin and snorting cocaine. They all involve ingesting a pharmacologically active substance that the brain discriminates as pleasurable. Beyond that, to suggest that this range of substances is similar is absurd and misleading on at least two important levels. First, the magnitude of the pharmacological effects are both quantitatively and qualitatively different as demonstrated in the scientific literature, including the Jones study cited by the Committee. Second, the Report fails to consider the very different environmental factors surrounding cigarette smoking and heroin and cocaine use. Cigarette smoking is legal, generally accepted in society and results in very mild effects during smoking. Cigarette smoking does not cause intoxication or any significant euphoria. Nor do people have to smoke more and more cigarettes per day to obtain the same effect. Both heroin and cocaine are illegal, their use is not accepted as a norm in society and their short-term effects cause significant disturbances in perception.

21. It has been suggested that reports on the numbers of smokers who say that they wish to quit smoking, and the success rate of those trying to quit, shows that cigarette smoking is as addictive as heroin or cocaine use. Again the social contexts are quite different, and as some researchers have shown, saying you want to quit to an interviewer and actually wanting to quit are quite different things.
22. We take the view that it is irresponsible, and certainly scientifically inaccurate, to suggest to the general population that taking heroin or cocaine is the same as cigarette smoking.

Ingredients

23. During the Committee's visit to our research laboratories in Southampton, we agreed to provide additional information on a variety of cigarette tobacco ingredients that gave concern to some of the Committee members. These issues were covered to some extent in our initial Memorandum (1). This Supplementary Memorandum responds to the Committee's request for additional information by providing a summary of discussions on the ingredients that have been held between the UK tobacco companies and the Department of Health's Tobacco Policy Unit (TPU) over the past several months.
24. The discussions were prompted by an article, that appeared on the internet rather than in a scientific journal and hence was not subject to peer-review, authored by Mr. Bates of ASH, Dr. Jarvis of the Imperial Cancer Research Fund (ICRF) and Dr. Donnelly of the Massachusetts Tobacco Control Program (12). In a press release accompanying the article, Mr. Bates stated "We have uncovered a scandal in which tobacco companies deliberately use additives to make their bad products even worse. Without telling anyone, they have been free-basing nicotine and engineering subtle changes to the brain chemistry of the smoker." (13) As demonstrated in our initial Memorandum and the additional scientific information presented in this Memorandum, the claims by ASH are both ill-informed and incorrect. We believe that the Department of Health has generally accepted the prevailing science on these ingredients. In one case we have agreed to undertake additional research and a protocol for that research is currently with the Department.
25. The actions of the Department of Health's Tobacco Policy Unit have been entirely appropriate. They took the concerns raised by ASH and sought scientific information to evaluate those concerns in order to arrive at science-based policy. We regret that the same cannot be said of ASH, who chose to base their views on selected sections of old documents rather than an examination of the scientific facts.
26. We understand that the Secretary of State for Health has requested further information on the brand by brand ingredient content of cigarettes sold in the UK. We are meeting soon with the Department of Health to conclude ways in which we may move forward on this issue.

Conclusions

27. The present inquiry into the Tobacco Industry and the Health Risks of Smoking has considered a wide range of issues and has covered many years of history. It has been our intention to play a helpful role in providing the Committee evidence on which it could base its recommendations.
28. We particularly appreciate that the Committee found time to visit our research laboratories in Southampton and the Depository of files in Guildford. We have also ensured that information requested by the Committee was forthcoming in a timely fashion.
29. We have stated that it is time to put aside some of the rhetoric of the past, and to move forward on sound, evidence-based approaches that deal with the many issues surrounding smoking. We believe that the Committee has an opportunity of recommending ways forward based on sound science and a full evaluation of the facts.

1. Statistics on smoking-attributable deaths

1.a Introduction

30. Smoking-attributable mortality estimates have been used to assess the scale of smoking-related health problems and are often communicated to the public as precise figures. It is understandable that public health authorities should wish to undertake such estimates in order to determine priorities. Relatively few estimates have been produced for causes of disease such as alcohol and poor diet.
31. This section responds to the request of the UK House of Commons Health Committee to provide more information on smoking-related mortality estimates. We cover the UK estimate of smoking-related mortality, the World Health Organisation's (WHO) estimate of world-wide smoking-related mortality and the WHO's predictions for future mortality, and the question of health priorities in developing countries.
32. This is an area of significant complexity since the diseases associated with smoking all have been determined to have multiple causes and because national mortality statistics do not separate lifetime smokers and non-smokers. Because of this, any estimate of this type is extraordinarily broad and not scientifically verifiable, in that it is not possible to determine within any population that the estimate is correct. The production of any estimate inherently relies on a variety of assumptions and uncertainties. Nothing in this note is intended to detract from the view that there are real risks of serious diseases associated with smoking. Nor is it intended to suggest that it is unreasonable for a public health authority to attempt to estimate the impact of risky products on health in order to set priorities. Rather, it points out the difficulties of arriving at reliable estimates for the impact of smoking on mortality, and why it is important to understand the methodology and assumptions used in producing the estimates when determining public health messages and public policy.

1.b UK estimates of smoking-related mortality

33. The Government White Paper on Tobacco (4) states "Smoking kills over 120,000 people in the UK a year – more than 13 people an hour." The reference used to support this estimate is the UK Health Education Authority's (HEA) 1998 paper, "The UK smoking epidemic: deaths in 1995" (3). A similar calculation produced by the Royal College of Physicians (10) for the UK population in 1997 provided an estimate of 117,400.
34. We shall take the HEA report to briefly describe the methodology used to produce the estimates. This HEA report, written by Christine Callum, acknowledges Sir Richard Doll, Sir Richard Peto and Nicholas Wald for their expert advice and comments.
35. The HEA report states that, "Deaths from smoking cannot be estimated directly. Individuals who die from their smoking cannot be identified. Even

were smoking status included on a death certificate it would not be possible to identify which deaths were actually caused by smoking since a proportion of the smokers, albeit small for some diseases, die from a disease that smoking can cause, not on account of their smoking but due to other causes of the disease.” (3)

36. Faced with this the HEA report states, “Deaths from smoking are estimated by comparing death rates for current smokers and ex-smokers with death rates for never smokers. The extent to which smoking adds to the mortality risks of never smokers can be used to estimate the number or proportion of deaths caused by smoking. This cannot be done directly from national statistics since without knowing the smoking status of the deceased, death rates of current smokers, ex-smokers and never smokers cannot be calculated. Were never smokers’ death rates transferable across place and time it would still be possible to estimate deaths due to smoking by subtraction from the death rate in the population. This can only be justified in the case of lung cancer, however and instead indirect methods are used based on relative risks.” (3)
37. Given that it is not possible to make these estimates on the basis of counting individuals, estimates have to be extrapolations, typically from a group of the population to national mortality statistics. This clearly has implications on the scientific validity of any estimated number, and on the accuracy and uncertainty of such a number. The key assumptions are as follows:
38. (a) Choice of disease to be included in the estimate

The HEA chose to include 19 disease classes in its calculations, two of which it suggested were diseases for which smoking is associated with a reduced risk (and hence used to reduce the estimated number):

Diseases with an increased risk associated with smoking:

- Cancer: lung, upper respiratory sites, oesophagus, bladder, kidney, stomach, pancreas, unspecified site and myeloid leukaemia
- Respiratory: chronic obstructive lung disease and pneumonia
- Circulatory: ischaemic heart disease, cerebrovascular disease, aortic aneurysm, myocardial degeneration and atherosclerosis
- Digestive: ulcer of stomach and duodenum

Diseases with a decreased risk associated with smoking:

- Parkinson’s disease, Endometrial cancer

39. Some of the choices on this list raise questions. For example, while epidemiological studies have reported a greater relative risk for pneumonia and influenza in groups of smokers compared to groups of non-smokers, pneumonia and influenza are caused by infections.

