Sensible Drinking

The Report of an Inter-Departmental Working Group

December 1995

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ANNEXES

1. INTRODUCTION

1.1 In reply to a Parliamentary question on 27 April 1994, the Government announced that an interdepartmental group of officials would be set up to carry out a review of the Government's sensible drinking message in the light of the latest evidence which indicated that drinking alcohol might give protection from Coronary Heart Disease (CHD). Details of the Group's work were published on 8 August 1994 together with an open invitation to submit evidence. In addition to the general invitation, specific interested individuals and organisations were invited to submit written evidence to the Group by 31 October 1994.

1.2 The terms of reference for the Group were:

i to review current medical and scientific evidence and its interpretation on the long term effects of drinking alcohol; and

ii to consider whether the sensible drinking message should be reviewed in the light of this, also taking into account current Government policies on the short term effects of drinking alcohol and any other factors considered relevant by the Group.

1.3 The Group included both medically and scientifically qualified members and generalists with relevant experience. Membership is at Annex A.

1.4 This report sets out the Group's findings, and what it considers these mean for the sensible drinking message. The Group has carried out its analysis and reached conclusions in the context of the United Kingdom. The conclusions are based on an objective evaluation of the evidence, but the Group has not sought to answer all the questions and resolve all the issues in a complex and controversial field where knowledge continues to develop. Its remit has rather been to analyse the present state of knowledge for the Government's consideration than to advance scientific analysis in this specialist area. The Group has also sought to indicate the areas of uncertainty which are relevant to its remit. it is important that here, as in other areas of public health, the limitations of the knowledge on which advice is offered to the public should be recognised.

Evidence Received

1.5 The Group received 89 submissions of written evidence. Of these, 9 were from the alcohol industry, 21 from scientific and academic sources, 22 from medical sources, 21 from the health promotion field and service providers, 15 from other organisations and 1 from a member of the public. A full list is at Annex B. In addition, the group examined a number of key documents which were referred to frequently in the evidence. A full bibliography is at Annex C. The Group has sought to examine the major published research relevant to their work.

1.6 Evidence which included extensive medical and scientific detail was independently assessed by Mr lan White, a medical statistician at the Medical Statistics Unit, Department of Epidemiology and Population Sciences at the London School of Hygiene and Tropical Medicine. Mr White summarised its findings and provided a critique of how the conclusions had been drawn from the research cited.

1.7 The Group also invited five experts, representing a range of views, to give oral evidence. Four were invited to discuss the whole range of issues: Professor Michael Marmot of London University, Mr John Duffy of Edinburgh University, Professor Sir Richard Doll of Oxford University and Dr Arthur Klatsky of the Kaiser Permanente Medical Center, California, USA. The fifth witness, Dr Moira Plant of Edinburgh University, gave evidence on women's issues. In addition, Professor Kay-Tee Khaw of Cambridge University, gave evidence to certain members of the Group on the same issue. The Group found these sessions extremely valuable and would like to record its thanks to the witnesses who gave so generously of their time and knowledge to assist its considerations.

Structure of the Report

1.8 The report considers present levels of alcohol consumption in the UK (Section 2) and the development of the current advice on drinking alcohol (Section 3). After a brief discussion of some factors taken into account in assessing the evidence (Section 4) it considers first the beneficial long term effects of alcohol (Section 5) and then the harmful effects (Section 6). The next sections deal with the effects of alcohol on overall mortality (Section 7), women and alcohol (Section 8), and some factors particularly relevant to the giving of advice in this area (Section 9). The Group's conclusions on the evidence are in Section 10 and recommendations for future action are set out in Section 11.

2. ALCOHOL CONSUMPTION IN THE UNITED KINGDOM

2.1 In all parts of the United Kingdom a large majority of people drink* although there are important variations. Information on drinking habits is collected every two years from people in Great Britain as part of the OPCS General Household Survey (GHS).[1] Similar information is collected for Northern Ireland in the Continuous Household Survey (CHS)[2]. The analysis by OPCS from the data collected in the 1992 survey (GHS92) and from the CHS is set out in Table 1.

2.2 Alcohol consumption varies greatly between countries and cultures. (The UK ranks 14th out of 20 OECD countries and 25th out of 40 countries in WHO Europe region in terms of alcohol consumption)[3] GHS 1992 shows that in Great Britain 73% of men and 89% of women aged over 18 drank below the present recommended levels.[1] Estimates of average consumption differ between Customs and Excise and sales data as compared with survey data. The Brewers and Licensed Retailers Association statistical handbook, using data from Customs and Excise related to the amount of alcohol sold, shows that, over the last 15 years, the annual average per capita consumption has been fairly steady at around 9 litres of pure alcohol for people aged over 15.[4] This makes no allowance for personal import of alcohol from abroad. General Household Survey data reports average annual consumption levels of 5.3 litres.[1] This latter figure is perhaps less accurate because of the general tendency for respondents to underestimate consumption.

2.3 The drinking habits of the population have only been monitored in the General Household Survey since 1984. However, historical data about alcohol consumption can be derived from Customs and Excise records of

alcohol duty. As noted in para 2.2 this probably provides a more accurate indication of total consumption than individual monitoring. The data show that the amount of alcohol consumed was considerably higher in the late 19th century than at present and concern about alcohol related harm was reflected at that time by the rise of the Temperance Movement.5 After 1900 consumption slowly declined until 1945. Then, following a Europe-wide trend, consumption rose again until levelling out some 15 years ago. Present per capita consumption would seem to be at about the same level as in 1911.[5]

**Throughout this report the term "drink" is used to mean "drink alcohol"*

TABLE 1: Alcohol consumption level by adults over 18 by sex 1992

United Kingdom Percent

Consumption level (units per week)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
			(4)+(5)				(9)+(10)	(9)+(10)			
			+(6)				+(11)				
	Base= 100%	Non-Drinker	Very low to moderate	Very low	Low	Moderate	Total high	Fairly high to high	Fairly	High	Very High
Men											
England	7087	6	67	10	36	21	26	21	14	7	6
Wales	396	5	66	10	32	24	28	22	15	7	6
Scotland	692	6	66	9	35	23	27	19	12	7	8
Great Britain	8175	6	67	10	36	22	26	20	14	7	6
Northern Ireland	2380	23	60				18	14			4
Women											
England	8163	12	76	22	39	15	12	10	8	2	2
Wales	480	15	74	22	39	13	11	9	8	1	2
Scotland	858	13	79	23	40	M	7	7	5	2	1
Great Britain	9501	12	76	22	39	15	11	10	8	2	2
Northern Ireland	2984	33	61				6	5			1

		Very low	**Low**	**Moderate**	**Fairly high**	**High**	**Very high**
Men		under 1	01-Oct	Nov-21	22-35	36-50	51 and over
Women		under 1	01-Jul	Aug-14	15-25	26-35	36 and over

Notes

(1) Data for Great Britain are taken from OPCS's General Household Survey. Data for Northern Ireland are taken from Northern Ireland's Continuous Household Survey, which is carried out on a similar basis.

(2) Alcohol consumption levels are based on the 'usual' amount of alcohol consumed on any particular occasion in conjunction with the frequency of consumption.

(3) The titles shown above for consumption levels are those adopted in the General Household Survey and are used for this purpose only.

(4) Figures have been adjusted to the nearest whole figure.

3. THE CURRENT SENSIBLE DRINKING

MESSAGE

3.1 The current sensible drinking message, as set out in the Lord President's Report on Alcohol Misuse (1991) and, for England, in The Health of the Nation (1992), is that drinking less than 21 units** per week by men and 14 units per week by women is unlikely to damage health.[6,7] The Health of the Nation sets a subsequent target for England of reducing the number of men drinking more than 21 units a week from 28% in 1990 to 18% by 2005, and the proportion of women drinking more than 14 units a week from 11% in 1990 to 7% by 2005. Similar targets have been set in the health strategies for other UK countries (details of these are given in Annex D).

3.2 Annex E sets out how this message was developed. Many other countries have also incorporated the concept of sensible or safe drinking levels into their national alcohol policy. At Annex F is a table which outlines the recommended drinking levels in some other countries.[8]

3.3 The 1994 OPCS Omnibus Survey of Drinking in Great Britain (carried out in February and March 1994) found that 22% of men and 18% of women interviewed who drank regularly were able to identify their correct recommended weekly level on the basis described above, within a margin of error of plus or minus 3 units.[9] In the 25 to 44 age group 80% of men and 77% of women had heard of recommended weekly levels. Overall, 58% of those interviewed knew the amount that made up one unit of their favourite drink.

***A unit of alcohol is 8 grams: the amount contained in half a pint of ordinary beer or lager or in a small glass of wine, or in a standard measure of spirits*

4. FACTORS TAKEN INTO ACCOUNT IN ASSESSING THE EVIDENCE

Association and causality

4.1 In evaluating medical and scientific evidence the Group paid close attention to the distinction between association and causality. Evidence may show that a particular factor and a particular type of disease or damage often occur together but it may not be possible to demonstrate how, or indeed whether, the one causes the

other. In other words, it is possible to identify an association without establishing causality. The evaluation of such evidence involves striking a balance. For example, it would be possible to place more weight on a weak association if a causal connection could be established. A strong association might need to be viewed more cautiously if no causal connection could be identified, especially if it was not clear that other possible causes had been eliminated.

Applicability to the UK of International Studies

4.2 In considering evidence the Group has taken the view that well conducted studies carried out in the UK itself are the best basis for drawing conclusions. However here, as in other public health areas, there are insufficient UK based studies to be able to rely on these alone. The Group has therefore also taken account of other studies from developed countries similar to the UK, whilst recognising the need for caution given international differences, even between otherwise generally comparable countries, in the incidence of disease. This issue has been raised for example in relation to international comparisons of all cause mortality (see Section 7).[10]

5. BENEFICIAL LONG TERM EFFECTS OF ALCOHOL

5.1 For a number of years studies have provided evidence that there is a relationship between moderate alcohol consumption and a reduced risk of death from all causes, and that this benefit was found in people who regularly consumed as little as 1 unit per day.[3,11,13,14] This section reviews the evidence for beneficial effects on cardiovascular disease and a number of other conditions. Recent studies have made it clear that the beneficial effects are not artefacts (phenomena produced by the analytical process) but strongly indicate a direct causal relationship. [12,13,15,16]

Coronary Heart Disease

5.2 It is now established that the main specific pathology which benefits from alcohol consumption is coronary heart disease.[3,12,18,19,20,21,22] CHD accounts for 66% of deaths due to cardiovascular disease which, in turn, accounts for about one third of all deaths in men and women in the United Kingdom and is a major cause of premature mortality.[7,23] About 71,000 people die of CHD in the UK each year, with about 27,000 of them under the age of 65.[23] In England CHD accounts for 2.5% of total NHS expenditure, and results in 35 million lost working days per year.[7]

5.3 The epidemiological evidence alone linking alcohol and CHD now makes the existence of a protective effect appear very likely.[11,19,20,22,24] The written and oral evidence received by the Group confirmed that most of the technical epidemiological criteria for a causal association are now fulfilled (see Annex G).[61]

5.4 A key issue previously complicating the epidemiological data has been the so called "sick quitter" hypothesis outlined by Professor A G Shaper.[17,25] This identified a number of relevant issues, but in particular it attributed higher mortality in people who did not drink to the effect of those who had given up drinking because of ill health. In addition, Professor Shaper has suggested that abstainers may carry a greater burden of ill health than

drinkers and consequently never take up drinking, or that abstainers are constitutionally predisposed to high risk of disease, in contrast with moderate drinkers who are similarly predisposed to low risk of disease.[17,25] However, a number of studies since 1987 have controlled for these factors so that we believe Professor Shaper's reservations cannot be considered as a major explanation of the cardio-protective effect.[13,21,22,24.27] Other confounding factors such as tobacco use, obesity, diet and age have now been controlled for in enough studies to allow us, on the basis of expert testimony, to be confident that the basic protective effect for CHD by alcohol is scientifically valid.[3,12,15,21,24]

5.5 The evidence shows alcohol consumption confers protection from CHD mortality, starting at levels as low as 1 unit a day.[3,12,21,24] A number of studies have established that, over a wide range of consumption, there is no more than a slight dose response relationship (i.e. drinking beyond 1 to 2 units a day confers only a little extra benefit).[21] Drinking in the range of 7 units to 40 units a week lowers the risk of CHD by between 30% and 50%.[12,11] However, the risk does rise above that of non drinkers at very high levels of consumption and there is evidence that people drinking more than 70 units a week (in excess of 80g per day) do have an increasing risk of CHD which might be dose related.[21,28,29]

5.6 Though a model of causation has not yet been established definitely, most of the evidence reflects increasing acceptance of biological explanations.[21,30] It is established that the major physical cause of CHD is a life long deposition of fatty tissue in coronary arteries (atheromatous plaque).[23,32] In addition, local coronary artery spasm and an increased tendency to form blood clots generate the symptom of chest pain (angina). These factors can lead to an acute narrowing or blockage of a major coronary artery and a clinical heart attack, leading to serious illness or death.[27]

5.7 Atheromatous plaques consist largely of cholesterol. Cholesterol is transported in blood combined with specific proteins (lipoproteins) which affect its metabolism. CHD is mainly linked with low density lipoproteins (LDL) which carry 70% of plasma cholesterol.[11,32] However, some forms of high density lipoproteins (HDO remove cholesterol from the surface of blood vessels. Put most simply it is acknowledged that a high ratio of LDL to HDL is associated with an increased risk of CHD mortality. Physical activity appears to raise HDL cholesterol but does not change LDL cholesterol levels. Alcohol, more than any other dietary factor, raises HDL levels in the blood.[32] In addition, however, alcohol lowers LDL blood levels, and it has been speculated that it is through these lipoprotein cholesterol pathways that alcohol inhibits the formation of coronary artery atheroma.[21,33,34,35]

5.8 Alcohol also directly affects advantageously a number of mechanisms associated with blood clotting and thrombosis.[21,30] It has been found to reduce platelet stickiness and aggregation, to reduce fibrinogen and to increase fibrinolysis. Again, it has been speculated that through these mechanisms alcohol consumption directly reduces the likelihood of coronary heart disease.[21,30]

5.9 In addition to these two major biological protective mechanisms, alcohol may also protect against coronary heart disease through a number of less widely acknowledged mechanisms. At low levels of consumption, alcohol may lower blood pressure and so may contribute further to reducing coronary risk.[36] Alcohol can also cause slight increase of coronary artery blood flow, and can reduce coronary artery spasm induced by stress.[36,37]The full significance of these additional mechanisms awaits further research.

5.10 Some epidemiological evidence suggests that about 50% of the protective effect comes from the HDL cholesterol mechanism and that the remainder comes from the clotting and other mechanisms but the exact apportionment of these mechanisms in any individual person may vary.[21,33]

5.11 There is also a body of evidence that predominantly wine drinking countries (for example France and others in the Mediterranean area) enjoy particularly low rates of CHD.[38,39] In addition to lifestyle factors, it has been suggested that wine itself may have constituents other than alcohol, for example antioxidants and flavonoids, which confer additional protection.[32,38] High consumption of wine has been suggested as one reason why CHD rates in France appear to be low in comparison with other western European countries.[39,40] However, overall, current research indicates that the major factor conferring benefit is probably alcohol rather than the other constituents of wine.[27,40]

5.12 At extremely heavy levels of consumption over long periods (80g or 10 units a day for 10 years or more) alcohol increases the risk of cardiac arrhythmias, cardiomyopathy and sudden fatal heart attack and some evidence for these pathologies suggests a dose response relationship.[28,29]

Adults who are not yet middle aged

5.13 We have considered the CHD evidence with regard to adults not yet in middle age (which we define for this purpose as being men below 40 and premenopausal women), and therefore not at significant risk for clinical CHD. It is well established that deposition of atheromatous plaque leading to CHD begins early in life for most people leading a "developed country" lifestyle.[41] It is reasonable therefore to speculate that moderate drinking in early adulthood might inhibit atheromatous plaque formation and so confer benefit in later life when CHD becomes clinically evident.

5.14 There is no reason to suppose that CHD alcohol related protective mechanisms are not present throughout adult life.[21] However, it is not possible from current available evidence and evidence we have received from expert advisors to confirm that the protection offered confers clinical benefit before middle age, when the risk of CHD becomes significant.[21,42,43] Very little specific data exists about the quantity and frequency of younger adult alcohol consumption related to CHD protection mechanisms and this is an area which would benefit from research.[21]

Strokes

5.15 Stroke accounted for 10% of all deaths in England and Wales in 1994. In England*** over 62,000 people die as a result of stroke each year, over 4,000 under the age of 65.[44] 85% of strokes are ischaemic (cerebral artery blockage causing infarction), and 15% are haemorrhagic either due to intracerebral haemorrhage (10%) or to subarachnoid haemorrhage 5%), ie bleeding from the arteries of the membranes which surround the brain's surface.[45] Mortality data for stroke in 1992 in England and Wales show that, for those aged under 65, in 33% of cases the cause of death was given as haemorrhagic stroke compared with 5% for ischaemic stroke; the type of stroke was not indicated in the remaining cases.[46]

Ischaemic Stroke

5.16 Most studies suggest that, for ischaemic stroke, there is an alcohol related beneficial effect with the relative risk compared with non drinkers being reduced by about 50%.[24,45,47,48,49,50] Evidence suggests that this Protective effect is fairly consistent within a range of consumption between 2 and 5 units a day for men and 2 and 4 units a day for women.[45,47,50] A number of studies suggest that regular drinking is more beneficial than irregular consumption.[45,50] There is some evidence that risk of ischaemic stroke does not increase at relatively high levels of intake.[45]

Haemorrhagic Stroke

5.17 There is, conversely, considerable evidence that regular alcohol consumption increases the risk of having haemorrhagic and subarachnoid strokes and there are probably no significant beneficial effects for these forms.[1] There is a significantly increased risk of haemorrhagic stroke at[24,25] consumptions as low as less than 2 units a day At higher consumption levels, in excess of 3 units, the relative risk increases two to three fold.[49,51] In most populations haemorrhagic stroke makes up a minority of all forms of stroke, but clinically this form tends to be the most severe, and is the most common cause of fatal stroke in men and women under 65.[45,46]

All Strokes

5.18 In summary, it appears that for one form of stroke alcohol has a definitely harmful effect, and for the other form a beneficial effect. Hence, we do not consider that it is possible to draw a definitive conclusion regarding the relationship of alcohol to all forms of stroke, as consumption levels, pre-existing hypertension, age and sex are all significant variables.