40. (b) Choice of a study to determine estimates of the relative risks associated with smoking

The HEA decided to use a US epidemiologic study to derive its estimates for the UK population. The HEA report states, “Estimates of relative mortality for each disease were derived from the American Cancer Society’s prospective study in the 1980s of one million adults in the US, which represents the best available approximation to the UK. This study was not representative of the US as a whole, over-representing the more highly educated and under-representing the most disadvantaged, but though absolute mortality rates were lower than those of the general population this should not invalidate relative risks. Cigarette smokers and ex-smokers in the study were found furthermore to be sufficiently alike in respect of past exposure to cigarette smoke to justify application of the relative risks from the study to the UK.” (3)

41. The American study, called CSP-II, is chosen in the absence of an appropriate UK study. The Report states that the only UK candidate is the British Doctors study, but that this lacked data in women and that the relative risks in men were lower than the American study because the study spanned a period of rising lung cancer relative risks.
42. Discussing the choice of CPS-II for such estimates, Davis and Hoel state, “One striking feature for the CPS-II data is that for all the diseases noted, men and women have similar RRs, except for lung cancer, where men have nearly twice the RR of women, and chronic obstructive pulmonary disease, where women smokers have a slightly greater RR than men. Cigarette smoking is assumed to be the chief cause of these increased RRs. On average, men will have smoked for longer period cigarettes with higher tar levels. Why are RRs so similar in men and women except for lung cancer? Three hypotheses need to be considered: [1] unlike other smoking-linked diseases, lung cancer has a much longer latency; [2] men may be genetically more susceptible to lung cancer (eg debrisoquine metabolism could be sex-linked; or [3] men may incur other risk factors than smoking for lung cancer, such as occupational exposures.” (6)
43. In the same letter Davis and Hoel also states “If one applies the RRs from CPS-II to the US overall, a major anomaly emerges. CPS-II lung cancer rates predict for ages 45-70 that about 70% (50% at age 70 to 100% at age 45) of the US males are smokers. Either the CPS non-smoker background rate is lower than that for the general US population or the RR is low for smoking. In either case, other risk factors for lung cancer must be involved in the general population.” (6)
44. The HEA report compares the historical smoking statistics of the American CPS-II population with the UK population, and concludes that they are sufficiently similar to extrapolate. This conclusion is questionable. In comparing CPS-II with the UK General Household Survey, HEA conclude that CPS-II smokers consumed considerably more cigarettes than UK smokers. If this were the case the CPS-II population relative risks would not be applicable to the UK. HEA state, however, that this could be explained by

the way in which the consumption was counted and in that, as they say “more importantly, evidence from a comparison of butt length indicates that in the US a smaller proportion of the cigarette is smoked than in the UK.”

Remarkably, on this essential point, the only reference given to support this statement, which is unlikely to be accurate, is a 1959 report by Doll and co-workers. (14)

45. (c) Determination of relative risks

The relative risks reported in the CPS-II study were used for current smokers and for ex-smokers. The HEA report considered whether the relative risks were likely to change within different age ranges of the population. Where this seemed to be the case, different relative risks were applied for deaths in different age categories. This differentiation was applied to ischaemic heart disease, cerebrovascular disease and pneumonia, each of which were considered to have lower relative risks associated with smoking at older ages.

46. Hence, the HEA report applies relative risks for lung cancer of 26.6 for current male smokers, 8.2 for former male smokers, 13.6 for current female smokers and 4.1 for former female smokers. For ischaemic heart disease, the HEA report assigns relative risks in male current smokers of 4.2 for ages 35-54, 2.6 for ages 55-64, 1.7 for ages 65-74 and 1.4 for ages 75+. For male former smokers, the respective relative risks were 1.9, 1.6, 1.4, and 1.1. For females current smokers, for the same age categories, relative risks of 5.2, 3.0, 2.1 and 1.4 were used, and for female former smokers the relative risks were 2.9, 1.1, 1.2 and 1.1.

47. The last three of these relative risks were not statistically significant. Several other relative risks used in the HEA report were not statistically significant, including the male current and former smoker relative risks for atherosclerosis and myeloid leukaemia, and female current and former smoker relative risks for bladder, kidney and stomach cancers, myeloid leukaemia and pneumonia, cerebrovascular disease (apart from the 65-74 age category) aortic aneurysm, myocardial degeneration, ulcer of the stomach and duodenum, and atherosclerosis in female former smokers. Despite the lack of statistical significance, the report still uses these relative risks to calculate attributed deaths.

48. (d) Estimates of percentages of deaths by disease to be attributed to smoking

The report assumes that the registered deaths for any disease are made up of deaths of people who have never smoked, exposed to never smokers' death rates plus deaths of ex-cigarette smokers, exposed to never smoker death rates and an excess risk associated with their earlier smoking, and deaths of current cigarette smokers, exposed to never smoker death rates and an excess risk associated with their smoking.

49. The report then used the 1994/1995 General Household Survey for Great Britain and the 1994/1995 Continuous Household Survey for Northern Ireland to estimate the proportions by age of current and former smokers. For

example, it estimates that for the group of men aged 55 to 64, 24% were current smokers, 45% were ex-smokers. Hence, presumably 31% were lifetime never smokers.

50. Percentages were calculated using the CPS-II relative risks. As the HEA report states “This method assumes that there is no difference according to cigarette smoking status in exposure to other risk factors for the disease.” (3) This assumption is not justified, and it is well documented that lifetime smokers on average have a greater exposure to a variety of risk factors (such as sedentary lifestyle, a poorer diet and greater consumption of alcohol) than lifetime non-smokers.
51. The report calculated the proportion of the number of deaths attributable to smoking (A) using the following equation:

$$A = [Pc(Rc-1) + Pf(Rf-1)] / [1 + Pc(Rc-1) + Pf(Rf-1)]$$

where Pc is the proportion of current smokers,
Pf is the proportion of former smokers,
Rc is the relative risk for current smokers compared with never smokers,
and Rf is the relative risk for former smokers compared to never smokers

52. So, for ischaemic heart disease for the group of males aged 55-64, the report estimates A as:

$$A = [(0.24 \times 1.60 + 0.45 \times 0.6)] / [1 + (0.24 \times 1.60) + (0.45 \times 0.6)]$$
$$= 0.654 / 1.654 = 40\%$$

This proportion is made up of 23% of current smokers and 16% of former smokers.

53. A variety of issues arise from this methodology. Firstly, the methodology and the lack of national mortality data do not allow scientific verification of the estimates. Secondly, any estimated percentages of deaths attributable to smoking have considerable uncertainties associated with them. One fundamental problem is that each of the diseases considered has multiple causes, and it is uncertain how these interact. Thirdly, the estimates are entirely reliant upon the applicability of the relative risks produced in the US CPS-II study to the UK population. CPS-II compared current, ex-smokers and never smokers in a population of typically affluent, well-educated caucasians. It is well accepted that this group is not representative of the US population, let alone the UK population. For example, the smokers in CPS-II (except for males in the 70-79 age range) had lower all cause death rates than the corresponding age-sex group in the US population. Fourthly, the relative risks used for the estimates are the average across the various smoking behaviours, but will be biased (in terms of the incidence of disease in each group) in the

smoker group by lifetime heavy smokers. The CPS-II smokers consumed more than UK smokers and so the relative risks applied may be too high.

54. In summary, there are considerable uncertainties surrounding the UK smoking-attributable mortality estimates.

1.c UK estimates of 50% of current smokers dying prematurely

55. The Government White Paper on Tobacco states, “half of all those who continue to smoke for most of their lives die of the habit; a quarter before the age of 69, and a quarter in old age, at a time when average life expectancy is 75 for men and nearly 80 for women.” The source for this statement is Peto and co-workers’ 1994 book on mortality from smoking in developed countries (15).
56. This estimate suffers from all of the methodological problems explained above. While the intention is clearly to inform people that smoking is very risky, the practical implications are that this estimate gives people no sense of how the risks associated with smoking vary dramatically by both the numbers of years smoking and by the numbers of cigarettes consumed per day.

1.d WHO estimates of current and future attributable mortality.

57. The WHO have estimated that smoking can be directly attributed to 4 million deaths around the world in 1998, and that by the end of the 2020s smoking will be related to 10 million deaths annually (5). These estimates are based on methodology produced by Peto, Lopez and co-workers (15). When this methodology was published in the Lancet, researchers from the US National Institute of Environmental Health Sciences, Davis and Hoel, stated that “This exercise is admirable in intent but flawed in execution. Peto et al disregard risk factors other than smoking; project from a selective sample of the upper middle class in the US to the entire socioeconomic stratum of other countries including some, such as Romania and Bulgaria, which are much less developed and more polluted; and ignore evidence that non-smoking lung cancer is increased in some countries and time trends that implicate other causes of disease besides smoking.” (6)
58. Interestingly, a co-author of the “Mortality from Smoking in Developed Countries” report has stated of the methodology “Implicit in this approach is the basic assumption that lung cancer is essentially uncausal (i.e. smoking) and that other co-factors have a negligible impact. This is clearly not the case for many developing countries where indoor air-pollution is a major cause of lung cancer (especially among non-smoking females, see Mumford, et al, 1987) and hence the approach suggested in this paper has been applied only to developed countries where the assumptions are more likely to apply and where, in addition, reliable cause of death data are readily available.” (16)
59. Current estimates, as presented in a World Health Report (5), separate the 4 million deaths in 1998 by WHO region, assigning 1,273,000 to Europe, 1,093,000 to the Western Pacific, 772,000 to the Americas, 580,000 to South

East Asia, 182,000 to the Eastern Mediterranean, and 125,000 to Africa. Comparing this data with other statistics presented in the World Health Report 1999 (5), that would mean in percentage terms, 14% of deaths in Europe, 9% in Western Pacific, 14% in the Americas, 4% in South East Asia, 5% in the Eastern Mediterranean and 1% in Africa.

60. The current estimates have considerable uncertainties, even more so than the extrapolation from the US to the UK. For example, the 1992 US Surgeon General's Report (17), written jointly with the Pan American Health Organisation, attempted to calculate a 1985 smoking-attributable mortality for the Americas arriving at an adjusted estimate of 526,000, with 100,000 of that related to Latin America and the Caribbean. The population of Latin American and the Caribbean is considerably greater than that of North America, yet the smoking-attributable mortality estimates for Latin America and the Caribbean were much lower than for North America.
61. The UK estimate of smoking related deaths is predominated by lung cancer, COPD and ischaemic heart disease (making up 111,400 of the 121,700 or 92%). The WHO's Global health statistics present the following data:

Region	Total deaths	LC	COPD	IHD	WHO
Africa	9,621	26	110	449	125
AMR	5,651	181	156	579	772
EMR	3,773	37	64	198	182
EUR	9,255	392	254	1,266	1273
SEAR	13,484	165	213	882	580
WPR	12,145	443	1,453	1,732	1093
WT	53,929	1,244	2,250	5,106	4,025

(in thousands)

AMR, Americas; EMR, Eastern Mediterranean; EUR, Europe; SEAR, South-East Asia Region; WPR, Western Pacific Region; WT, world total.

LC, lung cancer; COPD, chronic obstructive lung disease; IHD ischaemic heart disease; WHO, WHO estimate of smoking-attributable deaths.

Source, World Health Report, 1999, Statistical Annex Table 2, pages 98-101 (5)

62. So, according to the WHO's estimates for 1998, a total of 53,929,000 deaths occurred in 1998. Of these, 1,244,000 were due to cancer of the lung, trachea or bronchus (2.3% of total).
63. In the UK estimates, attributed lung cancer deaths are approximately 25% of the total smoking attributed deaths. WHO use this approximation to estimate the global figure of 4 million. However, for this to be an appropriate

extrapolation, the CPS-II population relative risks should apply to all countries around the world. This is not the case. For example, while the UK HEA study assigns 90% of male lung cancer deaths and around 80% of female lung cancer deaths to smoking, it is by no means certain that this proportion should be valid for many parts of the world. For example, Peto and co-workers in their publication “Mortality from smoking in developed countries, 1950-2000” (15), assign different estimates of the percentage of smoking attributable mortality to different countries.

64. It is interesting to compare the estimates for the UK (21% of all deaths) with those for France (12% of all deaths). Certainly the estimates are in part disparate because of the risk attributed to French female smokers is much lower than that attributed to French males. But, according to Peto (15), COPD and vascular disease trends in French males are different to lung cancer trends, both of the former falling rapidly.

Annual male death rates/ 100,000

Date	Fr. Lc	Fr. COPD	Fr. Vasc	UK lc	UK COPD	UK Vasc
1955	23.3	39.7	489.3	73.8	109.0	734.3
1965	39.6	45.1	454.9	100.9	116.6	710.5
1975	52.4	55.9	431.5	109.4	94.8	668.3
1985	65.6	32.7	332.0	100.7	78.2	551.1
1990	68.0	28.3	258.5	87.8	62.3	460.3
1995	69.4	24.3	198.3	76.2	49.8	383.7

Fr. Lc – French lung cancer; FR. COPD, French Chronic Obstructive Pulmonary Disease; Fr. Vasc. French vascular disease; UK lc, UK lung cancer, UK COPD, UK Chronic Obstructive Pulmonary Disease, UK Vasc., UK Vascular Disease. Source: Peto et al, Mortality from smoking in developed countries 1950-2000, Oxford University Press, 1994 (15)

65. Hence, while French male lung cancer rates have risen by more than 3 times from 1955 to 1995, French male COPD rates have fallen since 1975 and French male vascular disease rates have fallen even more (more rapidly than UK rates). For France, Peto assigns 91% of the male lung cancer deaths to smoking, 68% of the COPD deaths and 15% of the vascular disease deaths. For the UK, Peto assigns 92% of the lung cancer deaths, 76% of the COPD deaths and 18% of the vascular deaths. However, if 68% of male COPD deaths were due to smoking, and assuming that the lung cancer deaths consistently relate to smoking as Peto suggests, then one would perhaps expect an increase in COPD rather than the observed decrease, unless a cause other than smoking has been declining. However, Peto’s estimates do not suggest that this is the case, certainly not between 1985 and 1995, since he assigns the percentage of COPD deaths to smoking as 63% in 1975, 68% in 1985 and 68% in 1995. Similarly for vascular disease, Peto’s estimates assign 13% of vascular disease deaths to smoking in 1975, 14% in 1985 and 15% in 1995.
66. The implication of this is that it is not possible to simply collect data on lung cancer mortality and extrapolate that data to other diseases in other countries to arrive at a global estimate.