**** 1992 data*

Gallstones

5.19 It appears that alcohol consumption may inhibit the formation of cholesterol type gallstones.[52,53,54] This is a significantly common pathology in middle aged people, but because not all cases are readily identifiable, the exact prevalence is difficult to determine. One study of US nurses has concluded that there is an inverse association between alcohol consumption and the risk of gallstones.[54] A similar effect has been observed in men but at higher levels of consumption.[53] It appears from these studies that alcohol consumption up to 40g/day (5 units) in men and up to at least 15g/day (2 units) in women confers protection against cholesterol gallstones.[53,54]

Other Beneficial Effects

5.20 We are aware that claims have been made that alcohol consumption has other beneficial effects on morbidity.[55] in particular, recent research suggests that alcohol consumption of 15-40g a day (2-5 units) reduces the risk of noninsulin dependent diabetes mellitus.[56,57,58] Other conditions cited include stress, rheumatoid arthritis, gastro-intestinal diseases and the common cold.[37,55,59,60,148] it has also been reported to have a beneficial effect on bone mineral density.[62] In our view this evidence is not sufficiently strong or consistent to inform public policy, and these areas would benefit from further research.

5.21 Finally, in relation to the beneficial effects of alcohol it is widely recognised that alcohol taken in moderate amounts may be followed by a positive mood and a sense of well being. These benefits to both the individual and society clearly exist but have not been studied scientifically.

6. HARMFUL EFFECTS OF ALCOHOL

Short-term effects and Drunkenness

6.1 Much of the short term harm associated with alcohol, for instance domestic and road traffic accidents, violent crime, domestic violence, child neglect and abuse is related to single episodes of intoxication, and consequently may not appear to be so obviously related to individual daily or weekly consumption.[3,63,64] There is, however, evidence that some indices of harm, for example rates of drunkenness offences, correlate broadly with changes in the average consumption of alcohol found for example in the UK between 1950 and 1980.[65] The short term effects are particularly associated with young adults.[66,143]

6.2 Evidence submitted to us from recent USA, Canadian and New Zealand studies indicates that indices of harm such as the prevalence of drinking and driving, being in trouble with the police and being involved in an assault rises fairly steadily with the average amount of alcohol consumed by the individual.[3,67,68,69]

6.3 Although no exact replication of the USA, Canadian and New Zealand studies of social harm and consumption has been carried out in the UK, similar findings have been reported in the Health Survey in 1993 linking likelihood of episodes of drunkenness and the level of consumption.70 Here it was found that 4% of men drinking up to 21 units a week report an episode of drunkenness each week. For those drinking between 21 and 35 units, 35 and 50 units, and in excess of 50 units, the proportions are 16%, 21% and 38% respectively, showing a clear relationship between frequency of drunkenness episodes and the amount of alcohol consumed.

6.4 The effect of alcohol on judgement is well known. Nowhere is this more in evidence than in the area of drinking and road accidents.[63] Even a relatively small amount of alcohol will affect driving ability and judgement.[63,71] For young and inexperienced drivers, the risk of having an accident is increased by a factor of 5 at the legal limit (80mg/100ml of blood); at twice the legal limit the risk of being involved in a fatal accident is increased more than 50 times.[145] One in 7 of all deaths on the road involve drivers over the legal limit.[145]

6.5 In addition to drink/drive accidents, which have fallen substantially during the last decade (the number of fatal drink/drive accidents has fallen from 1,170 in 1984 to 510 in 1994) the problem of the drinking pedestrian is of considerable importance.[146] Around half of all pedestrian deaths between the ages of 16 and 60 are of people who have blood alcohol levels above the drink/drive limit.[147]

Long-term effects Cirrhosis of the Liver

6.6 In 1992 there were 3,056 deaths (1,753 men and 1,303 women) from cirrhosis of the liver in England and Wales. Of these, 967 (56%) of the cases in men and 540 (41%) of the cases in women were alcohol related.[46]

6.7 A number of prospective studies of general populations have examined the relationship between daily consumption at the start of the study and subsequent mortality at time of follow up.[72] The results show that the risk increased steadily with increasing daily consumption, but do not allow a consensus about a precise threshold of consumption below which there is no risk of development of cirrhosis.[29,72,73]

6.8 Between 8 and 30% of long term heavy drinkers identified in the clinical population of problem drinkers ever develop cirrhosis. One UK authority considers that around 20 units of alcohol daily for 5 years is probably the minimum associated with significant liver damage.[74] it appears that the likelihood of light to moderate drinkers developing cirrhosis is very remote .[72]

Cancer

6.9 In 1981, Doll and Peto estimated that 3% of all cancers might be attributed to alcohol.[75] Over the last 20 years a number of studies have established that alcohol may have an association of varying significance with cancers of the oral cavity, pharynx, larynx, oesophagus, liver, rectum and colon and breast.[29,76,77,78] In assessing this area the Group has drawn on specific reviews and conclusions prepared by the Department of Health's expert Committees on Mutagenicity and Carcinogenicity (See Annexes H and 1 for reports).

6.10 The Committee on Mutagenicity concluded from its review of the evidence (Annex H) that the consumption of alcoholic beverages does not present any significant concern with respect to their mutagenic potential. Hence it can be safely stated, based on current evidence, that alcoholic beverages, alcohol itself, and its most significant metabolite in the body, acetaldehyde, do not cause genetic changes in body cells which might lead to cancers or other diseases.

6.11 The Committee on Carcinogenicity in its report (Annex 1) explored other mechanisms possibly relating alcohol causally with various cancers. The main conclusions of the review are given below.

"i) We *conclude* that

a. The epidemiological evidence supports the view that drinking alcohol causes a dose-related increase in the risk of squamous carcinomas of the upper aerodigestive tract as a whole, and for cancers of the oral cavity, pharynx, larynx and oesophagus. There is less information for cancer in these sites in women, but the available data show similar risks in both sexes. The epidemiological data suggest that alcohol causes cancer independently of smoking. Relative risks, at heavy drinking (>70g ethanol/day), after controlling for the confounding effects of smoking, vary between 3-15 fold depending on the tumour site. There is convincing evidence of an increase in relative risk at intakes above about 40g ethanol per day. The evidence is less convincing at intakes between 20-40g ethanol/day. The epidemiological data do not allow a quantification of relative risk at lower levels of drinking, but it is not possible to exclude a small increase in relative risk at intakes below 20g ethanol/day. The tumour types causally associated with alcohol are relatively rare and thus the number of cases which could be attributed to low levels of drinking would be very small.

There are a number of additional conclusions which can be drawn in respect of causally related cancers:

b. The risk of cancer at susceptible sites increases with the frequency of drinking. The results of studies investigating the duration of drinking associated with an increased risk of cancer are inconsistent and have generally only considered periods in excess of 20 years. No conclusions can be drawn from the available epidemiological data with respect to the minimum duration of drinking which will result in an increased relative risk at vulnerable sites.

c. The results of case-control studies are generally consistent with a reduction in relative risk of head and neck cancers following abstinence from drinking. The epidemiological data suggest that abstaining for periods of 10-15 years may reduce the risk of cancer to that of non-drinkers but it is not possible to draw definite conclusions on this aspect.

d. The epidemiological data show that risk of cancer associated with drinking alcoholic beverages is due to the consumption of ethanol. Differences in risks attributed to particular types of beverage result from cultural and regional differences in drinking habits. There is no convincing evidence of beverage-specific effects.

e. Smoking increases the risk of alcohol associated head and neck cancers. it would be prudent to assume that all levels of smoking will increase the risk of alcohol associated cancers.

f. The precise role of poor nutritional status induced by heavy drinking in the aetiology of alcohol associated cancers is unclear.

ii) We *conclude,* that heavy drinking of alcohol is associated with primary liver cancer. Most tumours occur in individuals who have cirrhosis. It is not possible, in view of the results of recent investigations concerning the aetiology of liver cancer (particularly with respect to HCV infection) to draw any definite conclusions about the size of the relative risk of liver cancer associated with alcohol drinking.

iii) Some epidemiological investigations have reported an association between alcohol and cancer of the stomach, colon, rectum, lung and pancreas. We *conclude* that the evidence does not support a causal association between those tumour types and drinking alcohol.

iv) We conclude that whilst there is no decisive evidence that breast cancer is causally related to drinking alcohol, the potential significance, for public health, of a weak causal association between alcohol and breast cancer is such that *we recommend,* in particular, that this matter be kept under review.

v) It is not currently possible to draw any firm conclusions from the available studies in animals regarding the mechanism by which drinking alcohol induces cancer in humans."

6.12 The Group endorses the views of both these expert Committees.

Hypertension

6.13 The Health Survey for England in 1993 shows that adult average blood pressures were found to be 137mmHg systolic and 76mmHg diastolic. Raised blood pressure is a very common condition, particularly among older people.[70,79] As blood pressure increases so does the risk of ill health. People with blood pressure of 160mmHg systolic and 95mmHg diastolic are about three times as likely to develop diseases associated with high

blood pressure and twice as likely to die from such diseases as people with blood pressure within the normal range and in the UK these levels are identified as the threshold of the clinical condition of hypertension.[70,79,80]

6.14 In the UK hypertension becomes increasingly common after age 35 and affects a third of men and women aged between 55 and 65.[70] The 1991-92 National Morbidity Survey shows that essential hypertension generates more general practice consultations than any condition other than upper respiratory tract infection and contraceptive management.[81] The incidence of common vascular morbidity and mortality, in particular CHD and stroke, increases in line with hypertension. Even low levels of hypertension significantly increase the risk of these diseases and it is at these levels that the bulk of them occur in the general population.[80] For instance, every increase in blood pressure of 9mmHg systolic together with 5mmHg diastolic from normal levels upwards increases the risk of stroke by 34% and of CHD by 21%.[82] In addition prolonged hypertension even at mild levels can lead to angina, congestive cardiac failure, peripheral vascular disease and renal disease which can cause many years of ill health even if they are not the ultimate cause of death.[79,80]

6.15 There have been many studies linking alcohol and hypertension over the last 20 years and at the individual level the capacity for alcohol to raise blood pressure affects everyone.[24,83,84,85] Most studies show a dose response relationship between drinking and both diastolic and systolic blood pressures, although about half the studies of women show a slight J-shaped relationship.[24,83,86] A cautious interpretation of the literature suggests that regular consumption of alcohol results in a dose dependent rise in blood pressure with a possible plateau at about 80g (10 units) a day.[87]

6.16 A number of studies have shown that each increment of 10g (1.25 UK units) of alcohol drunk per day increases systolic pressure by an average of 1-2mmHg and diastolic pressure by 1mmHg.[83,88,89,90] That said, it is not possible on the basis of the literature to establish the exact point, in terms of alcohol consumption, at which the health advantages, for those age groups for whom they apply, offset the disadvantages of raised blood pressure. However, a generally accepted clinical view would be that for men the rise in blood pressure produced by 4 units a day (about 6mmHg systolic blood pressure and 4mmHg diastolic) would give rise for concern.[7] There is also mounting evidence that "binge" drinking is particularly associated with significantly raised blood pressure.[85]

6.17 The biological mechanisms by which alcohol raises blood pressure have now been shown to be independent of the majority of confounding variables and support the view there is no significant threshold for alcohol consumption and raised blood pressure.[84,91] It has been estimated that alcohol consumption is primarily responsible for as much as 11% of hypertension in men and is second only to obesity as an acquired determinant of this condition.[83,84,92]

6.18 The long term consequences of alcohol induced hypertension for the individual will reflect a balance between hypertension related cardiac and vascular damage and alcohol related improvements in relative risk in pathologies such as CHD and ischaemic stroke. Drinkers who already have hypertension may run significant additional risk from hypertension-related diseases specifically as a result of their drinking.

Reproduction, Pregnancy and Infant Development

6.19 In addition to written and oral evidence[93] the Group based their views on alcohol and pregnancy on the report prepared by the Department of Health's Expert Committee on Toxicity (see Annex J), The Committee report:

2. "Many studies have been carried out in the last 20 years to try to identify the effects of ethanol in pregnancy and to establish intake levels at which these effects occur. Amajor problem in interpreting the human studies is the large number of confounding factors, including poor nutrition, licit and illicit drug intake and smoking, all of which have known adverse effects on pregnancy. Other factors also contribute to the variability of these studies; including difficulty in verifying intake of ethanol, patterns of consumption and polymorphism in ethanol metabolism. In post-natal developmental studies, environmental factors are also critically important.

3. Despite all the variables, there is general agreement, from both human and animal studies, that ethanol has the potential to induce the following effects: abortion; fetal growth retardation; facial and other dysmorphologies; and impaired post-natal physical and mental development.

4. Most studies agree that 2 drinks [16g of ethanol] per day and above may be associated with reduced birthweight which is one of the most sensitive parameters. Some studies have found effects at lower levels, but most have not. However, there is no good evidence that 1 or 2 drinks [8 or 16g of ethanol] per week has any adverse effect.

5. There are both human and animal data that suggest that binge drinking can also produce these adverse effects listed [above]. There is evidence that adverse effects can be induced at all stages of pregnancy.

6. The full spectrum of physical and mental handicaps known as Fetal Alcohol Syndrome is only seen in the offspring of alcoholic women. On the other hand, adverse effects on cognitive and behavioural development might be observed as indicators of ethanol-induced damage in the offspring of women with lower ethanol intakes.

7. There is limited evidence that ethanol may also impair reproductive function in men and fertility in women, but this evidence is inadequate so far as the identification of the intakes at which these effects are induced."

6.20 The Committee on Toxicity recommends:

i. any new advice to pregnant women should be in terms of "units" of alcohol per day, since "binge drinking" can also affect the fetus.

ii. to any new advice which may be formulated on sensible drinking limits, a caveat should be added to the effect that: women who are pregnant or who are likely to become pregnant, should keep their alcohol intake substantially below limits suggested for non-pregnant women.

6.21 The Group endorses the Committee's views.

Mental Illness and Neurological Disorders

6.22 Extremely heavy drinking - which is defined here and elsewhere, unless otherwise specified, as consumption levels in excess of 80g (10 units) a day - over long periods of time, is strongly associated with a number of significant psychiatric disorders.[94] These include clinical depression which may lead to attempted suicide or suicide, personality deterioration, sexual problems, amnesia, cognitive dysfunction (intellectual impairment), dementia, alcoholic hallucinosis, alcohol dependence syndrome and delirium tremens.[91,95,96] Together with dietary insufficiency it is also associated with a number of neurological disorders including epilepsy, peripheral neuropathy (damaged peripheral nerves) and the Wernicke-Korsakoff Syndrome (this condition is very rare but can result in irreversible damage to the central nervous system).[94,95,96]

6.23 Extremely heavy drinking is strongly associated with depression and suicide.[94] Clarification of causality is not easy in cases of co-morbidity, for example co-existent alcohol dependence and depression, but it is increasingly accepted that, as well as clinical depression predisposing individuals to harmful levels of alcohol consumption, heavy drinking in the absence of predisposing psychiatric illness, can depress mood and exacerbate anxiety symptoms.[94,97]

6.24 People who have been in hospital for treatment for problem drinking have been shown to be 75 times more likely to commit suicide than the general population.[98] Studies in the United Kingdom have shown that 39% of men and 8% of women who attempted suicide were chronic problem drinkers and alcohol consumption preceded attempted overdose in 70% of men and 40% of women.[99,100]

6.25 Extremely heavy drinking also leads to psychological and physical dependence on alcohol, a condition which is strongly associated with a wide range of medical, social and legal problems.[101] The 1993 England Health Survey, using a dependence rating scale, records that 9% of men and 5% of women were classified as dependent problem drinkers**** and concludes that the likelihood of alcohol problems rises with consumption.[70]

*****Defined as drinkers who experienced 2 or more out of 3 indicators of physical dependence and 3 indicators of psychological dependence*

In 1994, the first OPCS Survey of Psychiatric Morbidity amongst adults between 16 and 64 in Great Britain found that 8% of all men and 2% of all women had identifiable alcohol dependency*****, and for men aged between 20 and 24, 17% were in this dependent category.[102]

6.26 Drinking at even heavier levels - more than 25 units a day - over a period of years is associated with brain damage and reduced cognitive function .[95,96] Some authorities consider that the cognitive impairment is a direct impediment to compliance and recovery in treatment programmes.[103] The clinical population of long term very heavy drinkers carries a substantial proportion of cognitively impaired patients. [104]

******Defined as drinkers who list 3 or more positive responses out of 12 statements (4 on Loss of Control, 7 on Symptomatic Behaviour and 1 on Binge Drinking)*

7. ALL CAUSE MORTALITY

7.1 Many of the issues discussed above have a direct influence on all-cause mortality, which combines the net effect of any reduction in mortality from the beneficial effects of alcohol and any increase in mortality from other causes. Most of the evidence we have examined has made some form of statement about alcohol consumption related to all-cause mortality.[10,27,42,43]

Alcohol and Mortality

7.2 The consumption of alcohol, both in the short and long term, is associated with a range of different types of mortality, morbidity and social problems. it is not easy to estimate the annual numbers of deaths caused by alcohol consumption, principally because of the presence of direct and indirect mechanisms. Estimates in the academic literature range between 5,000 and 40,000 deaths per annum and reflect a wide range of methodological approaches.[11,105] The Department of Health has commissioned a research study in this field to try to establish a more reliable mortality figure.