1.e WHO extrapolations

67. The WHO extrapolation of 10 million smoking-attributable deaths by the end of the 2020s depends, in epidemiologic terms, on a variety of factors, including accuracy of the current estimate (which is uncertain), an increase in tobacco consumption in key populations from 1980 to 2030 (this is not the current trend), an assumption that the circumstances of world-wide smokers will mimic those of affluent Americans in the 1980's (which is unlikely), and a reduction in other causes of disease such as HIV/AIDS and road traffic accidents (which WHO do not predict). Hence this extrapolation is highly speculative and not fairly-based, let alone scientifically verifiable.

1.f Global burden of disease

68. The World Health Report for 1999 (5) also estimates for 1998 the leading causes of mortality and the burden of disease for its regions. For mortality, both sexes, the world rank is:

Rank	Disease	% of total	(ooo)
1	Ischaemic heart disease	13.7	7,375
2	Cerebrovascular disease	9.5	5,106
3.	Acute lower respiratory infections	6.4	3,452
4.	HIV/AIDS	4.2	2,285
5.	COPD	4.2	2,249
6.	Diarrhoeal disease	4.1	2,219
7.	Perinatal conditions	4.0	2,155
8.	Tuberculosis	2.8	1,498
9.	Cancer of trachea/lung/bronchus	2.3	1,244
10.	Road traffic accidents	2.2	1,171

69. Different regions have very different rankings. For example, Africa has HIV/AIDS ranked 1, estimated to cause the death of 19% of the total. In Africa, cancer of the trachea, lung and bronchus is ranked 38th at 0.3%. Road traffic accidents are ranked higher as a cause of death than lung cancer in Africa, the Eastern Mediterranean and South East Asia, and similar in the Americas.
70. Mortality statistics do not give any account to the age of dying, and so WHO also calculate DALY's (disability adjusted life years). These are intended to be the units to measure the global burden of disease and are calculated by combining the losses from premature death, defined as the difference between actual age of death and life expectancy at the age in a low-mortality population, and the loss of health life resulting from disability.

71. For the world in 1998, WHO rank DALYs as:

Rank	Disease	% of total
1.	Acute lower respiratory illness	6
2.	Perinatal conditions	5.8
3.	Diarrhoeal diseases	5.3
4.	HIV/AIDS	5.1
5.	Unipolar major depression	4.2
6.	Ischaemic heart disease	3.8
7.	Cerebrovascular disease	3.0
8.	Malaria	2.8
9.	Road traffic accidents	2.8
10.	Measles	2.2

72. A further way at looking at the global health burden is the WHO's calculation of years living with disability (YLDs). The WHO's calculations for 1990 (7) gave:

Rank	Disease or injury	(ooo)
1	unipolar major depression	50,810
2.	iron-deficiency anaemia	21,987
3	falls	21,949
4.	alcohol use	15,770
5.	COPD	14,692
6.	bipolar disorder	14141
7.	congenital anomalies	13507
8.	osteoarthritis	13275
9.	schizophrenia	12,183
10.	STDs excluding HIV	12,100

73. The WHO has estimated that worldwide in 1990, about 5 million people died of injuries of all types, two-thirds of them men. Most of these deaths were heavily concentrated in young men. (7)

74. Predicting injuries in 2020, WHO state "according to baseline projections, road traffic accidents could rise to third place from ninth worldwide. Violence, currently nineteenth, could rise as high as twelfth place and suicide could climb from seventeenth to fifteenth place." (7)

75. On infectious diseases, the WHO state, "Infectious diseases are now the world's biggest killer of children and young adults. They account for more than 13 million deaths a year – one in two deaths in developing countries. Over the next hour alone, 1 500 people will die from an infectious disease – over half of them children under five. Of the rest, many of them breadwinners and parents. Both are vital age groups that countries can ill afford to lose." (8) WHO continue, "Almost one in three children are malnourished. One in five are not fully immunised by their first birthday. And over one third of the world's population lack access to essential drugs. Against this backdrop of poverty and neglect it is little wonder that deadly infectious diseases have been allowed to gain ground. Today some of the poorest countries are paying a heavy price for the world's complacency and neglect." (8)

1.g Conclusions

76. While smoking-attributable death estimates may be seen to be useful by some public health authorities as a way to inform about the risks of smoking, such estimates are not scientifically verifiable and are inherently uncertain. Consideration of global health priorities illustrates that while smoking is an important public health issue, much of the developing world, in particular, has other more pressing priorities.

2. Comparisons between smoking and ‘hard drugs’

2a. Introduction

77. Several witnesses to the Committee during its current inquiry have suggested that tobacco smoking is comparable to the taking of drugs such as heroin and cocaine. Mr. Hesford has referred to a study on smoking and cocaine use by Jones et al (9), and there has been reference to the recently published study by the Royal College of Physicians (RCP), “Nicotine Addiction in Britain” (10). In order to assist the committee, this Supplementary Memorandum addresses these two studies.

2.b The Jones study

78. This research study, undertaken by researchers at the Johns Hopkins University School of Medicine, compared the subjective and physiological effects of intravenous administration of cocaine and nicotine in ten cigarette-smoking cocaine abusers. The study recruited 15 volunteers, but five dropped out for “personal reasons”. For each of the remaining ten volunteers, eleven sessions were conducted – four to ascertain that the doses given to the subjects were tolerable and a further seven experimental sessions. The subjects each had an i.v. catheter fitted in their dominant arm, and during the session a single dose of either placebo, cocaine (10, 20 or 40 mg/ 70 kg) or nicotine (0.75, 1.5 or 3.0 mg/70 kg) was administered. The subjects were then asked a series of subjective questions and monitored for a variety of physiological end-points.
79. Jones et al found, “At doses that produced comparable ratings of drug effect (40mg/70 kg cocaine versus 1.5mg/70kg nicotine), cocaine produced significantly greater good effects, whereas nicotine produced greater bad effects.” The study observed, “The drug versus money measure showed that the highest cocaine dose was worth twice [to the test subjects] as much as the highest nicotine dose. Thus, intravenous cocaine and nicotine can be differentiated by their subjective and reinforcing effects.”
80. In the discussion section the paper states, “Nicotine and cocaine produced qualitatively different subjective effects. Nicotine, but not cocaine, produced dose- and time-dependent increases in “bad effects” and “jittery”. In contrast to the negative subjective effects produced by nicotine, the high dose of

cocaine produced maximal ratings of liking that tended to be greater than those produced by the high doses of nicotine.”

81. Hence, while the study does identify some similarity in some of the subjective scores of i.v. cocaine and nicotine, it clearly distinguished between the two, with cocaine being significantly more reinforcing.

2.c Royal College of Physicians Report

82. The RCP concludes that “nicotine is highly addictive, to a degree similar or in some respects exceeding addiction to ‘hard’ drugs such as heroin and cocaine.” This conclusion is primarily based on difficulty to quit, and as such is an unfair comparison.
83. The Report considers a variety of types of data to assess such comparisons. Section 2.5 considers animal self-administration studies. The results described were mixed. Some studies on monkeys produced similar results for cocaine and nicotine, while in others the “rates and consistency of responding were less striking”. Reporting on studies in dogs, the Report says “its rewarding effect, although powerful, was less strong than that of cocaine.” Experiments with rats provided mixed results with the Report stating, “It is, however, apparent in most experiments that nicotine is a weaker reinforcer than cocaine, its self-administration is acquired more slowly and maintained under a narrower range of conditions.” No comparisons of self-administration of nicotine to heroin were reported.
84. Section 2.6 considers nicotine neurochemistry. The report hypothesises that heroin, cocaine and nicotine act similarly by stimulating neurotransmission at dopaminergic synapses. The report states that “the effects of nicotine on the system depend on its ability to influence the flow of impulses to the terminal field. In this respect, nicotine differs from cocaine and amphetamine which exert their effects by binding to the presynaptic dopamine transporter located at the nerve terminal membranes.”
85. Moreover, while initially suggesting the hypothesis that nicotine acts to release dopamine, the report continues by concluding that “There is now good evidence that the plasma concentrations of nicotine commonly found in habitual smokers during the day are sufficient to desensitise the nicotine receptors on the mesolimbic dopamine neurons which appear to mediate the rewarding properties of the drug which reinforce its self-administration. As a result, the administration of a nicotine bolus no longer causes increased dopamine release in the nucleus accumbens. These results have significant consequences for the dopamine hypothesis of nicotine addiction. So, if the comparison is to be made between nicotine and cocaine on the basis of dopamine release, then the two seem to be very different. The RCP report suggests that perhaps dopamine release is important for people who do not smoke frequently, and that “other neural mechanisms must probably also contribute to the ‘rewarding’ properties of the drug which reinforce addiction.”

86. Section 4.4 of the Report considers further whether nicotine is comparable to hard drugs. It states that “The answer to this question is complicated by consideration of the specific criteria considered and the dosage form evaluated.” In considering dosage delivery forms the Report suggests that tobacco manufacturers employ techniques in cigarette design “to maximise the addictive effects of nicotine.” This is entirely inaccurate, as covered later in this memorandum.

87. The report then covers several areas of comparison:

(a) Incidence, prevalence and progression

The report states that “addiction to nicotine is far more common than addiction to cocaine, heroin or alcohol, and the rate of graduation from occasional use to addictive levels of intake is highest for nicotine in the form of cigarettes.” This, of course, is not a reasonable comparison. Despite the Report stating that crack cocaine is readily available in the US, it is clear that the access to heroin and cocaine is very different from cigarettes. More importantly, the consequences of use are very different. Heroin, cocaine and alcohol all produce intoxication, nicotine does not. The implications of this on incidence, prevalence and progression are significant. Any use of these substances at the same rate as smoking cigarettes would make the person entirely dysfunctional in society.

88. (b) Remission and relapse

The report states that rates and patterns of relapse are similar for nicotine, heroin and alcohol, and probably for cocaine. However, this is an illogical comparison since a relapse to smoking does not have the same personal and social consequences as a relapse to heroin, cocaine or alcohol.

89. The percentage of people stating that they wish to quit is used to suggest that smoking is more addictive than other substances. However, such reports can be misleading. Kozlowski and co-workers stated “How better to avoid the pesterings of a physician or another interviewer than to say (whether believing it or not) that he wants to and has even tried to give up cigarettes? And if the questioner asks if the attempts to stop have been serious, who would want to confess to a half-hearted effort? Yet, the answers to the questions on “wanting to quit” and “trying to stop” have regularly been used uncritically – as if smokers now *must* be telling the truth.”(18)

90. (c) Reports of addictiveness by drug abusers

Two studies discussed in the report gave disparate findings, one suggesting that the pleasurable effects of smoking were higher for tobacco than heroin and the other finding the opposite.

91. (d) Psychoactivity and euphoria

The Report does not answer this issue directly, concluding that “variation [between the effects of different drugs] probably reflects qualitative differences in the effects of the drugs and not quantitative differences of addictiveness.” As Woody and co-workers wrote in the journal, *Addiction*, “tobacco has few or no sedative effects, especially when compared to alcohol and narcotics; tobacco differs from cocaine and amphetamines by its relative lack of stimulant properties and its inability to produce paranoid states and the other severe organic mental syndromes that are associated with dependence on these drugs.” (19)

92. Other researchers have compared the stimulating effects of various substances and behaviours. Warburton stated “Alcohol, amphetamines, amyl nitrite, cocaine, heroin, marijuana, and sex were significantly more stimulating than tobacco.” “On the pleasurable-relaxation dimension, alcohol, heroin, sex, sleeping tablets and tranquillisers were significantly more relaxing than tobacco.”(20)

93. (e) Reinforcing effects

The report concludes that “[c]ocaine appeared to be the more powerful reinforcer in several studies in which nicotine has been directly compared to cocaine.” However, the report also notes that “such studies do not provide a basis for predicting how the reinforcing effects of drugs will compare in products used outside of the laboratory.”

94. (f) Physical dependence

The report concludes that “The symptoms of withdrawal from cigarettes appear to exceed those for all other forms of nicotine delivery; they are less severe than those produced by alcohol or heroin, but more severe than those from cocaine.”

95. However, it is notable that the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (21), while concluding that a substantial number of people defined as being dependent on cocaine have few or no clinically significant withdrawal symptoms on cessation, states that others suffer acute withdrawal symptoms (a crash) that includes “depressive symptoms with suicidal ideation.”

96. (g) Tolerance

The Report suggests that nicotine, cocaine, heroin and alcohol can produce intoxication and disorientation, but tolerance to the intoxicating effects of nicotine and heroin is sufficiently pronounced to be relatively uncommon in users with stable supplies of drugs.” However, DSM-IV states that “nicotine intoxication rarely occurs and has not been well studied.” DSM-IV states that “Individuals with heavy use of opioids and stimulants can develop substantial

(e.g tenfold) levels of tolerance, often to a dosage that would be lethal to a non-user.”

2.d Conclusions

97. The Report concludes this analysis by stating “The pharmacological effects of nicotine are not identical to those of heroin, alcohol or cocaine – nor, for that matter, are the effects of cocaine identical to those of heroin.” But that “We can conclude that tobacco dependence is a serious form of drug addiction which, on the whole, is second to no other.”
98. In our view, this conclusion is neither based on the science on this issue, nor on the well documented effects of ‘hard’ drugs such as cocaine and heroin. Rather the view comes from failing to account for the quite different social environments and short-term consequences that clearly separate cigarette smoking from ‘hard’ drugs.

3. Ingredients discussions with the Department of Health

3.a Introduction

99. During the Committee’s visit to our research laboratories in Southampton, Dr. Stoate and other members asked questions about the use of certain cigarette tobacco ingredients. While these matters were covered our initial Memorandum to the Committee (1), we agreed to provide additional information. In particular the following covers the discussions that UK tobacco manufacturers have had with the Department of Health over the last six months or so.
100. In December 1998 the Department of Health’s Tobacco Policy Unit (TPU) wrote to the Tobacco Manufacturers’ Association (TMA) and asked if additives were used to increase the bio-availability of nicotine, with specific reference to alkaline additives such as ammonia; ease the initiation of new smokers to the products, with specific reference to additives which make the product ‘smoother’ or more palatable; dilate the airways, with specific reference to cocoa and its constituent theobromine; or facilitate inhalation.
101. The TMA sought the opinion of a number of Industry scientists on the above issues and a written response was provided to the TPU. The TPU replied to the TMA written response in August 1999 and raised a series of more detailed questions concerning the use of additives such as ammonia or ammonia producing substances, cocoa and sugars. In the letter, the TPU referred to a number of citations contained in the ASH/ICRF document ‘Tobacco Additives – Cigarette Engineering and Nicotine Addiction’ (12) as the source of their further concerns surrounding the use of these additives.
102. A number of Industry representatives met with the TPU and it was agreed that Industry Scientists, DOH representatives and appropriate members of the Tobacco Advisory Group should meet to discuss the issues surrounding the

use of specific additives. Subsequently, Tobacco Industry scientists made a series of 3 presentations to the UK DOH on the following 3 topics: Ammonia, smoke pH and nicotine (September 1999), cocoa and theobromine (October 1999), and acetaldehyde and sugars (November 1999).