7.3 An analysis which we undertook of annual mortality in the UK as an aggregate of separate alcohol related conditions suggests that about 25% of alcohol related deaths are due to accidents, often presumably related to short term drinking episodes, and that the bulk of the remainder are due to disease related to long term alcohol consumption.[106] The pattern of mortality is markedly different at different stages. In young adults CHD and long term alcohol related diseases make very little contribution to overall mortality over half of which is accounted for by preventable causes, especially accidents, including road traffic accidents, and violence in both of which alcohol is frequently implicated.[107,108] In a large US sample the relationship between alcohol use and mortality up to the age of 60 was shown to be linear.[109] Beyond middle age CHD contributes to premature mortality, but since alcohol consumption, as explained above, also protects against this form of death there is a balance to be drawn between deaths caused and saved by alcohol.

7.4 An attempt has been made in New Zealand to identify the aggregate effects of alcohol on mortality.[110] Recent research in that country has shown that, although alcohol was estimated to have caused 20% of all deaths between the ages of 15 and 34, over the whole population alcohol had resulted in overall prevention of deaths, largely because of 3.5% of deaths postponed among those aged 65 and over. However, if the number of person-years of potential life lost and saved is used to calculate an aggregated figure, alcohol use caused a net loss of 9,500 person-years per annum.[110] Clearly the way in which mortality is discussed and presented, whether it be in terms of percentage of lives, or years lost, gives different perspectives on the impact of alcohol onsociety and may therefore influence policy.[111] An analysis of this kind in the UK has not been carried out and further research would be needed to clarify the complexity of the aggregate effect of alcohol on mortality.

7.5 All cause mortality is clearly a key consideration in developing advice on drinking levels and degrees of risk though, as pointed out above, since alcohol related morbidity and social harm are also strongly related to patterns of drinking and levels of consumption, it is not the sole consideration.[65]

7.6 As noted in paragraph 4.2 above there are reasons to be cautious about generalising all cause mortality data from one country to the population of another where, for instance, CHD rates may be much less and cultural

and dietary factors may also be so different as to weaken comparison.[10,12] We have considered these arguments but conclude that there is sufficiently comparable data from similar European and developed nation cultures to use such international data along with British data in considering the significance of all cause mortality in the UK.

Shape of the All Cause Mortality Curve

7.7 All the evidence we have received confirms that the relationship between all-cause mortality and alcohol consumption follows a J-shaped curve.[11,12,13,14,15,24,112,113,114,115,116,117,118,119,120] Non drinkers have higher all-cause mortality than light and moderate drinkers, and heavy drinkers have even higher allcause mortality than either group. The protective effect is neutralised and then overtaken by an increasing risk of mortality from other causes. There is, therefore, a cross-over point in terms of alcohol consumption where the relative risk of death becomes equal to that of non-drinkers.

7.8 However, as Sir Richard Doll told the Group, in order to minimise mortality in a public health context: "the appropriate comparison for people drinking somewhat more than the suggested limit is those drinking somewhat less, and not with abstainers. The 'cross-over level' above which the risk among drinkers starts to exceed that amongst abstainers is not of any particular relevance to public health. What matters, at least in terms of mortality, is the level at which the risk starts to increase to an important extent with regard to dose".[12,43]

7.9 Most researchers have based their assessment of where the recommended upper level of alcohol consumption should be placed at the point where they judge the evidence indicates a steady increase of relative risk rising significantly from a lowest all-cause mortality point on the J-shaped curve.

7.10 Identifying the point where relative risk increases significantly is not an easy matter as most of the evidence we have received refers to the flattened nature of the base of the curve, particularly in European countries. Most researchers are actually unable to identify a precise level corresponding to minimal all-cause mortality and, therefore, favour a band within which they consider relative risk levels to be much the same. The evidence we have studied for men of all ages identifies a band of minimal mortality associated with a weekly consumption of between about 7 and 28 units a week. We emphasise that this band of minimal mortality cannot be entirely risk free, and reflects consumption levels which still carry a low risk of conditions such as some cancers, and some diseases related to raised blood pressure (see para 6.9).[80,84]

8. WOMEN AND ALCOHOL

8.1 The problems of giving accurate advice and information about sensible drinking are nowhere more evident than in this area.[149] There is no doubt that essentially alcohol affects men and women very similarly and that the broad spectrum of alcohol related disease and social problems for both sexes is more similar than it is different. However, there are important differences. Firstly, in spite of increasing scientific work on women's drinking over the last 10 years, there is still a less secure scientific literature from which to make conclusions about women as compared with men.[93] In particular, sufficient studies on all cause mortality do not exist to indicate clearly the advantages or disadvantages of alcohol to women as compared to men.[24]

8.2 In general in the United Kingdom women drink significantly less than men.[1] Many women in middle age and beyond are very light drinkers. There is thus very little data linking high levels of consumption in women with a variety of alcohol related diseases.

8.3 The tissue in a woman's body contains a lower proportion of water than a man's and this means that, in a man and a woman of the same weight, a given amount of alcohol will produce a higher tissue concentration in the woman.[121,122] In addition the "average" woman weighs 58kg, considerably less than the "average" man (70 kg), and has correspondingly less tissue to absorb the alcohol.[70] Taking these two factors together means the same amount of alcohol will produce a significantly higher tissue concentration in the "average" woman.[123] In addition, women may metabolise alcohol at a slower rate than men, so the alcohol may remain in their tissues longer.[93]

8.4 In addition, we have considered evidence which suggests that, at equivalent doses of alcohol for men and women, women are more vulnerable to tissue damage and the onset of diseases such as cirrhosis of the liver, and possibly physical dependence.[73,93,124] This is not a universally accepted difference according to our understanding of the literature and, where it might be relevant, it may only be effective at very high levels of consumption.

8.5 There are also differences in patterns of pathology and disease between men and women. For instance, until old age, rates of female CHD are substantially less than for men, a difference which is particularly marked in pre-menopausal women.[125] The reason for this is thought to be that hormonal changes only present in the menstrual cycle influence lipoprotein levels and, in particular, raise HDL which provide natural protection against CHD.[141] In the United Kingdom 23% of women's deaths are from CHD and 15% are for stroke as compared with 30% of male deaths from CHD and 9% from stroke[23,44]

8.6 Rates of breast cancer increase with age, although the rate of increase slows after the menopause presumably due to hormonal factors.[126] The Committee on Carcinogenicity concluded that there is no compelling evidence of causality linking alcohol and breast cancer and any biological mechanisms must remain at present very speculative.[78] However in spite of inconsistencies in the evidence a number of studies have concluded that there is a weak association between alcohol and cancer of the breast.[116,127] Cancer of the breast affects one in 12 women and causes more deaths than any other cancer in women aged between 35 and 65.[125] Due to this high incidence and the significance for public health, the Group endorses the Committee on Carcinogenicity's view that it is necessary to keep the relationship between alcohol and breast cancer under careful review.

8.7 It is not possible to weigh up definitively all these contrasting factors and produce an authoritative statement about women and alcohol. The scientific evidence simply does not, at present, allow that clarity. It does appear though that, on balance, there is sufficient indication from the physiology and the patterns of illness for women overall to be advised to drink at lower levels than men, and to take this into account when making their individual choices. This view was endorsed in all the expert evidence taken by the Group.

9. GENERAL PUBLIC HEALTH ADVICE

9.1 The sensible drinking message is a general public health message aimed both at improving individual health by giving individuals the best possible information on risks and benefits and also at reducing the prevalence of alcohol problems in the population as a whole. This section considers some relevant factors for the giving of such advice, then briefly reviews the groups within the general population for whom special advice may be appropriate.

Whole Population Theory

9.2 The drinking behaviour of a population in terms of consumption can be analysed using a whole population epidemiological technique which produces fairly consistent predictions.[42,128] The whole population theory applied to alcohol consumption was first propounded by the French mathematician, Ledermann, who argued that there was a fixed relationship between average per capita consumption of alcohol, the number of problem drinkers and the amount of alcohol related harm.[129,130] Ledermann predicted that doubling or tripling average consumption would lead to a four or nine fold increase in the numbers of problem drinkers. This marked differential led to the idea of manipulating average consumption through price and access controls to reduce the incidence of problem drinking.[131,132]

9.3 Although subsequent work has failed to support the rather extreme claims of the mathematical model,[3,132,133,134,135,136] most experts still posit a dynamic correlative relationship between average consumption and the level of problem drinking and would be very concerned that any relaxation of the sensible drinking message might lead to increased consumption resulting in more alcohol problems.[3,24,42] The Group received significant expressions of concern on this final point from many of those submitting written evidence.

9.4 However there are difficulties in applying a whole population approach to alcohol consumption, especially in the UK. The nature of the causal relationship between average per capita consumption and alcohol misuse and problems is still poorly understood and there does not appear to be any a priori reason why the approach should apply universally.[10,133,136] For example, it has been possible to reduce the number of alcohol related fatal road traffic accidents without reducing the per capita consumption of the population as a whole by getting the "don't drink and drive" message widely accepted by drivers. There is also the ethical problem of seeking to modify behaviour which is in itself not harmful to the individual concerned to create a climate which may influence some of those indulging in harmful behaviour to change. This is why current health promotion advice is couched in terms of advising those drinking above the recommended levels to cut down, not of trying to get everyone to reduce their drinking and we believe this approach should continue in the UK. Equally, it has to be recognised that price is a major determinant of consumption and we have assumed in making our recommendations that price relativities will not change in such a way as to encourage irresponsible consumption.[3,105,137]

Distribution of Alcohol Related Harm

9.5 it has long been recognised that very heavy drinkers are not the major source of alcohol problems in society.[138.139] This is because, although people drinking at lower risk levels will not have the same likelihood of

developing a particular condition as those drinking at higher levels, the much larger population drinking at the lower level means that the majority of alcohol related harm may well occur in this group. Such harm cannot be addressed therefore by targeting only the most serious misusers. Advice to discourage alcohol misuse needs to be addressed also to individuals drinking at levels at which the incidence of problems begins to rise.

ISSUES REQUIRING SPECIAL CONSIDERATION

People Aged under 16

9.6 In relation to those below 16, a Health Education Authority survey, Tomorrow's Young Adults" (1992), which examined the attitudes of 9-15 year olds in England in 1989, found that 22% of those interviewed had had their first alcoholic drink by the age of 8 years and 89% by age 13; 12% reported that they drank at least once a week.[140] In the 11-15 age group 31% had had a drink in the previous week and of those 5% of the girls and 3% of the boys had consumed more than 14 and 21 units respectively.[140] These figures give cause for concern particularly as most authorities would, in any case, consider that the levels of sensible drinking recommended to adults are not appropriate for people aged under 16, especially those who have not reached physical maturity.[142]

Short term episodes of intoxication

9.7 Short term intoxication may well take the form of heavy social drinking, for instance by young men in pubs and clubs on Friday and Saturday nights. This kind of consumption pattern, which is found to some extent in people of all ages, can lead to varying degrees of disorder and even, on occasion, to serious violence.[143] People need to make sensible choices about whether, when and how much to drink, and how to resist ill-advised persuasion and pressure. Clearly any public health message should include advice about avoiding short term episodes of intoxication, particularly in circumstances which potentially give rise to the greatest risk to the individuals concerned and indeed third parties.

Non-drinkers

9.8 Middle aged or elderly non-drinkers may wish to consider the possibility that light drinking might be of benefit to their overall health and life expectancy. The same would apply to middle aged or elderly people who drink very infrequently and at very low consumption levels (for example, less than 7 units a week). There will be some people who, on medical grounds, should, most certainly, not take up drinking or increase their consumption from really low levels. Other people choose not to drink for other reasons – for example religious objection. Non-drinkers, like others, can still, if they wish, make other changes to their lifestyle to lower the risk of CHD and improve their health generally.

Drink Free Days

9.9 Excessive drinking can adversely affect the normal physiological function of tissues which then need time to recover fully.[144] After an episode of heavy drinking it is advisable therefore to refrain from drinking for 48 hours to allow this.[150,151] Breaks in consumption are only a short term measure and people whose pattern of drinking places them at significant risk should seek professional advice. Such breaks in consumption are not required on health grounds for people drinking at low risk levels of daily consumption.

10. FINDINGS AND CONCLUSIONS

10.1 This section of our report draws together and briefly discusses the findings of the previous sections and sets out conclusions in the light of these.

Beneficial Effects from Alcohol

10.2 The Group concludes from the evidence it has received that light to moderate consumption of alcohol confers a protective effect against a number of serious diseases, in particular CHD and ischaemic stroke, and also against cholesterol gallstones. CHD, which is such a common pathology in the UK, is the main disease which is advantageously affected by alcohol. Even if the biological mechanisms conferring protection are present for young adult drinkers, the benefits are only clearly evidenced when risks of CHD become significant, that is for men over 40 and post-menopausal women.

10.3 The benefit for ischaemic stroke is more difficult to assess in terms of the whole population, but again, at an individual level, light to moderate drinking reduces the likelihood of this type of stroke in the middle aged and elderly. However, the risk of haemorrhagic stroke (less common but more likely to be fatal) is dose related to alcohol consumption with relative risk increasing from as low as 2 units a day or less and is more common in under 65s. We do not consider it is possible to draw a definitive conclusion regarding the relationship of alcohol to all forms of stroke.

10.4 The evidence we have received suggests that, to obtain the major part of the health benefit relative to mortality and morbidity from all causes, drinking at levels as low as about 1 unit a day for either men or women would be sufficient, and no significant additional benefit is obtained at a level above 2 units as there is only a slight dose response effect. The health benefit is more evident from regular daily drinking, and may be lost with irregular heavy drinking or binge drinking, which appear to exacerbate many of the problems associated with alcohol.

Is Wine More Beneficial Than Other Alcoholic Drinks?

10.5 We have examined current evidence on health benefits related to specific drinks. We recognise that, in addition to alcohol itself, wine has other constituents which may produce additional benefits. However, we do not find that at present there is convincing evidence that confirms wine as being any more beneficial than other alcoholic drinks.

Risks from Long Term Heavy Drinking

10.6 People drinking at levels commonly identified with serious problem drinking or physical dependence on alcohol experience a heavy burden of health as well as social problems.As the majority of diseases are dose related and do not occur at a sudden threshold of alcohol consumption, it follows that there is a range of consumption where the individual drinker has a very low risk of contracting any of these pathologies. Beyond this range, however, alcohol, at different levels of consumption, increases the risk of a wide variety of conditions such as raised blood pressure, liver cirrhosis, cardiovascular disease (apart from CHD) and cancers of the mouth, pharynx and oesophagus. Heavy long term consumption is also associated with mental illness, neurological

disease and liver cancer. In addition, much of the social pathology and harm related to alcohol, such as family and employment problems and crime, also have a broad relationship to long term heavy patterns of consumption.

The problem drinker

10.7 Our recommendations are for the individual drinker in the normal drinking population. They are not framed particularly to influence clinical treatment of problem drinkers or indeed their recognition. We wish to move away from a culture of advice on consumption levels which has been interpreted by some as categorising all those who drink above the currently recommended levels as heavy or problem drinkers when, clearly, the vast majority of them are not.

Alcohol and All Cause Mortality

10.8 All cause mortality is at its lowest at modest drinking levels (at about 1 unit a day for men and women) and does not exceed the mortality level of abstainers until consumption levels which are somewhat higher than the current recommended sensible drinking levels of 14 units per week for women and 21 units for men. After that, the all cause mortality begins to increase significantly as the benefits of alcohol consumption are overtaken by the more harmful effects. in summary, light to moderate drinkers fare best, abstainers not as well, and heavy drinkers worst.

Women and alcohol

10.9 We recognise that although alcohol affects men and women very similarly there are important differences. Clarifying some of these is difficult because of a limited research literature. We note however that in the UK women of all ages drink less than men and therefore the prevalence of some alcohol related diseases is much lower for women.

10.10 Women weigh less than men on average and, taking into account physiological factors of differences in tissue concentration of water and rate of alcohol metabolism, along with possible increased vulnerability to tissue damage at equivalent doses to men, we conclude that women should be advised to drink less than men.

10.11 Women also have important differences in patterns of pathology and disease as compared with men. As women are less likely to die of CHD than men at all ages below 75, the overall benefit of alcohol from CHD is less evident for women as compared to men. in particular, women have very low CHD rates until the menopause so the major alcohol-related CHD benefit is for post-menopausal women.

10.12 Breast cancer affects 1 woman in 12 and is the commonest cause of death from cancer in women aged between 35 and 65. As alcohol consumption is associated with breast cancer in some studies, the Group takes the view that, because of the public health significance of a causal explanation, if one were subsequently to emerge (as some experts expect), the relationship between alcohol and breast cancer should be kept under careful review.

10.13 We also recognise that alcohol consumption (other than at very low levels) is associated with particular risks to fetal and early infant development and thus that there is a need for women who are pregnant or hoping to become pregnant to keep their alcohol intake low. Specific advice on this is considered at para 10.28 below.

General Approach to The Sensible Drinking Message

10.14 We recognise the importance placed by many experts on the whole population theory, and their concern that any change in drinking patterns which might lead to increased average consumption will lead to increased alcohol problems. It has indeed been argued that the purpose of a sensible drinking message should be to bring down everyone's level of consumption so as to reduce the risk of numbers of heavy drinkers increasing. The Group accepts that, although there is statistical support for the whole population theory, there are examples – like that of drinking and driving – which show that public education can change undesirable behaviour without lowering the level of drinking by the population as a whole.

10.15 We see value in setting benchmarks to enable people to monitor their own drinking levels. However, advice to the general population is just that. By definition it is not applicable to all individuals. There is considerable variation in many individual characteristics – for example, body weight – and general advice needs to be considered in the light of these differences.

10.16 The current message has sometimes been interpreted as a rigid limit, suggesting there is a critical difference for men between drinking 20 and 22 units a week. We do not believe that this approach reflects the scientific evidence.

Daily Versus Weekly Consumption

10.17 We have weighed, carefully the advantages and disadvantages of casting specific consumption advice in weekly or daily amounts, and what the measure of consumption might be. We are satisfied that, in the United Kingdom, the unit of alcohol (representing 8g of ethanol), is already sufficiently part of the currency of public health education about alcohol for it to be used in our recommendations.

10.18 The evidence also shows that weekly consumption levels can have little relation to single drinking episodes and may indeed mask short term episodes of heavy drinking which, as explained, often correlate strongly with both medical and social harm. There are also a number of areas – such as drinking in pregnancy – where our expert advice was to frame our recommendations in such a way as to draw attention to levels of daily drinking. A daily amount can also be helpful in deciding how much to drink on a single occasion and thus help people to avoid drunkenness. In addition, the evidence shows that there can be benefit in regular drinking, so long as it is moderate (see 10.4). For these reasons we have chosen to express our recommendations in terms of daily drinking.

Guidance on Sensible Drinking

10.19 In arriving at specific advice on sensible drinking we have taken account of the following factors:

- setting daily benchmarks can help individuals to decide how much to drink on single occasions and to avoid excessive drinking with its attendant health and social risks.

- drinking alcohol confers a significant health benefit in terms of reduced CHD mortality and morbidity on **men aged over 40 and postmenopausal women.** In terms of all cause mortality and morbidity the benefit can be largely gained by drinking as little as 1 unit a day on a regular basis. Consumption above 2 units a day does not confer any major additional health benefit.

- men who drink more than 3 to 4 units a day run an increasingly significant risk of illness and death from a number of conditions, including haemorrhagic stroke, some cancers, accidents and hypertension.

- for women there are a number of additional factors to be taken into account: differences in average weight and tissue density from men and the effects of the menopause, as well as the patterns of female mortality and the possible risk of breast cancer. These factors point to setting a lower overall level than for men.

- **women** who drink more than 2 to 3 units a day run an increasingly significant risk of illness and death from a number of conditions, including haemorrhagic stroke, some cancers, accidents and hypertension.

10.20 In the light of these factors our advice on sensible drinking is as follows:

MEN

- The health benefit from drinking relates to men aged over 40 and the major part of this can be obtained at levels as low as one unit a day, with the maximum health advantage lying between 1 and 2 units a day.

- Regular consumption of between 3 and 4 units a day by men of all ages will not accrue significant health risk.

- Consistently drinking 4 or more units a day is not advised as a sensible drinking level because of the progressive health risk it carries.

WOMEN

- The health benefit from drinking for women relates to postmenopausal women and the major part of this can be obtained at levels as low as one unit a day, with the maximum health advantage lying between 1 and 2 units a day.

- Regular consumption of between 2 and 3 units a day by women of all ages will not accrue any significant health risk.

- Consistently drinking 3 or more units a day is not advised as a sensible drinking level because of the progressive health risk it carries.

Drink-Free Days

10.21 After an episode of heavy drinking it is advisable to refrain from drinking for 48 hours to allow tissues to recover. This is a short term measure and people whose pattern of drinking places them at significant risk should seek professional advice. Such breaks are not required on health grounds for people drinking within the recommended benchmarks (para 10.20).

Non-Drinkers

10.22 The Group recognises that middle aged or elderly men and postmenopausal women who drink infrequently (less than 1 unit a day) or not at all may wish to consider the possibility that light drinking might benefit their health. Equally, some people do not wish to take up drinking, for religious or other reasons, or there

may be medical grounds for them not to do so. These people may, like others, make other changes to other aspects of their lifestyle to improve health and lower the risk of CHD.

Excessive drinking and episodes of intoxication

10.23 We do not consider that there is a certain and inevitable relationship between, for instance, alcohol and violent crime but we accept the evidence of a significant association. There is a similar association with accidents, many of which, like road traffic accidents, are avoidable when the individual drinker carefully assesses the effect that his or her drinking might have on their driving. Drinking and driving is governed by legislation and has been the subject of much Government publicity. But there are many other situations where individuals need to exercise responsibility and personal control and so need to consider their alcohol consumption and the circumstances around it, to avoid significant problems.

10.24 If people choose to drink at a higher level than our recommended benchmarks set out in para 10.20, this would be particularly true.

Situations where it is not appropriate to drink at all

10.25 In addition, we consider that individuals should be advised not to drink at all in situations where, for safety reasons, cognitive ability and physical co-ordination should not be impaired. Examples of these are:

- before or during driving
- before swimming
- generally, before or during active physical sport
- before using machinery, electrical equipment, ladders etc.
- before working or in the workplace when appropriate functioning would be adversely affected by alcohol
- when taking medication, where alcohol is contraindicated.

The precise advice - for example how long before an activity to refrain from drinking - will vary from one situation to another.

Alcohol and Children and Young People

10.26 Our conclusions set out in paras 10.23-25 above, apply particularly to young adults (16-24 year olds) as binge drinking is a common and hazardous pattern of drinking in this age group (see para 9.7). General Household Survey data have shown consistently that most people drink at the highest consumption levels in their lives while they are between these ages.

10.27 In addition, we are very concerned about people aged under 16 who may not have reached physical maturity who are drinking at or above the levels of sensible drinking recommended to adults. Drinking by young children raises obvious concerns about its social desirability and the adequacy of supervision by parents and carers. Parents and carers of children who do drink alcohol should try to ensure that these children are aware of

its hazards and that it is only consumed in moderate and safe quantities for their age group with reference to their physical development.

Alcohol and Pregnancy

10.28 In the light of the evidence received, our conclusion is that, to minimise risk to the developing fetus, women who are trying to become pregnant or are at any stage of pregnancy, should not drink more than 1 or 2 units of alcohol once or twice a week, and should avoid episodes of intoxication.

Overview of the Effects of the Group's Conclusions

10.29 There are three main elements in the Group's conclusions on sensible drinking as outlined above:

i redefining the benchmarks for sensible drinking (paras 10.19-20 above);

ii reducing episodes of excessive drinking and intoxication (paras 10.23-24 above);

iii supplementing i and ii with specific messages addressed to particular groups of the population or people drinking in particular settings (paras 10.25-28).

The Group would like to stress that they see these three elements as forming a coherent strategy and that all three need to be taken forward together in future health education work. Such work needs to build on an increased public awareness of all these issues so that people can make better informed choices and be more aware of the amount they are drinking - thus reducing underestimation - and of whether their drinking is appropriate to their particular circumstances at any time.

10.30 We believe that, as long as this coordinated approach is followed, including our assumption on price (see para 9.4 above), our recommendations will provide individuals with better advice on which to act whilst at the same time not increasing the problems caused by alcohol in the population as whole. We also consider it is essential that our recommendations about daily benchmarks are always publicly presented firmly within the context of the other advice we have given, both on the risks and the benefits of drinking.

RECOMMENDATIONS FOR FUTURE ACTION

11.1 The Group recommends that the future strategy for health education on sensible drinking should be firmly based on the following points:

i moderate consumption of alcohol has a beneficial effect on CHD (paras 5.2-5.12). This effect is evident in men over 40 and post-menopausal women (paras 5.13-5.14, 10.2 and 10.4);

ii people who do not drink, or drink very little (less than 1 unit a day) and are in the age groups where there is a significant risk of CHD (men over 40 and post-menopausal women) may, therefore, want to consider the possible health benefit of light drinking. But some will wish to continue to abstain - for very valid reasons - and may instead wish to explore the health benefit of other lifestyle changes which are open to everyone (paras 9.8 and 10.22);

iii there is sufficient evidence to suggest that women should be advised to drink at lower levels than men (paras 6.19-6.21, 8.1-8.7, 10.9-10.13);

iv setting points of reference helps people to monitor their drinking but it needs to be appreciated that individuals vary and such points are therefore only benchmarks and not rigid limits (paras 10.14-16);

v the advice on these benchmarks should retain the use of units of alcohol and be cast in daily rather than weekly terms (paras 10.17-10.18);

vi advice on sensible drinking needs to take into account the CHD beneficial effect and the level at which significant health risks begin to emerge (paras 9.5 and 10.19);

vii guidance on drinking levels for men should be:

a. the health benefit from drinking relates to men aged over 40 and the major part of this can be obtained at levels as low as one unit a day with the maximum health advantage lying between 1 and 2 units a day;

b. regular consumption of between 3 and 4 units a day by men of all ages will not accrue significant health risk;

c. consistently drinking 4 or more units a day is not advised as a sensible drinking level because of the progressive health risk it carries (para 10.20);

viii guidance on drinking levels for women should be:

a. the health benefit from drinking relates to post-menopausal women and the major part of this can be obtained at levels as low as about one unit a day with the maximum health advantage lying between 1 and 2 units a day;

b. regular consumption of between 2 and 3 units a day by women of all ages will not accrue any significant health risk;

c. consistently drinking 3 or more units a day is not advised as a sensible drinking level because of the progressive health risk it carries (para 10.20).

ix after an episode of heavy drinking it is advisable to refrain from drinking for 48 hours to allow tissues to recover. This is a short term measure and people whose pattern of drinking places them at significant health risk should seek professional advice (para 9.9 and 10.23);

x people should be advised not to drink at all in situations where this could be a danger to themselves or others e.g. when driving (para 10.25);

xi the exercise of responsibility and personal control may be important in other settings also, particularly when the benchmarks are exceeded. The need to avoid episodes of intoxication should be stressed more strongly in advice than it has in the past not least in view of the possibility of accidents, disorder and even violence (paras 6.1-6.5, 9.7, 10.23-10.24).

xii in particular, young people need to be aware of the specific risks from excessive drinking that relate to their lifestyle and of the need to minimise these risks to prevent harm to themselves and others (paras 9.7, 10.23-10.26).

xiii women who are pregnant or trying to become pregnant should not drink more than one to two units of alcohol once or twice a week and should avoid episodes of intoxication (paras 6.19-6.21, 10.28);

xiv parents and carers of children who drink alcohol should try to ensure children are aware of its hazards and that it is only consumed in moderate and safe quantities for their age group with reference to their physical development (paras 9.6 and 10.27);

xv the recommendations above need to be presented as a whole, not in isolation, and guidance on benchmarks for regular drinking (vii and viii above) must be presented in the context of the overall risks and benefits from drinking (paras 10.29 and 10.30).

ANNEX A **(Para 1.3)**

MEMBERSHIP OF THE INTER-DEPARTMENTAL GROUP ON SENSIBLE DRINKING

Mr G J F Podger - Chairman - Head of Health Promotion Division, Department of Health.

Mr D Belfall - Head of Health Policy at Public Health Directorate, Scottish Office.

Mr P M Boyling - Head of Alcoholic Drinks Division - Ministry of Agriculture Fisheries and Food (to April 1995).

Mr R Melville - Head of Food and Drink Industry Division - Ministry of Agriculture Fisheries and Food (succeeded Mr Boyling from April 1995).

Dr R Harding - Consumers and Nutrition Policy Division - Ministry of Agriculture, Fisheries and Food.

Dr R Kimber - Head of Road Safety Division - Department of Transport.

Mr B Kinney/Mr D Spelman - Criminal Policy Department - Home Office.

Ms L Lockyer - Branch Head, Health Promotion Division - Department of Health.

Dr H G Major - Medical Adviser to the Secretary of State for Transport - Driver and Vehicle Licensing Agency.

Dr D C McInnes - Principal Medical Officer - Health Promotion Division - Department of Health.

Dr E Rooney - Head of Health Promotion Policy Branch - Department of Health and Social Security, Northern Ireland.

Mr A G Thornton - Head of Public Health and Family Division, Welsh Office.

Dr R Tunbridge - Research Programme Manager, Road Safety Division, Department of Transport.

Air Commodore H A Wober - Director of Health for Defence Medical Services Directorate, Ministry of Defence.

Secretariat (Department of Health)

Mr M T Skinner - Leader of the alcohol policy team, Health Promotion Division.

Dr A P Thorley - Senior Medical Officer, Health Promotion Division.

ANNEX B **(Para 1.5)**

LIST OF CONTRIBUTORS OF WRITTEN EVIDENCE TO THE INTER-DEPARTMENTAL GROUP ON SENSIBLE DRINKING

Addiction Research Foundation

Advertising Association

Advertising Standards Authority

Aintree Hospitals NHS Trust

A1-Anon Family Groups

Alcohol Advisory Service For Coventry and Warwickshire

Alcohol Concern

Alcohol Counselling and Prevention Service

Alcohol Counselling Service (Richmond)

Alcohol in Moderation (AIM) (3 papers)

Alcohol Problems Clinic

American Medical Association

Arson Prevention Bureau

Association of British Insurers

Association of Chief Officers of Probation

Association of Chief Police Officers in Scotland

Association of Nurses in Substance Misuse

Mr A Bedford

Brewers and Licensed Retailers Association

British Heart Foundation

British Liver Trust

British Medical Association

British Medical Association Scottish Office

Campaign for Real Ale (C.A.M.R.A)

Canadian Centre on Substance Abuse

City of Wakefield Transportation and Engineering Department

Conservative Medical Society

Decanter Magazine

Professor Sir Richard Doll

Mr J C Duffy

Edinburgh Health Care

Professor Griffith Edwards

Gin and Vodka Association

Ms Christine Godfrey

Greater London Alcohol Advisory Service

Guys and St Thomas Medical and Dental School

Health Education Authority

Health Education Board for Scotland

Health Promotion Agency

Highland Regional Alcohol Practitioners

Institute of Alcohol Studies

International Distillers and Vintners Ltd

Dr J Kemm

Kingston Alcohol Advisory Service

Dr A L Klatsky

Liverpool and South Sefton Health Authority

London School of Hygiene and Tropical Medicine

Professor M Marmot

Medical Council on Alcoholism

Merseyside, Lancashire and Cheshire Council on Alcohol

National Association of Cider Makers

National Centre for Research into the Prevention of Drug Abuse

Ninewells Hospital Dundee

Norfolk Health Commission

Office of Population Censuses and Surveys

Dr A Paton

Periodical Publishers Association

Professor M Plant

Portman Group

Radio Authority

Dr B Ritson

Royal College of General Practitioners

Royal College of General Practitioners Scotland

Royal College of Nursing

Royal College of Physicians

Royal College of Psychiatrists

Royal College of Psychiatrists Scotland

Royal College of Surgeons

Royal Free Hospital

School Health Education Unit

Scottish Council on Alcohol

Professor A G Shaper

Society for the Study of Addiction

South Birmingham Health Authority

South Warwickshire Health Authority

Swiss Institute for the Prevention of Alcohol and Drug Problems

University of California

University of Leicester

University of Portsmouth

University of Wales (2 papers)

Warwickshire Health Authority

Professor R Williams

Wiltshire Constabulary

Wine and Spirit Association of Great Britain and Northern Ireland

Wine Institute

ANNEX C **(Para 1.5)**

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ANNEX D **(Para 3. 1)**

ALCOHOL IN THE HEALTH STRATEGIES FOR SCOTLAND, WALES AND NORTHERN IRELAND

Scotland

1. "Scotland's Health - A Challenge To Us All" (1992) confirmed the target set in "Health Education in Scotland" (1991) of reducing the proportion of men drinking over 21 units a week and women drinking over 14 by 20% from the 1986 proportions (24% for men and 7% for women) by 2000.

Wales

2. "Health Promotion Wales - Plans for Action 3" sets the following targets:

- "to reduce the percentage of men to below 10% and of women to below 5% who exceed the recommended sensible limits of alcohol consumption - 21 units for men and 14 for women by the year 2002 (baseline 1988: women 10%, men 29%, aged 18-64)

- to reduce below 3% the percentage of men and below 0.5% the percentage of women who consume harmful amounts of alcohol - 50 units for men and 36 units for women weekly, by 2002 (baseline 1988: women 2%, men 7%, aged 18-64"

Northern Ireland

3. The Regional Strategy for Health and Personal Social Services in Northern Ireland (1991) set targets to reduce the proportion of 12 to 64 year olds drinking more than the recommended sensible levels (21 units per week for men and 14 units per week for women) to 25% (from 33%) for men and to 7% (from 11%) for women by the year 1997.

Summary Table

4.	Country	% Reduction	Period
England	M	36	1990-2005
	F	36	
Scotland	M	20	1986-2000
	F	20	
Wales	M	67	1988-2002
	F	50	
Northern Ireland	M	27	1988-1997
	F	36	

ANNEX E

HISTORY OF THE SENSIBLE DRINKING MESSAGE

In 1976 the Government issued a consultative document "Prevention and Health: Everybody's Business".' This reflected concern about the rising number of admissions to hospital for alcoholism and alcoholic psychosis and death rates from cirrhosis of the liver. The document saw the level of alcoholism as being related to overall levels of consumption and said that these could be subject to three sets of controls: legal, fiscal and social. At the individual level drinking was a matter of personal choice.

The Health Departments published a further booklet "Drinking Sensibly" in 1981.[2] This defined alcohol misuse as "drinking to excess or drinking in situations which are not appropriate, when the effect in either case is to Put the drinker or others at risk of harm", and introduced the idea of "sensible drinking". Although the booklet called for a programme of public education in sensible drinking it did not define this.

In 1984, the Health Education Council (the predecessor of the Health Education Authority) published the first edition of its pamphlet "That's the Limit.[4] This drew on material from a similar pamphlet which had been developed by health educators and clinicians working in the field of addiction in the North East of England.[3] This gave advice on sensible drinking - described as the amounts, well within the "safe limits", to which people should limit their drinking. These were defined as 18 "standard drinks" (equivalent to units) a week for men and 9 for women. "Too much" was defined as 56 a week for men and 35 for women.