3.b Presentation 1 – Ammonia, smoke ‘pH’ and nicotine

103. The objective of this presentation was to address the scientific evidence pertaining to the TPU concern that the addition of ammonia and ammonium compounds may increase the bio-availability of nicotine, and also cover a number of ammonia-related issues discussed in the ASH article.

104. Specifically the content of the presentation addressed the following issues concerning the use of ammonia and ammonia compounds:

Why are these compounds used in the cigarette manufacturing process?
What effects do these compounds have on the “pH” of mainstream smoke?
Do these compounds affect the amount of nicotine transferred from tobacco to mainstream smoke?
Do the compounds affect the amount and rate of nicotine uptake from the respiratory system to the brain?
Do the compounds affect the accuracy of the FTC method of determining the nicotine content of mainstream smoke?

105. Ammonia compounds are used in some cigarette brands, primarily US style products, as flavourants. They react during tobacco processing and smoking with certain substances (predominantly sugars) and form flavour compounds which contribute to the flavour characteristics of US style products. Ammonia in the form of diammonium phosphate (DAP) is used in some forms of reconstituted tobacco sheet as a processing aid in addition to the aforementioned flavour modification role.

106. It has been claimed by ASH that tobacco manufacturers add ammonia compounds to tobacco in order to increase smoke ‘pH’, increase the amount of free (unprotonated) nicotine thereby increasing the rate of nicotine delivery to the brain. (12) ‘pH’ is a measure of the quantity of the hydrogen ions in a dilute aqueous solution at equilibrium. If the ‘pH’ is known, the acid/base equilibrium theory can be used to hypothesise the relative portions of nicotine in the diprotonated, monoprotated and unprotonated (free) form for a dilute aqueous solution of nicotine. Under certain experimental conditions it is certainly true that as the solution becomes more alkaline, the amount of nicotine in the protonated form decreases and the amount in the unprotonated form increases.

107. Cigarette smoke is a complex mixture which is not at equilibrium and is not a dilute aqueous solution thus it is scientifically questionable to apply the acid/base equilibrium theory to smoke ‘pH’ in order to determine the amounts of protonated and unprotonated nicotine in mainstream smoke. Additionally, there are a number of methods for the measurement of smoke ‘pH’, most of which involve either bubbling smoke through water, or extracting smoke

condensate from a Cambridge filter pad. The various methods produce different values for smoke 'pH', thus producing a real difficulty in relating a reading of smoke 'pH' to the quantities of nicotine present in the protonated and unprotonated forms in mainstream smoke. At best measures of smoke 'pH' can provide an indication of the relative molar concentrations of water soluble acids and bases in the solution of which the 'pH' is measured and can give directional information on acidity/alkalinity of smoke from a range of products.

108. It has been claimed that ammonia is added to the tobacco in order to enhance nicotine transfer from tobacco to mainstream smoke. Tobacco scientists in the US recently observed that whilst unprotonated nicotine is transferred from tobacco to smoke at lower temperatures than protonated nicotine, under the relatively high temperatures achieved during tobacco combustion both forms of nicotine will transfer to smoke with comparable yields and efficiencies. (22) The research finds that the use of ammonia or ammonia compounds in commercial products does not enhance nicotine transfer.
109. ASH also claim that the addition of ammonia 'helps cheat the federal test for levels of tar and nicotine'. They suggest that increasing pH results in nicotine moving from the particulate phase into the gas phase and that gaseous nicotine will evade detection in the FTC method by passing through the Cambridge filter pad. A study by Bevan in 1995 reported that the Cambridge pad method collected in excess of 99.9% of nicotine from both a flue-cured (acidic smoke) and an air-cured (alkaline smoke) cigarette (23). Additionally Ellis et al (22) showed that in excess of 99.9% of nicotine generated from a range of experimental cigarettes both with and without added ammonia compounds was trapped and recorded using the FTC methodology. Thus the experimental data does not support the ASH claim.
110. Published data from a chemical analysis of 10 common brands from the US market (24) demonstrate the inter-relationships between ammonia in tobacco, ammonia in mainstream smoke, 'smoke pH' and nicotine and tar yields. This data, obtained from commercially available cigarettes, finds no relationship between ammonia in tobacco and ammonia in mainstream smoke, no relationship between mainstream smoke ammonia and 'smoke pH', and no relationship between ammonia in tobacco and nicotine delivery. Rather, it found that nicotine and smoke ammonia yields correlated with 'tar'.
111. If the allegations concerning the addition of ammonia compounds to tobacco were true one would expect that for each of the 3 'tar bands' i.e full flavour, lights and ultra lights, brands with lower ammonia levels in tobacco would have significantly lower in mainstream ammonia yields, 'smoke pH' and nicotine yield than corresponding brands with higher tobacco ammonia levels. Analysis of the Rickert data does not find these effects.
112. Furthermore, it is known that other nitrogen containing constituents naturally present in tobaccos (such as amino acids and proteins) are primarily responsible for the ammonia content of mainstream smoke, and not the addition of ammonium compounds at commercial levels.

113. Nicotine retention (i.e. difference between amounts inhaled and exhaled) within the respiratory system is very high ($> 90\%$) of the inhaled amount irrespective as to whether the cigarette smoke is acidic or alkaline. (25) Consequently, the influence of any cigarette design change on the percentage of nicotine retained during inhalation of smoke would be minimal.
114. The site of nicotine absorption within the respiratory system will influence the rate of nicotine uptake to the central nervous system (CNS). Uptake of nicotine to the brain is more efficient, in terms of rate, when nicotine is absorbed in the alveoli/small airway regions of the lung than if absorption occurs in the mouth and upper airways. In comparison with the mouth/upper airway, the alveolar region of the lung has thinner membranes, a more extensive blood supply, a greater surface area, and a more 'direct' circulatory pathway to the brain (i.e. it does not enter the venous return and pass through the right-hand side of the heart.)
115. Research studies report that nicotine vapour (100% unprotonated or free nicotine) is predominantly absorbed in the mouth and upper airways and that this is a relatively slow route of nicotine absorption. (26) It is thought that nicotine is predominantly in the particulate phase of smoke as it leaves the cigarette in a concentrated smoke 'bolus' at around ambient temperature. On entering the mouth during the puff process and the upper respiratory system during inhalation, the smoke temperature will be raised from ambient to body temperature and the smoke bolus will be diluted with air, both will tend to volatilise nicotine from the particulate to the gas phase. If the smoke is made more alkaline, the volatility of nicotine will increase (i.e. it will have a greater tendency to leave the smoke particle). Thus increasing 'smoke pH' will tend to volatilise nicotine from the particulate to gas phase at an earlier point as the smoke particle travels from the mouth via the conducting airways to the alveolar region of the lung. Since the nicotine vapour studies demonstrate that gaseous nicotine can be absorbed in the mouth and upper airways, an increase in 'smoke pH' will result in more of the delivered nicotine being absorbed in the mouth/upper airway and hence less being available for absorption at the alveolar site. The consequences of this change in site of nicotine absorption would be to reduce the rates and amounts of nicotine uptake to the brain.
116. While experimental research has found that 'smoke pH' is a factor influencing mouth absorption of nicotine, the 'smoke pH' is irrelevant when one considers absorption at the alveolar site. Once nicotine enters biological fluids the form of nicotine (the ratio of unprotonated to protonated nicotine) will be determined by the pH of the body fluid.
117. The olfactory and gustatory sensations give rise to what is often described as the flavour character of the cigarette and the reaction between ammonia and sugars in tobacco can produce flavour compounds which produce subtle changes to the flavour character of the cigarette, primarily through olfactory mechanisms. The common chemical responses to cigarettes smoke (described as mouthful, irritation, impact etc.) are not mediated via olfactory or gustatory mechanisms but involve the stimulation of afferent (sensory) nerve endings in

the mouth, pharynx, larynx and nose. Nicotine is involved in the genesis of the impact sensation, and also to some extent in throat irritation.

118. The ASH article (12) describes the term ‘impact’ as a response in the brain to dopamine and other neurotransmitters released following the stimulation of brain receptors by nicotine. They also cite a number of extracts from Tobacco Company documents which discuss an increase in impact following an elevation of ‘smoke pH’. It is thus implied that an elevation of ‘smoke pH’ increases the bio-availability of nicotine in the brain which produces an enhanced stimulation of receptors in the brain.
119. The ASH definition of the term ‘impact’ and the mechanism responsible for initiating the impact response is incorrect thus leading to a false interpretation of the ‘smoke pH’ effect. ‘Impact’, ‘throat hit’ and ‘throat kick’ are sensory terms used to describe the short-lived sensation perceived in the throat during the inhalation of tobacco smoke. As the impact sensation occurs immediately on inhalation of smoke, and the minimum time delay between commencing smoke inhalation and absorbed nicotine reaching the brain is in the order of seven to ten seconds, it is clear that the impact sensation is not mediated by nicotine entering the blood-stream, travelling to the brain and stimulating nicotinic receptors in the brain region. A more plausible explanation is that nicotine stimulates afferent nerve endings in the throat region resulting in activation of nerves supplying this region (e.g hypoglossal, glossopharyngeal and superior laryngeal nerves) which rapidly conduct electrical signals to the brain.
120. As previously discussed, changing the acid/base balance of smoke will alter the amounts of nicotine absorbed in the mouth/throat region. Increasing the alkalinity of smoke will result in more of the delivered nicotine absorbed in this region (and less available for absorption in the alveolar region), a greater stimulation of sensory nerve endings and a higher perceived impact sensation.
121. In sum, the science illustrates that the allegations made by ASH regarding the purpose and effect of the use of ammonia and ammonium compounds as cigarette ingredients are misconceived.

3.c Presentation 2 – Cocoa

122. The DOH expressed a concern that cocoa may be used as a tobacco additive to dilate the airways and facilitate deeper inhalation of smoke. ASH have suggested that, “Additives such as cocoa may be used to dilate the airways allowing the smoke an easier and deeper passage into the lungs exposing the body to more nicotine and higher levels of tar.” (12)
123. Cocoa contains the methylxanthine, theobromine, which can relax bronchial smooth muscle but is less potent than other xanthines such as theophylline and caffeine. Unlike theophylline, theobromine is not used clinically as a bronchodilator. Cocoa is used in cigarettes as a casing material in US blended cigarettes and enhances the characteristic burley tobacco flavour. It does not impart sweet or chocolate-like taste characteristics. It should also be noted

that casings are not used in Virginia products and thus over 90% of products sold in the U.K market do not use cocoa casings.

124. At the maximum permitted use level for cocoa of 5% and a typical theobromine content of cocoa of 2.6%, a cigarette would contain approximately 1mg of theobromine. It is possible to estimate a maximum daily intake of theobromine of 5.2mg/day, based on a 5% cocoa application level, measured theobromine transfer from tobacco to smoke of 13% and a cigarette consumption rate of 40 per day.
125. The ASH article (12) contains a citation which claims that bronchodilation was observed with a 10mg oral dose of theobromine. This is incorrect. The Simmons study (27) reports that bronchodilation was achieved in a group of asthmatics with a dose of 10mg per kg (that is, a person of 70 kg weight would receive 700 mg) and that the average dose of theobromine used in the study was in fact 468mg. The Simmons study also measured peak theobromine blood levels of 9.8mg/l and a theobromine half life of 5.5 hours.
126. We are not aware of any published or unpublished studies of theobromine plasma levels in smokers of cocoa cased cigarettes. A calculation of the theoretical plasma concentration of theobromine was made for cigarettes containing 1mg theobromine and a cigarette consumption rate of 40 per day. The calculation uses a theobromine half-life of 5.5 hours (27) and assumes that 100% of the delivered theobromine is absorbed in the lung. The theoretical maximum plasma concentration of theobromine is 0.08mg/l. This is approximately 100th of the clinically effective plasma level quoted by Simmons et al.
127. The Simmons et al (27) study considered orally administered theobromine. It is possible that the dose required to produce bronchodilation may be lower when administered by the inhalation route. A recent publication on the effects of cocoa on isolated guinea pig trachea, using water extracts of cocoa, demonstrated dose related contractions of tracheal smooth muscle probably mediated via cholinergic pathways (28). This is consistent with an irritant, bronchoconstrictor effect of cocoa (possibly theobromine) rather than bronchodilation.
128. Many researchers have studied the immediate airway response to cigarette smoke inhalation and mild, transient bronchoconstriction, probably mediated via cholinergic pathways, is frequently reported as the outcome. There are no studies comparing the airway responses to cigarettes containing and not containing cocoa. Following discussions with the TPU and their scientific advisors we agreed to design and conduct a study aimed at addressing the influence of cocoa casings on the bronchomotor response to cigarette smoke inhalation. A draft protocol has been prepared and submitted to the TPU for comment. We are currently awaiting a reply from the TPU.
129. The ASH article (12) claimed that theobromine induced bronchodilation could facilitate nicotine intake. Nicotine delivery is a function of both cigarette design and human puffing behaviour. Puffing is a mouth action and does not

involve the lungs, consequently changes in puff volume will influence the amounts of nicotine (and other smoke components) delivered in each puff to the smoker. However, changes in inhalation parameters or airway calibre will have no influence on the amounts of nicotine delivered from the cigarette.

130. The key question is whether the amounts of nicotine absorption are influenced by airway expansion or deeper inhalation depth. Although there is no doubt that the amounts of nicotine absorbed into the blood are greater after the inhalation of smoke than in the non-inhalation condition, most smokers are 'inhalers' and typical post puff inhalation depths are in the order of 400-700ml. Research has found that virtually 100% of the nicotine delivered from flue-cured cigarettes (no added flavours or cocoa) was retained in the respiratory system during normal inhalation. This implies that as nicotine retention from products not containing cocoa is essentially complete, any potential influence of cocoa on nicotine retention would be minimal. Zacny et al (29) examined the potential influence of changing post-puff inhalation depth and breath-hold time on the time-course and amounts of nicotine absorbed into plasma. Increasing inhalation depth from 10% vital capacity (VC) to 60% VC did not influence the rates or amounts of nicotine absorbed into the blood. The 10% VC inhalation depth represents a typical inhalation depth during normal smoking behaviour and the 60% VC inhalation is an extremely high inhalation volume. Zacny et al also reported that increasing breath-hold time from zero to 16 seconds had no effect on nicotine absorption but increasing puff volume from 15ml to 60ml produced a linear increase in the amounts of nicotine absorbed into the blood. The authors concluded that the amounts of nicotine absorbed were influenced by the size of the puff but not by large changes in inhalation patterns. It should be noted that the results from the Zacny study are also relevant to the issue of bronchodilation as a large increase in inhalation depth results in a dilation of the airways.
131. One can conclude, on the basis of the above, that nicotine delivery or absorption would not be enhanced by bronchodilation.
132. The ASH article (12) also claimed that glycyrrhizin, an ingredient of liquorice, is added to tobacco because of its bronchodilator properties. Liquorice is derived from the roots of the *Glycyrrhiza glabra* plant and is used as a casing material in some US style products to modify the burley flavour character. The maximum permitted application level of liquorice in the U.K is 4%. As casings are typically not used in Virginia style cigarettes the overwhelming majority of products sold in the U.K market do not use liquorice as an ingredient. A cigarette would theoretically contain about 2mg of glycyrrhizic acid when cased with liquorice at the 4% application level (based on around a 6% glycyrrhizic content of liquorice). This can be compared with the Council of Europe permitted maximum intake of glycyrrhizic acid of 50mg/kg/day.
133. There are no scientific references to support the claim that glycyrrhizic acid is a bronchodilator. However, there are claims that liquorice may have anti-tussive properties. Glycyrrhizic acid is not transferred intact from tobacco to cigarette smoke hence a smoker would not inhale glycyrrhizic acid when smoking a cigarette containing liquorice casings. One can conclude that in