The 1987 edition of the leaflet used "units" (a concept developed in clinical practice) for the first time. The "sensible limit" - described as the amount to which people should limit their drinking if they wanted to avoid damaging their health (a phrase also used in all subsequent editions) - was now set at 21 units a week for men and 14 for women. "Too much" was said to be 36 units for men or 22 for women. The same figures were repeated in the 1989 edition.

Three of the medical Royal Colleges - General Practitioners, Psychiatrists and Physicians -issued reports on alcohol in 1986/7.[5,6,7] All three reports endorsed the 1987 Health Education Council line on sensible drinking. For the Psychiatrists this meant revising downwards considerably advice they had given in 1979 that the upper level of sensible drinking should be 56 units a week for both sexes.

The Government officially adopted the 1987 advice of the Royal Colleges in the report "Action Against Alcohol Misuse" (1991)[8] prepared by the Ministerial Group on Alcohol Misuse which met under the chairmanship of the Lord President from 1987 to 1991. The chapter on the sensible drinking message summarises Government policy as follows: "The Government is committed to encouraging people to drink sensibly, keeping within the recommended sensible limits and drinking only in appropriate circumstances". In his introduction to the report the Lord President said "The Government does not wish to discourage the sensible consumption of alcohol, but is committed to reducing alcohol related harm".

In 1992 the sensible drinking message was used to set the baseline for targets to reduce alcohol misuse in "The Health of the Nation" and the other national health strategies (see Annex W.' "Health of the Nation" said that

"drinking less than 21 units per week by men and 14 units per week by women is unlikely to damage health" and went on to say that sustained drinking in excess of these levels progressively increased the risk.

In 1995 the three Royal Colleges revisited their work in the light of later scientific findings, including those on the protective effect for CHD, but concluded that the limits adopted in 1987 did not require changing. Their report to this effect is among the evidence the Group have considered.[10]

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ANNEX F **(Para 3.2)**

SENSIBLE DRINKING MESSAGES IN SOME OTHER COUNTRIES

RISK LEVEL	LOW RISK+	INTERMEDIATE RISK	HIGH RISK	NOTES
Australia (NH&MRC 1992)	Men less than 4 standard drinks* per day++ Women: less than 2 standard drinks per day	Men: 4-6 standard drinks per day Women: 2-4 standard drinks per day	Men: 6 plus standard drinks per day Women: 4 plus standard drinks per day	*One standard drink equates to 8-10 grams absolute alcohol
United Kingdom	Men: less than 21 standard drinks* per week Women: less than 14 drinks per week		Men: 8 plus standard drinks per day Women: 5 plus standard drinks per day	*One standard drink equates to 10 grams absolute alcohol
New Zealand (Alcohol Advisory Council)	Men: 3-4 standard drinks per day Women: 2-3 standard drinks per day		Men: 6 plus standard drinks per day Women: 4 plus standard drinks per day	No equivalent in terms of grams of absolute alcohol is specified
Canada (Addiction Research Foundation)	Men: up to 2 standard drinks* per day Women: are advised to not exceed one-third of the limit set for men	Men: 3-6 standard drinks per day	Men: 7 plus standard drinks per day	*One standard drink equates to 13.6 grams absolute alcohol
Sweden (State Alcohol Monopoly)	Men and Women not to exceed more than 50 grams	Men and Women drinking 51- 250 grams absolute alcohol per week	Men and Women drinking in excess of 251 grams absolute alcohol per week	
Denmark (National Board of Health)	Men: less than 21 units* per week Women: less than 14 units per Week			*While no absolute alcohol equivalence is provided the note is made that Danish units contain more absolute alcohol than British units
USA (US Department of Health and Human Resources)	Men: no more than 2 drinks* per day Woman: no more than 1 drink per day			*A drink equates to 12 grams absolute alcohol

(After Hawks, D.V. (1993))

- Different terms used by different authorities to describe drinking of varying risk.

++While limits are expressed here in terms of the number of standard drinks per day or per week, most authorities recommend at least 2 alcohol free days per week.

ANNEX G **(Para 5.3)**

ALCOHOL CONSUMPTION AND CORONARY HEART DISEASE: INFERRING CAUSALITY

In order to infer causality between the association of alcohol consumption and coronary heart disease. the epidemiological data can be assessed using the widely accepted criteria described by Hill*. These are specifically discussed below.

1. Consistency of Association

International ecological country-based comparisons, analyses of time trends, case control, cohort and clinical studies throughout the world have all consistently demonstrated an inverse association between moderate alcohol intake and CHD.

2. Strength of Association

In both case control and cohort studies the relative risk of CHD from moderate alcohol consumption (10-15 grams per day) compared with no consumption ranges from 0.4 to 0.7. Generally this was significantly different from 1.0 and implies a moderately strong association. Although it is possible that an as yet identified confounding factor could explain this association, it would have to be found twice as frequently amongst moderate drinkers as among heavier drinkers to account for this strong inverse association. it is unlikely that a confounding factor could have consistently remained unidentified in these studies.

3. Specificity of Association

In general, moderate alcohol consumption has been demonstrated to be more specific for a decreased prevalence and incidence of CHD than for almost any other disease. The effect is most significantly found for CHD, and where it is also found less strongly expressed in diseases such as ischaemic stroke and gallstones there are possible common biologically related mechanisms.

4. Dose-Response

The reduction in risk for very light drinkers is impressively large and is maintained for moderate drinkers but does not continue to zero for heavier drinkers. Other factors at high consumption levels influence the reducing risk including cardiac arrhythmias and sudden coronary death. There is not therefore strong evidence for a clear dose response relationship across increasing alcohol consumption.

5. Temporal sequence

The temporal sequence criterion states that cause must predate the effect. No specific study has followed drinking problems over time, and so relating patterns temporarily to the incidence of CHD. However, an increasing body of evidence from both time trend and cohort studies indicate that moderate levels of alcohol intake precede the onset of CHD and CHD mortality

6. Independence

A number of case control and cohort studies have used statistical analysis techniques to adjust for the potentially confounding associations of tobacco use, obesity, dietary habits, socioeconomic status, personality type and other know risk factors. The association between moderate alcohol consumption and CHD has been found to be independent of these major risk factors in these studies. It is possible that confounding could still explain the associations. However it would have to be common enough to be found in a diversity of populations.

7. Biological Plausibility

This is an important criterion for causality. It is established that the major cause of CHD is life long deposition of fatty tissue in coronary arteries (atheromatous plaque). In addition local coronary artery spasm and an increased tendency to form blood clots reduce coronary artery blood supply and generate the symptom of chest pain (angina). These factors can lead to an acute narrowing or blockage of a major coronary artery and a clinical heart attack leading to serious illness or death. There is increasing evidence that alcohol consumption reduces the likelihood of such a coronary episode by (a) directly influencing lipoprotein cholesterol chemical pathways so as to inhibit the formation of atheromatous plaque and (b) affecting advantageously a number of mechanisms associated with blood clotting and thrombosis.

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ANNEX H **(Para 6.10)**

REPORT OF THE COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT STATEMENT ON ALCOHOLIC BEVERAGES

Introduction

1. Government has established an interdepartmental Group to review the current health and related advice on alcohol intakes in the light of recent claims that alcohol consumption may reduce the incidence of coronary heart disease. As part of the health input into this group the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) was asked to advise on the mutagenicity of ethanol and alcoholic beverages.

2. The COM gave detailed consideration to comprehensive reviews of the available data on the mutagenicity ethanol, its principal metabolite acetaldehyde and alcoholic beverages per se at meetings held in October 1994 and February 1995. The main components of alcoholic beverages are water, ethanol and, in the case of sweet

liquors, sugar. It was therefore felt that the review, covering data on alcoholic beverages themselves plus ethanol and its metabolite acetaldehyde was adequate to enable conclusions to be drawn regarding the mutagenic potential of the range of alcoholic beverages consumed by the general public.

3. It was recognised that alcoholic beverages contain small amounts of a significant number of volatile and non-volatile organic compounds formed during production storage and maturation. The Committee agreed that it was not essential or practical to review these constituents individually for their mutagenic potential.

4. The conclusions reached with regard to the mutagenic potential of ethanol, acetaldehyde and alcoholic beverages are given below.

Ethanol

5. The mutagenic potential of ethanol was summarised as follows:

(i) In vitro studies do not suggest that ethanol has any mutagenic potential. Negative results were consistently obtained in studies using Salmonella typhimurium TA 1535, 1537, 1538, 98 and 100 and in more limited studies using TA 102. Negative results were also obtained in mammalian cells using the mouse lymphoma assay and in metaphase analysis studies for the investigation of clastogenicity. Conflicting results were obtained in studies to investigate SCE induction with some positive results reported at high concentrations of ethanol.

(ii) Negative results were obtained in the sex linked recessive lethal assay, and also in the Somatic Mutation and Recombination Test (SMART assay) in Drosophila melanogaster.

(iii) Negative results were consistently obtained from *in vivo* studies in rodents (rats, mice and hamsters) designed to detect clastogenicity (using either metaphase analysis or the micronucleus test) in bone marrow despite the use of very high dose levels equivalent to several grams/kg per day by lavage or in the drinking water. An increase in SCEs has been reported in fetal cells when pregnant animals were given very high dose levels of ethanol (5 g/kg/bw or more).

(iv) Ethanol has been fairly extensively investigated for genotoxic effects in germ cells, mainly using the dominant lethal assay. Negative results were obtained in the majority of cases. A number of poorly described experiments have been reported using very high dose levels with inconsistent results obtained. The Committee considered that data from these studies could not be extrapolated to realistic exposure conditions. It was concluded that there is no evidence that ethanol induces germ cell mutations *in vivo*.

Acetaldehyde

6. The Committee noted that significant amounts of acetaldehyde occurred in the body as a product of intermediary metabolism but that these were transient due to the rapid conversion to acetic acid. The following conclusions were reached with regard to the mutagenic potential of acetaldehyde.

(i) The Committee noted that the data set available on acetaldehyde was generally of poor quality.

(ii) Negative results have been obtained with acetaldehyde using the Salmonella assay in tests that were not specifically designed to prevent vapour loss but the compound has been shown to produce gene mutations in

mammalian cells. It has been more extensively investigated for its ability to induce chromosome aberrations and SCEs in mammalian cells and positive results have consistently been obtained in the absence of exogenous metabolic activation. These *in vitro* studies indicate that acetaldehyde has mutagenic potential.

(iii) Data from *in vivo* studies were too limited to draw definite conclusions. Negative results were obtained in one study using an adequate protocol to investigate SCE induction in bone marrow following administration of dose levels up to 0.5 mg/kg bw (associated with marked toxicity) using the i.p route. Acetaldehyde was reported to produce DNA-protein crosslinks in the nasal mucosa of rats in an old study of limited value, following exposure by inhalation to levels of 1000 ppm and above but not at (or below) 300 ppm. These data provide only preliminary information that covalent binding occurred at a high dose level.

(iv) The mutagenic profile of acetaldehyde is very similar to that of formaldehyde. The compound has direct acting mutagenic potential *in vitro*, but would only be expected to have the potential of in vivo activity at sites where it is not rapidly metabolised to acetic acid (see COC statement for information on the animal carcinogenicity bioassays with acetaldehyde).

Alcoholic Beverages

7. The Committee considered the published data on alcoholic beverages which mainly consisted of experimental studies, both *in vitro* and *in vivo,* on concentrated extracts of these products. in addition an unpublished report (in Press) on HPRT mutant frequency in circulating T cells in humans with known levels of intake of alcoholic beverages was considered. The following conclusions were agreed:

(i) There is some evidence that concentrated extracts of wines and spirits (covering a wide range of types) may have mutagenic activity in bacteria. Activity was inconsistently seen across all types of wines or spirits, with about 10-20% of commercial samples showing some activity. In some cases this was 'direct-acting' in others S-9 was required. A higher proportion of the concentrated extracts of home made wine and spirits had mutagenic activity than commercial samples. These results suggest the presence of low and variable amounts of different compounds with mutagenic potential. In view of the enormous number of organic compounds known to be present in low levels (many hundreds) no conclusions can be drawn regarding the identity of the compounds involved.

(ii) The *in vivo* mutagenicity of alcoholic beverages has not been adequately investigated and no definite conclusions can be drawn. There was no convincing evidence that concentrated extracts from alcoholic beverages have *in vivo* activity in the bone marrow of animals. No data are available in animals for tissues other than the bone marrow.

(iii) There are a limited amount of data from both *in vitro* and *in vivo* studies to suggest that concentrates from alcoholic beverages have some mutagenic potential. This is probably due to the presence of unidentified mutagenic contaminants which have been concentrated to high levels during the extraction process. The significance of the results of studies using concentrates in relation to the consumption of alcoholic beverages is questionable.

(iv) There are no adequate published studies in humans which have investigated the mutagenic effects of drinking different alcoholic beverages. There are some unpublished data available which suggest that any effects are small. Analysis of HPRT mutant frequency in circulating T cells of 143 adults whose alcohol consumption was known (0-56 UK units) did not reveal any relationship between alcohol consumption and HPRT mutant frequency. Furthermore, registered alcohol dependent individuals did not have an elevated mutant frequency.

Overall conclusions

It was agreed that the consumption of alcoholic beverages does not present any significant concern with respect to their mutagenic potential.

Secretariat May 1995

ANNEX I (Para 6.11)

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

STATEMENT FOR THE INTERDEPARTMENTAL GROUP ON SENSIBLE DRINKING

Introduction

1. We have been asked by the Interdepartmental Working Group on the Sensible Drinking Message to review the current literature relating to the carcinogenicity of alcoholic beverages, and to interpret these data in relation to the current Sensible Drinking Message. 1 The Sensible Drinking Message states that if men drink less than 21 units of alcohol per week and women 14, they are unlikely to damage their health (A unit of alcohol contains 8 grammes of ethanol - the amount in half a pint of ordinary beer or lager or in a small glass of wine, or in a standard measure of spirits). Thus <21 units per week is equivalent to < 24 g ethanol/day and <14 units per week is equivalent to < 16 g ethanol/day. it is also stated that drinking in excess of 50 units a week for men Ge >57 g ethanol/day) or 35 units for women (>40 g ethanol/day) is definitely dangerous.

2. The World Health Organization's International Agency for Research on Cancer (1ARC) published a monograph entitled "Alcohol Drinking" in 1988. The IARC Working Group concluded that there was sufficient evidence for the carcinogenic effects of drinking alcoholic beverages in humans.[2] The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver were causally related to the consumption of alcohol. No definite conclusions were drawn in respect of cancer of the colon, rectum, stomach, breast and lung. No association was found for cancers of the urinary bladder, ovary, prostate and lymphatic and haematopoictic systems.

Objectives of review

3. The COC review has been based on the IARC monograph (including critical studies cited by the Working Group) and on the extensive literature relating to epidemiology and animal studies published from 1988 to June 1995. We reviewed these data with four main objectives.

First to estimate relative risks of developing cancer at each of the sites considered by the IARC Working Group to be causally associated with alcohol drinking.

Secondly, to examine the nature of the trends in the frequency and duration of drinking required to increase the risks of these cancers; to inquire whether abstinence reduces such risks; to identify (if possible) which particular components of alcoholic beverages are carcinogenic in humans; and to evaluate the degree to which the association between cancer and drinking alcohol is confounded by other factors, notably smoking.

Thirdly, to review the available epidemiological data for cancer at other sites in order to determine whether alcohol drinking has a causal role.

Fourthly, to consider whether studies in animals suggested a plausible mechanism for the carcinogenic effects of alcohol observed in humans.

Evaluation of epidemiological data on alcohol

4. The results of epidemiological studies reviewed in this statement clearly demonstrate that moderate to heavy drinking of alcohol causes malignant tumours of the oral cavity, pharynx, larynx and oesophagus; but assessing the magnitude of the relative risk (ie risk compared with non drinkers), particularly at low levels of drinking, is very difficult. Because cancers caused by drinking alcohol occur at sites where cancer is relatively rare in the UK while consumption of alcoholic beverages is common, it follows that the actual risk of developing cancer at low levels of drinking is very small (see paragraphs 6 and 7 below). Factors which complicate the assessment of the epidemiological data can be grouped into three main areas.

First, estimates of alcohol intake are very imprecise, mainly because it is difficult to obtain an accurate history of drinking from individuals over the long period of time required for the development of alcohol associated cancers. Problems involved in collecting and interpreting this information include:

a) inaccurate or biased recall of drinking leading to underreporting of alcohol consumption.

b) Changes in individual drinking patterns over time.

c) Cultural and regional variations in drinking habits.

d) Differences in quantifying alcohol intakes in separate studies - for example total beverage consumption (usually as gram ethanol/day or as units per week) or as consumption of specific types of beverage such as wines or beers.

e) inadequate and inconsistent stratification of exposure groups. Many authors included both moderate and heavy drinkers in the same exposure group.

Secondly, the accuracy of diagnosis and reporting of tumours may vary considerably. The prime sites at risk from drinking alcohol are in the head and neck. The relevant tumour type (squamous carcinoma) is generally easy to diagnose, but the detailed topography of some areas, particularly the subdivisions of the pharynx and to a lesser extent the larynx, is complicated and may vary in different accounts. It is sometimes difficult to determine the

precise site of origin of tumours in these regions. The accurate diagnosis of tumours in other susceptible organs such as the liver is more problematic where different modalities (eg clinical examination, radiology, serology, biopsy, autopsy) with differing diagnostic sensitivities and specificities have been used to identify tumours. For example, the essential distinction between primary hepatocellular carcinoma and metastatic carcinoma may be difficult without histopathological evaluation.

Thirdly, the assessment of dose response data reported in epidemiological studies is difficult, particularly at lower levels of drinking where the numbers of individuals are often too low for the small elevations in relative risk to reach statistical significance at the conventional 5% level. This issue might be resolved by undertaking a meta-analysis of the data for each site, although the problems of dosimetry would still remain.

5. We have not defined a threshold level of drinking associated with an increased risk of cancer since, implicit in the statistical analyses of doseresponse data from the epidemiology studies reviewed in this paper, is the general assumption that such a threshold level does not exist. Instead, we have attempted to estimate the level of alcohol drinking where there is convincing evidence of an increase in the relative risk of cancer at susceptible sites. There may be a very small risk of cancer at lower levels of drinking, but the studies reviewed were not capable of demonstrating an increased risk at such low levels of alcohol consumption.

Consumption of Alcohol in the UK

6. A brief comment on the national patterns of alcohol drinking is necessary to provide a context in which the epidemiological findings can be interpreted. The most extensive published survey of drinking habits in the UK was conducted by the Office of Population Censuses and Surveys (OPCS) between April 1992-March 1993.[56] Overall, 6% of male respondents and 12 % of female respondents were non-drinkers. 27% of male respondents drank more than 24 g ethanol/day (6% above 57 g ethanol/day) and 11% of female respondents consumed more than 16 g ethanol per day (2% above 35 g ethanol/day). These figures have remained relatively constant over the period from 1984 to 1992. The only changes reported during this time were a 2-3% increase of women at all age groups drinking more than 16 g ethanol/day and a4% increase of men aged 45-64 drinking more than 24 g ethanol/day. Per capita estimates of ethanol intakes have also been published for the period 1960-1993, based on the sale of alcoholic beverages (See Figure 1 (Annex 1).[57] These data suggest that alcohol drinking increased substantially during the late 1960's and 70's to a level equivalent to about 9 litres of 100% ethanol/person/year (approximately 20 g ethanol/day) which has remained relatively constant during the 1980's to date. It is likely that the rise in popularity of drinking wine was mainly responsible for the reported increase in overall alcohol consumption.

Incidence of newly diagnosed cancer cases in UK

7. Table 1 (Annex 2) presents information on the number of new cases of cancer registered in England and Wales (1989) and in Scotland (1990) at a number of sites. Combined data for England, Wales and Scotland presented in Figure 1 (Annex 2). Cancers at sites generally considered to be causally associated with alcohol drinking – oral cavity, pharynx, oesophagus and larynx and possibly primary liver cancer - are relatively uncommon, so that the numbers of individuals likely to develop cancer at lower levels of drinking will be very small.

8. Cancers at certain other sites, mainly large intestine and breast, may also be associated with alcohol, but the IARC Working Group was unable to determine whether the association was causal. Some of these cancers, most notably breast cancer, are common. There would be serious public health implications if even a small proportion of common cancers was attributable to alcohol consumption, and we have examined this aspect in considerable detail to determine whether the original conclusions reached by the IARC Working Group in 1988 are still valid in the light of the further information now available.

Cancers of the upper aerodigestive tract and certain specific bead and neck cancers.

9. The most recent epidemiological studies published after the IARC monograph continue to demonstrate a dose-related association between the consumption of alcohol, expressed as grams ethanol consumed per day, and squamous carcinomas of the oral cavity, pharynx, larynx, and oesophagus. The association between cancer at these sites and drinking alcohol has been reported in studies of both smokers and non-smokers. The epidemiological findings are consistent with the view that drinking alcohol is causally associated with head and neck cancers independent of smoking, although the latter is recognised as an important potential confounding factor. (The interaction between smoking and drinking is discussed later in paragraph 40).

Most investigators have adjusted estimates of relative risk associated with alcohol intake for the confounding effects of smoking, although the adequacy of data on tobacco consumption varies in the different accounts. Most of the dose-response data have accumulated from studies of men, with considerably less information available for women (in whom these tumours are much less frequent). There are only a few reports, for example, which deal exclusively with cancers of the larynx in women.[3,4] The available data for women are, however, broadly compatible with those derived for men.

Cancers of the upper aerodigestive tract

10. There is clear evidence from both cohort and case-control studies that heavy consumption of alcohol is associated with an increase in the incidence of squamous carcinomas of the upper aerodigestive tract, combining the oral cavity, pharynx, larynx and oesophagus. [2,58-65,70] There are insufficient data available from prospective studies to draw any conclusions regarding doseresponse relationships. Most case-control investigations found a dose-related association, although there is considerable variation in the slope of the doseresponse between the different reports.[60-65] No evidence of a dose-response was found by Merletti et al (1989), in their population-based investigation of cancer of the oral cavity and pharynx in patients living in Turin.[66] Discrepancies in the quantification of alcohol consumption and smoking, and the inclusion of different combinations of anatomical sites and subsites in the various reports, may explain the apparent lack of consistency in estimates of relative risk. It is therefore difficult to quantify the magnitude of the relative risk of upper aerodigestive tract cancer at any particular level of consumption; for example there was a 10 fold variation in the estimates of relative risk at ≥ 75 g ethanol/day with a range between 2-20.

11. We *conclude* that most case-control studies show a dose-response relationship. It is not possible from the available data to derive precise estimates of relative risk for upper aerodigestive tract cancer, analysed as a single

entity, associated with specific levels of consumption. On balance, the data support the view that there is convincing evidence of an increase in relative risk at intakes above approximately 40 g ethanol/day. The evidence is less convincing at intakes between about 20-40 g ethanol/day. it is not possible to exclude a small increase in relative risk at lower intakes of alcohol below 20 g /day. There are fewer studies in women, but the data are compatible with those obtained for men.[2,60,62]

Cancers of the oral cavity

12. Results from both cohort and case-control studies are consistent with a dose-related association between drinking alcohol and cancer of the oral cavity.[2,62-64,67-69]

13. We *conclude* that there is convincing evidence of an increase in relative risk at intakes above approximately 40 g ethanol/day with a large increase in relative risk of the order of 8-15 fold associated with intakes in excess of about 70-100 g ethanol/day. The evidence is less convincing at intakes between about 20-40 g ethanol/day. Most studies show a clear dose-response relationship. It is not possible to exclude a small increase in relative risk at lower intakes of alcohol below 20g/day. There are fewer studies in women,2-1 but the data are compatible with those obtained for men.[2-4]

Cancers of the pharynx

14. The epidemiological data, based mainly on case-control studies, demonstrate a dose-related association for cancers of the pharynx, analysed either as a single entity or subdivided into oropharynx hypopharynx.[2,4,63,67,69,71-72]

15. We *conclude* that there is convincing evidence of an increase in relative risk at intakes above approximately 40 g ethanol/day with a 5-12 fold increase in relative risk associated with intakes in excess of 80 g ethanol/day. The evidence is less convincing at intakes between about 20-40 g ethanol/day. Most studies show a clear dose-response relationship. It is not possible to exclude a small increase in relative risk at lower intakes of alcohol below 20 g/day. There is no convincing evidence of a variation in sensitivity to alcohol in respect of cancer of the oropharynx, hypopharynx or pharynx (analysed as a single entity). Once again, there is less information in women, but the data are compatible with those obtained for men.[2-4] (The Committee noted the special category of hypopharyngeal (post cricoid) cancers associated with the Plummer-Vinson syndrome which occurs almost exclusively in women, but there is no evidence that the tumours are causally associated with alcohol).

Cancers of the oesophagus

16. Findings from both cohort and case-control investigations are consistent with a dose-related association between drinking alcohol and squamous carcinoma of the oesophagus[2,4,32,69,73-75] A few epidemiological studies have investigated a potential association between the consumption of alcohol and adenocarcinoma of the lower oesophagus and oesophagogastric junction,[6,7,8] but it is not possible to draw any conclusions from the results. The evidence is inconsistent, both positive and negative associations with alcohol being reported, and it is often difficult to assess the point of origin and local extent of these cancers.

17. We *conclude* that there is convincing evidence of an increase in relative risk at intakes above approximately 30-40 g ethanol/day with a 3-8 fold increase in relative risk associated with intakes between ≥40-100 g

ethanol/day. The evidence is less convincing at intakes between about 20-30 g ethanol/day. Most studies show a clear dose-responserelationship. It is not possible to exclude a small increase in relative risk at lower intakes of alcohol below 20 g/day. There are fewer studies in women, but the data are compatible with those obtained for men. There is insufficient information to draw any conclusions regarding an association between adenocarcinoma of the oesophagogastric junction and drinking alcohol.

Cancers of the larynx

18. The epidemiological data, derived primarily from case-control studies, show a dose-related association for cancer of the larynx.[2,63,64,71,73,76-79] The dose-response relationship is relatively shallow compared with other head and neck cancers. Some authors have reported results which suggest that the relative risk of supraglottic cancer associated with drinking alcohol is greater in comparison to the risk of cancer of the glottis.[64,67,76] The precise anatomical localisation of tumours in different regions of the larynx is, however, sometimes difficult to determine.

19. We *conclude* that there is convincing evidence of an increase in relative risk at intakes above approximately 40-70 g ethanol/day with a 3-9 fold increase in relative risk associated with intakes in excess of 70-100 g ethanol/day. The evidence is less convincing at intakes between about 20-40 g ethanol/day. Most studies show evidence of a dose-response relationship. It is not possible to exclude a small increase in relative risk at lower intakes of alcohol below 20 g/day. it is not possible to draw any definite conclusions with respect to subsite variation within the larynx.

Summary table of risks of cancers of upper aerodigestive tract (combined) and individual head and neck cancers

Cancer site	Evidence for dose response	intake for convincing evidence of increase in RR* (g ethanol/day)	RR at heavy drinking
Upper aerodigestive tract	Most case-control studies. Insufficient evidence from cohort studies	40 g/day	Not determined
Oral Cavity	Most studies show clear dose response	-40 g/day	1-5 (-40-70 gld) 8-15 (-70-100 g/d)
Pharynx	Most studies show clear	-40 g/day	5-12 (-80 g/d)
Oesophagus	Most studies show clear	-30-40 g/day	3-8 (-40-100 g/d)
Larynx	Most studies show evidence	-40-70 g/day	3-9 (-70-100 g/d)

**Level of intake where there is convincing evidencefrom epidemiology studies of a small but statistically significant increase in relative risk (RR). The data do not exclude a small increase in relative risk at lower levels of alcobol drinking.*

Cancer of the liver (bepatocellular carcinoma)

20. The most recent studies on alcohol and primary liver cancer are consistent with those reported by the IARC, showing an association at high levels of consumption; but concurrent infection with viral hepatitis B or C (HBV, HCV) in patients with primary liver cancer complicates the assessment of the association between drinking alcohol and liver and cancer.

21. Most prospective and case-control investigations support the conclusion that heavy drinking of alcohol is associated with hepatocellular carcinoma. No association was reported in one recent prospective study from Japan of drinking alcohol and liver cancer.[153] Estimates of relative risk in men derived from case-control studies which controlled for HBV infection varied between 2-7 for intakes of more than 80 g ethanol/day.[5,73] There is little evidence of a dose-response when all the available epidemiological data are considered. There are fewer studies in women, but the data are compatible with those reported in men.[73,80] The great majority of hepatocellular carcinomas associated with heavy alcohol consumption occur in those patients with established liver cirrhosis. Chronic HCV infection has recently been demonstrated to be a risk factor for cirrhosis and hepatocellular carcinoma.[81-85] This information was not available to the IARC Working Group in 1988, but the IARC have now concluded that chronic infection with HCV is causally associated with primary liver cancer.[155] Preliminary evidence from one small case-control study of Japanese alcoholics with hepatic cirrhosis suggests that a high intake of alcohol (>130 g/day for at least 10 years) may enhance the development of hepatocellular carcinoma associated with HCV infection.[86] The data from this study also indicate that hepatocellular carcinoma in alcoholics (with accompanying cirrhosis) who do not have co-existing HBV or HCV infection appears to be quite rare.[86] There is currently no published investigation of alcohol drinking and primary liver cancer undertaken in UK which also considered HCV infection, and the implications of the Japanese study should be treated with some caution since the prevalence of HCV infection in Japan (1.14% of blood donors) has been reported to be higher than in the UK (0.08% of blood donors).[155]

22. We *conclude* that heavy drinking of alcohol is associated with primary liver cancer (hepatocellular carcinoma). Most tumours occur in individuals who have cirrhosis. it is not possible, in view of the results of recent investigations concerning the aetiology of liver cancer (particularly with respect to HCV infection) to draw any definite conclusions about the size of the relative risk of liver cancer associated with alcohol drinking.

Cancer sites not considered by IARC to be causally associated witb alcohol

23. We have evaluated the epidemiological data published since the IARC review to determine whether the conclusions reached by the IARC working group are still valid in the light of the more recent information now available. Conclusions for individual cancers are given below.

Cancer of the stomach

24. The IARC Working group concluded that there were little aggregate data to suggest a causal role for alcohol in the aetiology of gastric cancer.[2] We *conclude* that the results of the small number of epidemiological studies published after the TARC review are still consistent with the conclusion that there is no association between drinking alcohol and cancer of the stomach.[89-94]

Cancer of the colon

25. The IARC considered that it was not possible to derive a conclusion for cancer of the colon: the epidemiological findings were inconsistent and many reports were uncontrolled for confounding dietary factors. Since the IARC review, a weak association between the consumption of alcoholic beverages and cancer of the colon was reported in women in one prospective study and in men in one case control study.[9,10] No evidence was documented, in either men or women, in three further prospective studies.[11-13] and in four other case control studies.[14-17] A recent meta-analysis documented a weak association between the consumption of 24 g ethanol/day and cancer of the colon (RR = 1.10 (CI 1.03-1.17)).[18]

26. We *conclude* that the results of epidemiological investigations of colon cancer are inconsistent. The size of the relative risk documented in studies reporting positive results is small and the data have not always been fully adjusted for confounding dietary variables. Thus there is insufficient evidence to associate drinking alcohol with cancer of the colon. The potential interaction between alcohol and the diet in the aetiology of colon cancer is discussed in paragraph 43.

Cancer of the rectum

27. The IARC concluded that some epidemiological surveys provided suggestive but inconclusive data for a causal link between alcohol, most often beer, and cancer of the rectum. Four prospective studies have been published since the 1ARC review.[9,11-13] A small dose-related increase in the relative risk of rectal cancer in men which was particularly associated with consumption of beer has been documented in a number of studies. Relative risks were between 2-4 at the highest levels of intake *(ca* >30 g ethanol/day). it is possible that confounding variables were not fully taken into consideration. The results of case-control studies published since the IARC review are inconsistent. 10,[14-17] Estimates of relative risk do not exceed 2 at the highest levels of intake *(ca* >30 g ethanol/day). A recent meta-analysis also documented a weak association between the consumption of 24 g ethanol/day and cancer of the rectum (RR = 1.10 (Cl 1.02-1.18)) and with the consumption of beer ≥ 2 drinks/ day) and cancer of the rectum (RR = 1.26 (Cl 1.13-1.41)).[18]

28. We *conclude* that the results of epidemiological investigations of rectal cancer are inconsistent. Some studies have documented a weak association between cancer of the rectum and alcohol consumption, particularly beer in men. The magnitude of the risk is small and inconclusive in respect of a causal role for alcohol or beer.

Cancer of the breast

29. There is an extensive literature available on the epidemiology of breast cancer. Known risk factors for breast cancer include age, ethnic group, family history of the disease, age at birth of first child, menarche and at menopause, history of biopsy for benign breast disease, socioeconomic status, obesity and, in premenopausal breast cancer, history of lactation.[25] Other proposed risk factors have been cited, such as parity (in addition to age at birth of first child), use of oral contraceptives and hormone replacement therapy but whether they are involved in the aetiology of breast cancer remain controversial. The IARC reviewed 4 large prospective studies and 13 case control studies with respect to alcohol. These studies provided evidence of a consistent dose-response relationship, generally with up to 1.5-2 fold risk. Confounding due to recognised factors was controlled in most of them, but the Working Group did not reach a firm conclusion as to whether a causal2 association had been established between drinking alcohol and breast cancer. We have reviewed 7 additional

prospective studies[95-99,149,151,17] new case-control studies[100-116] and two meta-analyses.[19,20] We have also considered a formal analysis of the data from six case-control studies which controlled for known dietary confounding factors'[117] and a recent authoritative review of the association between alcohol and breast cancer.[118] An additional qualitative review of the design and conduct of 38 case-control study reports published[21] between 1980 and 1992 has also been considered.[21]

30. The Committee agreed that the adequacy of control for confounding by known and/or alleged risk factors varied in the different accounts. A weak dose-related association was reported in most cohort studies and in some hospital based case-control studies. The results of population based casecontrol investigations did not generally support an association.[21] A small statistically significant dose-related increase in relative risk was reported in the two meta-analysisreports (RR at 3 drinks/day 1.38 (Cl 1.23-1.55)).[19,20] The Committee noted that small increases in relative risk documented in the epidemiological studiesranging between approximately 1.2 to 3 and were associated with a highly variable consumption of alcohol (*ca* 1-60 g ethanol/day). It was agreed that clear evidence of causality had not been demonstrated.

31. We *conclude* that while there is no decisive evidence that breast cancer is causally related to drinking alcohol, the potential significance, for public health, of even a weak association between alcohol and breast cancer is such that we recommend, in particular, that this matter is kept under review.

Lung cancer

32. The IARC Working Group concluded that there was no evidence that drinking alcohol had a causal role in lung cancer. A weak association was found in one prospective cohort study which analysed a relatively small number of cases over a short follow up period.[22] Two more recent case-control investigations did not report any evidence of an association.[119,120]

33. We *conclude* that the data are consistent with the view reached by the IARC that lung cancer is not associated with drinking alcohol.

Cancer of the pancreas

34. The IARC Working Group considered that the consumption of alcohol was unlikely to be causally related to cancer of the pancreas. A large number of epidemiological investigations on the possible association between pancreatic cancer and alcohol have been published since the IARC monograph.[23,24,121-129] It is difficult to undertake such studies because pancreatic cancer is rapidly fatal and a large number of proxy interviews have to be used. Most epidemiological investigations do not report an association between alcohol and cancer of the pancreas. Evidence of a weak association has been documented in two of the three recently published prospective cohort studies[23,24] and in one study of alcoholics.[11]

35. We *conclude* that the balance of available evidence supports the view that drinking alcohol is not associated with cancer of the pancreas.