view of the uncertainty surrounding the bronchodilator properties of glycyrrhizic acid together with the fact that it does not transfer from tobacco to cigarette smoke, it is highly unlikely that the incorporation of liquorice into cigarettes results in bronchodilation.

3.d Presentation 3 - Part 1 – Acetaldehyde

134. The TPU, on the basis of the ASH article (12), expressed concerns that sugars in tobacco breakdown during the combustion process to form acetaldehyde which acts synergistically with nicotine in the brain.
135. There are a number of published articles that report that polysaccharides and not sugars are the precursors of acetaldehyde in tobacco smoke. (30, 31) Research available for many years concludes that components of tobacco leaf and stem such as cellulose, hemicellulose, starch and pectin are the primary sources of acetaldehyde in mainstream smoke, and that sugars added as casing materials do not significantly contribute to acetaldehyde yields.
136. An examination of the relationship between acetaldehyde yields in mainstream smoke and the sugar content of tobacco for a range of products in European markets reveals a very weak relationship between sugars and acetaldehyde and confirms the conclusion reached from the experimental data.
137. Average acetaldehyde yields for US Commercial brands have significantly declined from 1975 to 1992. As acetaldehyde yield is correlated with tar yield for a given blend style, the changes in cigarette design features used to reduce tar yields over this period have also resulted in a reduction in acetaldehyde yields.
138. Hence, we conclude that sugars are not added to increase acetaldehyde yields and that polysaccharides (e.g cellulose) are the major precursors of acetaldehyde.
139. In order to examine the claim that nicotine and acetaldehyde act synergistically in the brain, it is worth contrasting some of the pharmacokinetic properties of the two substances. Key differences exist between the two substances in terms of sites of absorption, stability and half-life's in blood. Compared with nicotine, acetaldehyde is far less stable and has a much shorter half-life and consequently is unlikely to reach the brain in detectable amounts following smoking.
140. The literature relating to the peripheral absorption of acetaldehyde and levels of acetaldehyde in the brain finds that peripheral administration of acetaldehyde (i.e. through mainstream smoke inhalation) does not lead to detectable levels of acetaldehyde in the brain. The rapid breakdown of acetaldehyde by the action of enzymes such as aldehyde dehydrogenase is the prime reason why this substance does not reach the brain in detectable levels.

141. Consequently, scientific data does not support the claims that the Tobacco Industry has added sugars to cigarettes in order to elevate mainstream acetaldehyde levels and potentiate the effects of nicotine in the brain.

3.e Presentation 3 – Part 2 - Sugars

142. In addition to the acetaldehyde aspect of sugar additives, concerns have been expressed by the TPU and ASH that sugars are added to cigarettes in order to mask the ‘unpalatable taste of nicotine’, and to make cigarettes taste sweeter and thus more attractive to children. The ASH article implies that unflavoured cigarettes are unacceptable to the smoker. It also implies that the sensory properties of nicotine are undesirable and are required to be modified by added flavours to make an acceptable cigarette.
143. This statement is clearly incorrect when one considers the UK market where the majority of products do not contain added flavours.
144. Flue-cured Virginia tobacco is naturally much higher in sugar content than air-cured burley tobacco. Traditionally, US blended styles of cigarettes have incorporated significant quantities of Burley tobacco into the blend. Sugar casings are predominantly added to the Burley portion of a US blended cigarette to partially replace sugars which are lost during the curing of Burley tobacco. Sugar based casing are not generally applied to Virginia cigarettes and these cigarettes account for the majority of products sold in the UK market.
145. Burley tobacco imparts specific flavour notes that are an integral part of the flavour spectrum of US style products. The addition of sugar casings to the Burley component of a traditional US blend improves the balance of the various sensory properties of the smoke, primarily by ameliorating the harshness of uncased Burley tobacco. Sugar casings also improve the ‘processability’ of tobacco by making the tobacco more pliable.
146. Although the addition of sugar casings improve the sensory properties of an uncased US blended product, typical cased US products are not demonstrably sweeter or ‘smoother’ than traditional uncased Virginia products. Additionally the sugar content of cased US blended products is generally lower than that of uncased Virginia products. A consumer sensory evaluation study conducted by our research centre compared the sensory properties of a range of commercially available products. Sensory results from two products, a US blended product and a Virginia product, were evaluated. Both were ‘full flavour’ products with similar tar yields. The US blended product which contained the added sugar was perceived as being marginally higher in irritation and lower in sweetness than the Virginia product which did not contain added sugar.
147. The mechanisms whereby sugars influence the sensory properties of cigarette smoke have been considered. Sugars pyrolyses to form acids which can alter the acid/base balance of mainstream smoke. Increasing the acidity of smoke will reduce the amounts of nicotine absorbed in the mouth/upper airway and

consequently less nicotine is available to stimulate sensory nerve endings in the throat region resulting in a reduction in sensations such as irritation and impact. The influence of sugars on the acid/base balance of smoke and its role in the flavour quality of cigarette smoke has been known for decades (31).

148. Increasing or decreasing the sugar content of foods or drinks modifies the perception of sweetness via an action involving taste receptors on the tongue and other areas of the mouth. However, sugars are non-volatile and when added to tobacco do not transfer as sugar to mainstream smoke but following combustion form other compounds e.g acids which do transfer into mainstream smoke. Thus the sensory response produced by adding sugars to tobacco is not analogous to the food or drink situation and indeed as stated by Gager et al (30) sugars are not added to tobacco to impart the taste and flavour characteristics traditionally associated with sugars in food or beverages.

3.f Conclusion

149. A detailed evaluation of the science, presented over the past months to the Department of Health Tobacco Policy Unit, shows that the allegations on ingredients made by the Imperial Cancer Research Fund and ASH are unfounded.
150. The TPU's actions in asking for scientific information related to the allegations have been entirely appropriate. The UK tobacco industry has answered the TPU's concerns in a series of open meetings. This is a sensible approach to these issues, allowing proper consideration of the facts rather than relying, as ASH have, on selected sections of old documents.
151. The TPU continue to have some concerns regarding the full disclosure of brand ingredient information. None of the ingredients permitted for use on UK products are a secret. They have appeared in the Independent Scientific Committee Reports and in Government papers and now on the internet. Moreover, the notion that anyone brand contains all of the permitted ingredients is unfounded.
152. We understand the Department's requirement for more information, and will be meeting with the TPU soon to find a sensible way forward.

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