Cancer at otber sites

36. Literature searches have identified some new publications which investigated the possible association between alcohol and cancer of organs and tissues included in this category by the IARC. There are no studies published since the IARC review which alter the conclusions reached by the Working Group.

37. We *conclude* that there is no convincing evidence of an association between drinking alcohol and cancer of the urinary bladder, ovary, prostate and lymphatic and haematopoietic systems, the skin, corpus and cervix uteri, vulva, testis, brain, thyroid and soft tissues.

Carcinogenicity of specific beverages in humans

38. For cancers causally related to alcohol, risk estimates tend to be highest for the most popular beverage consumed in the geographical area under study. For example the highest risk of oesophageal cancer in studies from Northern France, Uruguay, and Northern Italy were associated with cider/apple jack,[2] wine/hard liquor,[32] and wine (not otherwise specified) respectively.[62] The available data support the view that variation in risk estimates for specific types of beverages reflect cultural and regional preferences in drinking patterns rather than differences in the composition of beverages.

39. We *conclude* that epidemiological findings are consistent with the view that the carcinogenic risk associated with the consumption of alcohol is proportional to ethanol consumption. For cancers causally related to alcohol, the observed variations in relative risks for specific beverages reflect geographical preferences for particular alcoholic drinks. The reported association between consumption of beer and cancer of the rectum (see paragraphs 26 and 27) has not been consistently reproduced, and hence we *conclude* that there are insufficient data to suggest any beverage-specific effect for cancer of the rectum.

Interaction with smoking

40. We have reviewed 1 prospective study and 15 case-control studies which specifically examined the occurrence of cancer in non-smokers who drank alcohol.[32,58,60,64-66,70,71,130-137,152] Evidence of an association between drinking alcohol and increased relative risk of cancer of the oral cavity, pharynx, oesophagus and larynx was documented in 12 of the 15 case-control studies reviewed which examined either non-smokers or minimal smokers. The clearest evidence has been reported for oesophageal cancer. Lifelong non-smokers were examined in 5 of these publications.[64,71,131-133] Thus the epidemiological data are consistent with the view that drinking alcohol is causally associated with head and neck cancers independent of smoking.

41. Smoking increases the risk of alcohol-associated head and neck cancers in[32,60,61,70,71,74,130,135,137,143] proportion to the amount of tobacco consumed. The results of case-control studies are conflicting as to whether the interaction between smoking and alcohol results in additive or multiplicative increases in relative risk of specific head and neck cancers at specific sites. It is not possible to determine the lowest levels of smoking required to increase the relative risk of alcohol associated cancer; the numbers of individuals investigated are often inadequate for the small elevations in relative risk of these comparatively rare tumours to reach statistical significance at the conventional 5% level. We *conclude* that it would be prudent to assume that all levels of smoking will increase the risk of alcohol-associated head and neck cancer.

42. There is no convincing evidence for an interaction between drinking alcohol and smoking in respect of cancers of the liver, stomach, large intestine, or breast. There is no evidence to suggest that alcohol affects the risk of cancers which are associated with smoking alone, pre-eminently cancer of the lung, but this topic has not been widely investigated.

Effects of alcohol on the diet

43. Poor nutritional status has often been described in heavy drinkers consuming ≥57 g ethanol/day in men and ≥40 g ethanol/day in women.28 Reduced intake of fresh vegetables and fruit has been reported in epidemiological surveys documenting higher risks of cancers of the upper aerodigestive tract associated with alcohol.[29-33] However, the precise role of poor nutritional status induced by heavy drinking in the aetiology of alcohol associated cancer remains obscure. There is insufficient evidence to draw any conclusions with regard to effects of alcohol on nutrition and primary cancer of the liver in individuals who are not alcohol dependent. Preliminary evidence from one prospective study has suggested that high intakes of alcohol in individuals whose diet is low in methyl donating groups (such as methionine) may be associated with cancer of the colon. Confirmation from other populations is required before any definite conclusions can be drawn with regard to these data.[154] There is insufficient evidence of a causal association between drinking alcohol and cancer of the colon (see paragraph 26).

Mechanism of carcinogenicity in humans

Mutagenicity

44. There is no convincing evidence that the carcinogenic effects of alcoholic beverages in humans occurs as a result of a mutagenic effect of ethanol itself, acetaldehyde (the initial metabolite of ethanol) or other beverage constituents. This subject is considered in detail in the statement from the Committee on Mutagenicity.

Carcinogenicity studies in animals

45. The carcinogenic effects of ethanol have been examined in a large number of published reports, mainly in mice, rats and hamsters often using very high dose levels.[34,38,39,43,138-140] Many of these studies are flawed in terms of their design, interpretation or both. Examples include the use of too few test animals, inadequate control groups, unrealistically high doses of alcohol and a failure to compensate for the resulting acute intoxification, and inadequate documentation of pathology. These studies have, however, given consistently negative results. A carcinogenicitybioassay in rats conducted to currently acceptable standards has recently been published.[150] No evidence of carcinogenicity was reported in male or female rats fed isocaloric liquid diets containing 1% or 3% ethanol for 2 years. We *conclude* that ethanol is not carcinogenic in animals.

46. Acetaldehyde, the initial metabolite of ethanol, has been shown to induce malignant nasal tumours in rats and laryngeal carcinomas in hamsters following inhalation exposure to high concentrations which induced intense local inflammation and epithelial degeneration.[36-37] The carcinogenic profile of acetaldehyde is probably due to sustained localised irritation of the respiratory tract. We *conclude* that the observation of tumours in animals exposed to high inhalation doses of acetaldehyde is not relevant to drinking alcohol.

47. The carcinogenicity of a number of individual alcoholic beverages has been examined in laboratory animals.[2,38,39] The studies have been inadequately performed and only a very limited range of beverages has been tested. No conclusions can be drawn.

48. We *conclude* that there are no data from carcinogenicity bioassays in animals which could explain the observed carcinogenic effects of alcohol in humans.

Studies of mechanisms

49. Many research groups have attempted to elucidate potential mechanisms for the carcinogenicity of alcohol. Proposals include modulation of known animal carcinogens. Both carcinogenic[41] and promoting[42] effects have been found and, in one study, tumour suppression.[43] The results of these investigations appear to be highly dependent on the chemicals chosen for study and the protocols used.[44,45] A number of possible mechanisms for the cocarcinogenic and/or tumour promoting effects of ethanol have been postulated which include ethanol-induced increases in activation of procarcinogens and the concentration of DNA adducts in target tissues, [46,47] lipid peroxidation in target tissues,[48,49] increased cell proliferation,[50,51,141] and impaired T-lymphocyte activation resulting in impaired cell mediated immunity[52,53]. Interaction between ethanol and other components of beverages may also be important. For example, enhanced cell proliferation in the rat oesophagus was recorded when a mixture of ethanol and 3-methylbutanol (a fusel alcohol present in spirits) were intubated, compared with ethanol alone.[142] The evidence for ethanol-induced increases in the endogenous levels of oestrogens, cited as a possible mechanism for breast cancer, is inconclusive.

50. Despite an extensive literature on alcoholic beverages, ethanol and acetaldehyde, we conclude that it is not possible to draw any firm conclusions regarding the mechanism by which alcohol causes human cancer.

Evaluation of sensible drinking message

51. We have evaluated the extensive epidemiological data linking cancer with drinking alcohol. There is a dose-related association for cancer of the upper aerodigestive tract (as a whole) and for cancers of the oral cavity, pharynx, larynx and oesophagus. There is no convincing evidence of a dose-response for primary cancer of the liver, which appears to be associated only with heavy drinking and cirrhosis. We have used data derived mainly from studies using groups of men or men and women. There is less information for women alone, largely owing to the comparatively smaller number of women who are heavy drinkers,[56] but the available evidence does not suggest that the risks to women are substantially different from those in men. We have estimated the relative risk for causally associated cancers in heavy drinkers which varies between 3-15 fold depending on tumour site. Convincing evidence of an increase in relative risk of cancer is difficult to obtain at low levels of alcohol consumption. On balance the data support the following conclusions.

a) the evidence is convincing for an increased relative risk of cancer at susceptible sites at intakes above about 40 g ethanol/day.

b) the evidence for an increase in relative risk is less convincing at lower intakes between about 20-40 g ethanol/day.

c) there may be a very small risk of cancer at still lower levels of drinking, but the studies reviewed were not capable of demonstrating an increased risk at such low levels of alcohol consumption.

it should be noted that cancers caused by drinking alcohol are relatively rare in the UK. Moreover, the relative risks for such cancers at low levels of intake are likely to be very low. Therefore, the actual risks of developing these cancers must also be very low. (see paragraphs 4-7 above).

52. The relative risk of cancer associated with alcohol increases with the frequency of drinking (ie a higher risk has been noted in daily drinkers).[4,73,143-145] A number of case-control studies have examined the relationship between the duration of drinking and increased risk of oesophageal cancer, but the results are inconsistent .[75,76,133,135,137,146,147] A trend between increasing relative risk and duration has been reported in some investigations whilst others show a similar increase in risk at all time points examined. These studies have focused. mainly on evaluating risks in individuals who have drunk alcohol for 20 years or more, and there is little information concerning shorter periods of drinking. It is thus not possible, at present, to define a minimum duration of drinking required at a particular level of consumption which will result in an increased relative risk of cancer at vulnerable sites.

53. The results of case-control studies are generally consistent with a reduction in relative risk of head and neck cancers following abstinence from drinking.[32,75,130,146,148] Most investigatorshave examined oesophageal cancer. The data suggest that for moderate drinkers the risk declines to that of nondrinkers after about 10 years.[32,75] In one recent study there was evidence that the period of abstinence required in former heavy drinkers consuming in excess of 85 g ethanol/day is longer (≥15 years); in former light drinkers consuming up to approximately 30 g ethanol/day the period of abstinence is shorter (≥5 years).[146] These latter results must, however, be viewed cautiously. Virtually no information on the underlying reasons why individuals gave up drinking was reported in these publications. One prospective study of exdrinkers documented a higher mortality rate for conditions other than cancer, such as cardiovascular disease and stroke.[59]

Conclusions

54 The main conclusions of our review are given below.

i) We *conclude* that

a) the epidemiological evidence supports the view that drinking alcohol causes a dose-related increase in the risk of squamous carcinomas of the upper aerodigestive tract as a whole, and for cancers of the oral cavity, pharynx, larynx and oesophagus. There is less information for cancer in these sites in women, but the available information show similar risks in both sexes. The epidemiological data suggest that drinking alcoholic beverages causes cancer independently of smoking. Relative risks, in heavy drinkers (≥70 g ethanol/day), after controlling for the confounding effects of smoking, vary between 3-15 fold depending on the tumour site. There is convincing evidence of an increase in relative risk at intakes above about 40 g ethanol per day. The evidence is less convincing at intakes between 20-40 g ethanol/day. The epidemiological data do not allow a quantification of relative risk at lower levels of drinking, but it is not possible to exclude a small increase in relative risk at intakes below 20 g ethanol/day. The tumour types causally associated with alcohol are relatively rare in the

United Kingdom and thus the number of cases which could be attributed to low levels of drinking would be very small. **(Paragraphs 9-19, 40, 51)**

b) The risk of cancer at susceptible sites increases with the frequency of drinking. The results of studies investigating the duration of drinking associated with an increased risk of cancer are inconsistent and have generally only considered periods longer than 20 years. No conclusions can be drawn from the available epidemiological data with respect to the minimum duration of drinking which will result in an increased relative risk at vulnerable sites. **(Paragraph 52)**

c) The results of case-control studies are generally consistent with a reduction in relative risk of head and neck cancers following abstinence from drinking. The epidemiological data suggest that abstaining for periods of 10-15 years may reduce the risk of cancer to that of non-drinkers, but it is not possible to draw definite conclusions on this aspect. **(Paragraph 53)**

d) The epidemiological data indicate that risk of cancer associated with drinking alcohol is due to the consumption of ethanol. Differences in risks attributed to particular types of beverage result from cultural and regional differences in drinking habits. There is no convincing evidence of beverage-specific effects. **(Paragraphs 38-39)**

e) Smoking increases the risk of alcohol associated head and neck cancers. It would be prudent to assume that all levels of smoking will increase the risk of alcohol associated cancers. **(Paragraphs 40-42)**

f) The precise role of poor nutritional status induced by heavy drinking in the aetiology of alcohol-associated cancer remains obscure. **(Paragraph 43)**

ii) We *conclude,* that heavy drinking of alcohol is associated with primary liver cancer. Most tumours occur in individuals who have cirrhosis. It is not possible, in view of the results of recent investigations concerning the aetiology of liver cancer, (particularly with respect to HCV infection) to draw any definite conclusions about the size of the relative risk of liver cancer associated with alcohol drinking. **(Paragraphs 20-22)**

iii) Some epidemiological investigations have reported an association between alcohol and cancer of the stomach, colon, rectum, lung and pancreas. We *conclude* that the evidence does not support a causal association between cancer at these sites and drinking alcohol. **(Paragraphs 23-28, 32-37)**

iv) We *conclude* that while there is no decisive evidence that breast cancer is causally related to drinking alcohol, the potential significance for public health of a weak causal association between alcohol and breast cancer are such that we *recommend,* in particular, that this matter be kept under review. **(Paragraphs 29-31)**

iv) It is not currently possible to draw any firm conclusions from the available studies in animals regarding the mechanism by which drinking alcohol induces cancer in humans. **(Paragraphs 44-50)**

September 1995

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TABLE 1 ANNEX 2

Registrations of newly diagnosed cases of cancer All ages. (selected sites)

			England/Wales[1]	(%)	Scotland[2]	(%)
			1989		1990	
All malignant neoplasms	(140-208)**	M	121,529	(100)	13,319	(100)
		F	144,447	(100)	14,132	(100)
Oral Cavity	(140-145)	M	1,264	(1)	233	(1.7)
		F	796	(0.5)	126	(0.9)
Pharynx	(146-149)	M	668	(0.5)	105	(1)
		F	366	(0.3)	44	(0.3)
Oesophagus	(150)	M	2,957	(2.4)	362	(1.8)
		F	2,224	(1.5)	301	(2.1)
Larynx	(161)	M	1,610	(1.4)	209	(1.6)
		F	372	(0.3)	72	(0.5)
Liver	(155)	M	734	(o.6)	117	(0.9)
		F	475	(0.3)	68	(0.5)
Stomach	(151)	M	6,608	(5.4)	652	(4.9)
		F	4,211	(2.9)	442	(3.1)
Colon	(153)	M	7,802	(6.4)	922	(6.9)

		F	9,102	(6.3)	1,196	(8.5)
Rectum	(154)	M	5,690	(4.9)	524	(3.9)
		F	4,565	(3.2)	470	(3.3)
Breast	(175)	M	215	(0.2)	17	(0.1)
	(174)	F	27,768	(19.2)	2,900	(20.5
Lung	(162)	M	25,276	(20.8)	2,969	(22.3)
		F	11,533	(8	1,721	(12.2)
Pancreas	(157)	M	2,930	(2.4)	323	(2.4)
		F	3,268	(2.3)	339	(2.4)

**= ICD Ninth edition code

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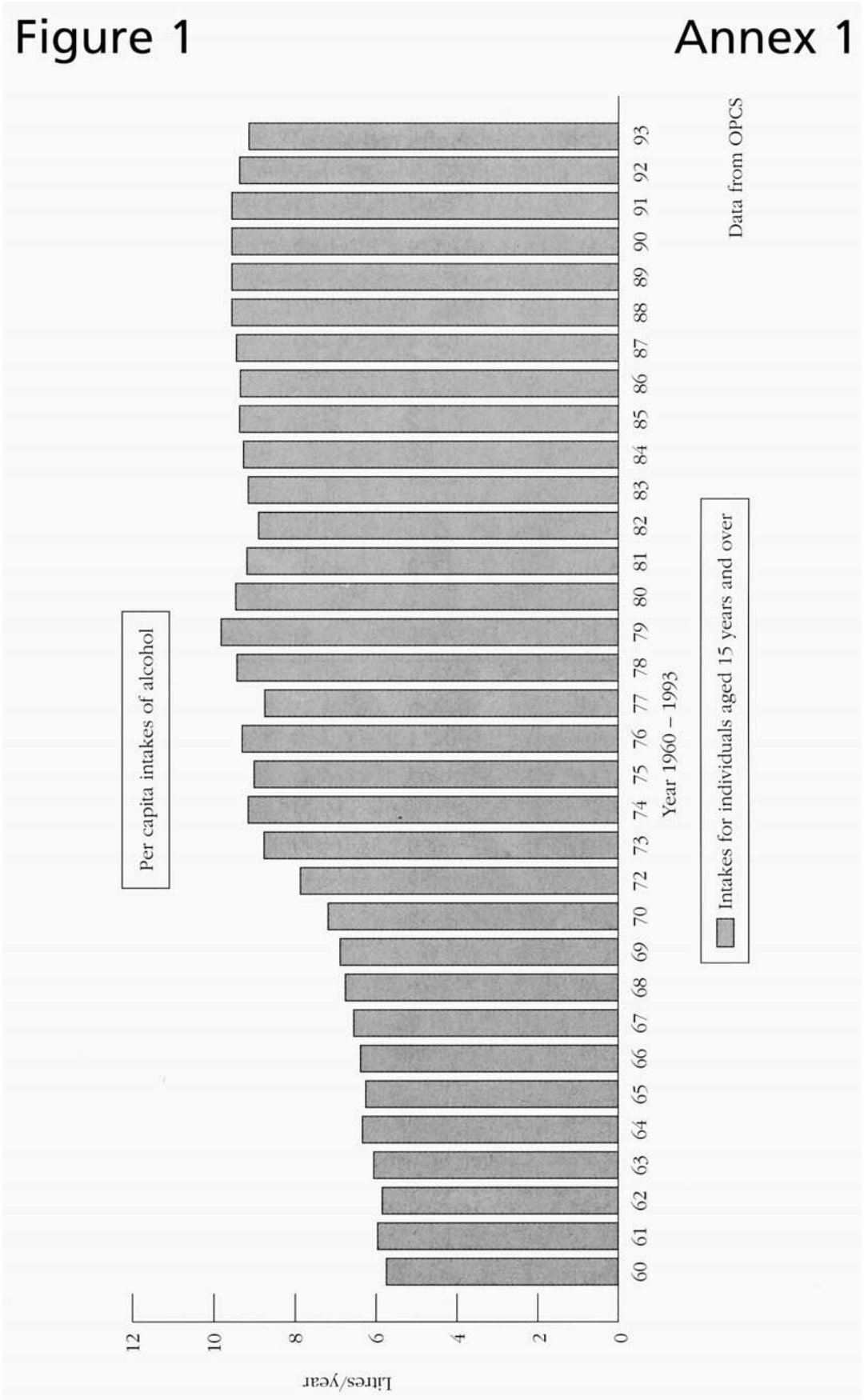
Figure 1

Annex 1



ANNEX J **(Para 6.19)**

STATEMENT BY THE COMMITTEE ON TOXICOLOGY ON THE EFFECTS OF ETHANOL INTAKE ON PREGNANCY, REPRODUCTION AND INFANT DEVELOPMENT

1. An Interdepartmental Group has been established to review the current health and related advice on ethanol intake, in the light of increasing evidence of some beneficial effect of ethanol at low doses on coronary heart disease. Previously, the Government has advised that if men drink less than 21 "units" per week and women drink less than 14 "units" per week (equivalent to 168g and 112g ethanol per week respectively), they are unlikely to damage their health. As part of this review, we were asked for advice on the harmful effects of ethanol on pregnancy, reproduction and infant development.

2. Many studies have been carried out in the last 20 years to try to identify the effects of ethanol in pregnancy and to establish intake levels at which these effects occur. A major problem in interpreting the human studies is the large number of confounding factors, including poor nutrition, licit and illicit drug intake and smoking, each of which can have adverse effects on pregnancy. Other factors also contribute to the variability of these studies; including difficulty in verifying intake of ethanol, different patterns of consumption and polymorphism in ethanol metabolism. in post-natal developmental studies, environmental factors are also critically important.

3. Despite all the variables, there is general agreement, from both human and animal studies, that ethanol has the potential to induce the following effects:- abortion; fetal growth retardation; facial and other dysmorphologies; and impaired post-natal physical and mental development.

4. Most studies agree that 2 drinks[1] per day and above may be associated with reduced birthweight which is one of the most sensitive parameters. Some studies have found effects at lower levels, but most have not. However, there is no good evidence that 1 or 2 drinks[1] per week has any adverse effect.

5. There are both human and animal data that suggest that binge drinking can also produce adverse effects listed in paragraph 3. There is evidence that adverse effects can be induced at all stages of pregnancy.

6. The full spectrum of physical and mental handicaps known as Fetal Alcohol Syndrome is only seen in the offspring of alcoholic women. On the other hand, adverse effects on cognitive and behavioural development might be observed as indicators of ethanol-induced damage in the offspring of women with lower ethanol intakes.

1 - where one drink is defined as 8g of ethanol equivalent to one unit in the current "sensible drinking message"

7. There is limited evidence that ethanol may also impair reproductive function in men and fertility in women, but this evidence is inadequate so far as the identification of the, intakes at which these effects are induced.

8. The principal studies which have reported adverse effects of ethanol intake on pregnancy, reproduction and infant development have been summarised by our Secretariat in Annex 1. These studies give a balanced

presentation of the data available and demonstrate the often conflicting results. This Annex also reports the effects of ethanol in animal reproduction studies and on the disposition of ethanol.

Recommendations

9. After due consideration, we recommend that:

(i) any new advice to pregnant women should be in terms of "units" of alcohol per day, since "binge drinking" can also affect the fetus.

(ii) to any new advice which may be formulated on sensible drinking limits, a caveat should be added to the effect that:

women who are pregnant or who are likely to become pregnant should keep their alcohol intake substantially below limits suggested for non-pregnant women.

ANNEX 1

1. The human epidemiological studies cited below have been controlled for confounding factors such as smoking, drug use, socioeconomic factors, nutritional status, maternal parity and other demographic characteristics, obstetric history, prematurity etc unless otherwise stated. The studies have been placed in order such that those relating to high maternal intakes are first.

Human Data

Fetal and Infant Development

2. In a prospective study of over 9000 subjects, in which mothers were divided into those who consumed less than c. 245g ethanol per week and those who consumed more than this amount, a significant decrease in birthweight of neonates of this second group was reported in comparison with the first (group mean birthweight 3255g and 3313g, respectively, $p<0.05$) (1). At this higher level of maternal ethanol intake, there was also a significant increase in small-for-dates and still-births and a decrease in placental weight. Ouellette and coworkers (2) have evaluated the effect of maternal ethanol intake during pregnancy in a smaller study consisting of 633 women. The women were divided into 3 groups: those who consumed approximately 245g ethanol per week and on occasion consumed at least 75 g (group 3); those who either abstained or drank less than once per month (group 1); and those who drank more than once per month but did not fulfil the criteria of the heavy drinkers in group 3 (group 2). Of the 322 babies born, 152 were in group 1, 128 in group 2 and 42 in group 3. Infants were classified as abnormal if they displayed congenital anomalies, growth abnormalities or abnormalities on neurologic examination. Of the 42 infants born to heavy drinkers, 71% were considered abnormal according to the above criteria compared with 35% in group 1 and 36% in group 2 ($p<0.001$ by chi-square, with 2 degrees of

freedom). The outcome of pregnancy has also been reported in mothers who consumed at least 390g ethanol per week (38 women) in comparison with abstainers (80 women) (3). The mean birthweight of the offspring of the drinkers was significantly less than those of the abstainers (2554g and 3094g respectively, $p<0.01$). The offspring of drinkers also had an increased incidence of physical abnormalities, with signs consistent with Fetal Alcohol Syndrome (odds ratio 16.9, $p<0.001$). This syndrome was first described more than 20 years ago (4) and affects approximately 10% of the offspring of alcoholic mothers.

3. Marbury and coworkers (5) reported that maternal ethanol intakes of c. 190 g per week or more during pregnancy increased the risk of placenta abruptio and, consequently, of stillbirths (odds ratio 2.8, 95% confidence interval 1.1-7.8). Over 12,000 women took part in this studyand information on their ethanol consumption was obtained by interview at delivery. Their data did not support an association between increased ethanol intake and decreased birthweight.

4. Other workers have studied the extent and duration of maternal ethanol consumption in relation to adverse fetal effect (6). Women were divided into 4 groups according to ethanol consumption (c. 30-60g per week; 60-150 g per week; 180-390 g per week; and greater than 420g per week). Women were also divided by duration of exposure into those who drank throughout pregnancy (mean ethanol intake 380g per week, range 30-2250) and those who stopped drinking after the second trimester (mean intake 320g per week, range 30-1260). Birthweight, head circumference and length were used as measures of intrauterine growth. Infants in the continued-drinking group were significantly smaller than those in the group of non-ethanol exposed infants ($p<0.04$) and had a smaller head circumference ($p< 0.01$). There was no difference in these parameters between infants in the continued-drinking group and in the stopped-drinking group. However, when the growth parameters of infants delivered by mothers in each of the four dose groups were compared (by analysis of variance procedures), there was a significant interaction between duration of exposure and dose level ($p<0.02$) with the most heavily drinking women who continued to drink having the most severely affected infants. Further evidence for the beneficial effects of reducing ethanol consumption before the third trimester on fetal growth development has been reported (7). Among a group of 69 female heavy drinkers, defined as those who consumed c. 168 g ethanol per week and at least once per month drank 75-90g per occasion (binge drinkers), 25 reduced ethanol consumption by the third trimester. Infants born to these women showed less growth retardation (8% infants below the 10^{th} percentile for birthweight) than those who continued to drink heavily throughout pregnancy (45% infants below the same 10^{th} percentile).

5. Streissguth and coworkers (8), in a study involving 1425 subjects, reported that increased maternal ethanol use was significantly related to decreased birthweight ($p=0.037$), length ($p=0.001$) and head circumference ($p=0.013$). Information on ethanol consumption was obtained by a single interview during pregnancy and women were allocated to one of 19 categories according to quantity and frequency, with the highest category being those who consumed c. 210g ethanol per week. Statistical methods used were multiple regression models adjusting for confounding factors and a gestational age squared term to adjust for non-linearity in the ethanol and gestational age distributions. A follow-up study also reported an association between maternal ethanol consumption and weight of offspring. When the mothers were divided into groupsaccording to ethanol consumption, the largest difference was between the lowest intake group (abstainers) and the highest intake group who drank more than c. 470g ethanol per week prior to pregnancy recognition (mean birthweight 3518g and 3184g respectively) (9).

This weight decrement was still apparent, but to a lesser extent at, 8 months of age but was not apparent at 18 months.

6. A further study using data from 31,604 pregnancies reported that the percentage of newborns below the 10th percentile of weight for gestational age increased sharply with increasing ethanol intake (5.8% for abstainers, 11.6% for maternal consumption of c. 210 g per week; 17.7% for maternal consumption of greater than 630 g per week) (10). Mean reductions in birthweight of offspring from maternal drinkers compared with non-drinkers ranged from 14g in those mothers consuming less than c. 70g ethanol per week to 165g in those consuming c.210-350 g ethanol per week. Consumption of c. 210-350 g ethanol per week was associated with a substantially increased risk of producing smaller infants (odds ratio of 1.96, confidence interval 1.163.31, p=0.01) as was consumption of c.70-140g ethanol per week (odds ratio of 1.62, 95% confidence intervals 1.26-2.09, p=0.0002) while the risk at intakes of c.70g per week or less was lower (odds ratio 1.11, 95% confidence interval 1-1.23, p=0.05). The decrease in birthweight observed in the offspring of mothers who consumed c. 70g ethanol per week or less during pregnancy may be of no biological significance.

7. Another study also reported an inverse relationship between ethanol consumption and birthweight, with an average intake of approximately 20g per week being associated with a mean decrease in birthweight of 76g (11). However, this result is not considered reliable, since the authors themselves report that the maternal self-assessment procedure for ethanol intake during pregnancy was likely to substantially under report actual intake.

8. Lumley and coworkers (12) reported a small and statistically insignificant, reduction in birthweight of offspring from mothers who consumed c. 45-90 g ethanol per week (5.6% of babies below 2.5 kg compared with 4.7% of babies from maternal abstainers). Significantly more babies weighed less than 2.5 kg at birth when maternal intakes averaged 210-315g ethanol per week in comparison with the combined percentages of abstainers and those of low and social intakes, defined as intakes of up to 90 g per week (14% in comparison with 4.9%, p< 0.025). Data on ethanol consumption were collected from the mothers in early pregnancy and over 15000 births were analyzed.

9. Rosett and coworkers (13) analyzed the effect of ethanol consumption on fetal development in a prospective study of 469 mother-infant pairs. Mothers were divided into three groups according to their reported pattern of ethanol use. Heavy drinkers were defined as those whoconsumed at least c. 168g per week and sometimes (at least once per month) consumed more than 75g ethanol per occasion (binge drinkers). Rare drinkers either abstained or consumed ethanol less than once a month and did not indulge in binge drinking. All women who drank more often than once a month but did not meet the criteria for heavy drinkers were classified as moderate drinkers. Growth measurements among offspring of heavy drinkers showed statistically significant reductions in comparison with rare drinkers (mean birthweight 2596g in comparison with 3298 g, p<0.001). The average birthweight for the other groups were: 3119g (reduced drinking in third trimester),and 3217g (moderate drinkers). A reduction in ethanol intake by the heavy drinkers (by either abstaining or reducing ethanol consumption so that they were no longer regarded as "heavy drinkers") resulted in significantly less offspring below the 10th percentile for birthweight in comparison with those whose mothers who did not reduce their intake (18% in comparison with 25%, p<0.05). A reduction in infant weight and length at 8 months of age has been significantly related to alcohol use during early pregnancy (14). At this age, the mean weight of infants of

mothers who consumed c. 420g ethanol per week or more during pregnancy was c. 8.5 kg, whereas the mean weight of those whose mothers consumed c. 105g ethanol per week or less was c. 8.8 kg ($p<0.03$). The mean lengths were 69.75 cm and 70.5 cm respectively ($p<0.05$).

10. A prospective study by Olsen and coworkers (15), which reported data on 2259 women, showed that birthweight of offspring was correlated to ethanol consumption (correlation significance -37.6, $p<0.05$). The mothers were grouped according to their ethanol consumption as follows: abstainers; c. 10-40g ethanol per week; 50-90g ethanol per week and greater than 100g per week and the correlation was carried out using all groups. However, these workers state that due to the adjustment procedure used for smokers/nonsmokers, this association might be subject to residual confounding. Other workers investigated the effects of ethanol in 952 pregnant women (16). Mothers were questioned about ethanol consumption at about 16 weeks of pregnancy. Maternal ethanol consumption during pregnancy of 120 g per week or more was associated with a gestational duration of, on average, 2.6 weeks less than abstainers ($p<0.001$). An ethanol intake of 100-119 g per week, as well as that of greater than 120g per week, was associated with a smaller head circumference ($p<0.05$ and $p<0.001$, respectively). Maternal ethanol intakes of below 100g per week were not associated with significantly shorter gestational age, smaller head circumference, shorter length or reduced birthweight.

11. Maternal ethanol intake has also been associated with adverse effects on neonatal behaviour – such as poor habituation and decreased ability to suck (8). A study on 468 infants at 8 months of age reported reduced mental and motor development and decreased height and weight when mothers consumed (during pregnancy) c. 210g ethanol per week or more, or consumed c. 170g per week and more plus c. 75 g ethanol on at least one occasion per month. it has also been reported that a maternal ethanol intake during pregnancy of c. 210g per week or more was related to a 7 point decrement in IQ of their offspring at 7 years of age (17). Learning problems were also reported to be associated with the binge pattern of drinking (more than 75g alcohol on one or more occasions). Another report studied neonatal behaviour in the children of 3 groups of women:- those who drank c. 360g alcohol per week throughout pregnancy; those who drank 420g alcohol per week but stopped drinking in the second trimester; and those who were abstainers (18). infants exposed to ethanol at any time during gestation had significant alterations in reflexive behaviour, less mature motor behaviour and an increased activity level in comparison with unexposed infants (p value range 0.05 to 0.01 according to activity). Infants whose mothers stopped drinking in the second trimester performed better than those whose mothers continued to drink throughout pregnancy. These results indicate that damage to the fetal CNS can occur when exposed to ethanol throughout pregnancy and that exposure during only the early part of pregnancy also seems to produce measurable adverse effects. Landesman-Dwyer and coworkers (19) carried out a prospective study comparing the offspring at 4 years of age of 2 groups of women - those who drank c. 105 g per week during pregnancy and those who drank approximately 14g per week. At four years of age, the offspring of mothers in the former group were reported to be less attentive and compliant with orders than those whose mothers were in the latter group. Maternal ethanol consumption during pregnancy has also been associated with adverse effects on developmental indices of the offspring at 13 months (20). Decreases in verbal comprehension and spoken language scores of the infants were associated with mothers who consumed on average c. 130g ethanol per week during pregnancy (number of subjects 84).

12. In contrast to the previous studies, another study has reported that there was no significant relationship between maternal ethanol consumption during pregnancy (605 women grouped into 24% abstainers; 50% consuming less than 105g per week; 12% consuming 105~210g per week; 5% consuming 210-315g per week; 4% consuming 315-420 g per week and 4% consuming greater than 420g per week) and birthweight, length, head circumference or neonatal behaviour (21).

Paternal Effects

13. Testicular atrophy, infertility and decreased libido are all associated with alcoholism (22). Furthermore, the data indicate the possibility of paternally mediated ethanol effects inoffspring (23), probably as a consequence of damage to sperm (24). Data concerning molecular changes to spermatic DNA and other genotoxic effects to germ cells caused by ethanol have been reviewed by the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment and are not considered here.

Female Fertility

14. There is an association between ethanol consumption and ovulatory infertility (25). A small but significantly increased risk of infertility was observed for women reporting an ethanol intake of approximately 100g per week (odds ratio 1.3, 95% confidence interval LO-1.7, $p<0.05$) which rose rapidly when ethanol intake increased above this level (odds ratio 1.6, 95% confidence interval LI-2.3, $p<0.05$) in comparison with those who did not drink. Thus advice on ethanol intake in relation to pregnancy and reproduction should also include advice to women who wish to become pregnant.

Animal Data

15. Animal research has been able to demonstrate that ethanol administration is teratogenic in several animal species in the absence of other potentially confounding variables associated with human studies. However, animal studies can be limited in that the high levels of ethanol necessary can severely compromise nutritional status of the animals. Most physical anomalies associated with ethanol exposure in humans have been duplicated in animal models when blood ethanol levels are high (400-800 mg/dl) (26, 27). Because rodents metabolise ethanol more quickly than humans, the dose must be higher in order that the same blood ethanol levels are attained. For this reason and the compromised nutritional status already mentioned, the animal data are not useful in identifying threshold levels of ethanol intake associated with adverse pregnancy outcomes.

Alcohol and Predisposition

16. Genetic polymorphism exists at the alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) gene loci, the two principal enzymes involved in ethanol metabolism and excretion (28). Ethanol is also oxidised via a microsomal ethanol oxidising system (cytochrome P450 2E1), but this is considered to be a minor route. Because of the genetic variation, some women and fetuses will metabolise ethanol and/or acetaldehyde faster than others, which may help to explain the variability in adverse pregnancy outcome observed with similar maternal ethanol intakes.

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