

Evidence Regarding the Level of Alcohol Consumption Considered to be Low-Risk for Men and Women

**By Eric Single, Mary Jane Ashley, Susan Bondy, James Rankin and Jürgen Rehm,
with the assistance of Maureen Dobbins**

**Prepared for the Australian Commonwealth Department of Health and Aged Care
Final Report—October 1999**

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Evidence Regarding the Level of Alcohol Consumption Considered to be Low-Risk for Men and Women

1. Introduction: background and goals of the literature review

This report comprises an update and summary of the best available evidence regarding low-risk levels of alcohol consumption. Its purpose is to provide background documentation and justification for the development of new drinking guidelines by the National Health and Medical Research Council (NHMRC). The Australian Commonwealth Department of Health and Family Services has contracted with Single and Associates, Research Consulting, Ltd., to undertake an examination of the evidence on alcohol, health and safety in the light of recent research and international developments. The project was carried out by a team of researchers consisting of Eric Single, Ph.D. (Canada), Mary Jane Ashley, M.D. (Canada), Susan Bondy, Ph.D. (Canada), Maureen Dobbins, Ph.D. (Canada), James Rankin, M.B., FRACP, FAFPHM (Australia) and Jürgen Rehm, Ph.D. (Germany).

A central requirement of the report was to review the available literature on:

- alcohol, health and safety in light of recent research and international developments;
- patterns of alcohol consumption;
- harms and benefits of alcohol consumption;
- the varying effects of alcohol consumption on different population groups;
- alcohol and pregnancy--for example, the effects of alcohol on the developing fetus; and
- 'binge drinking' and 'alcohol free days'.

Information on these topics was identified and collected primarily from the peer-reviewed scientific literature. Reviews of evidence underpinning low-risk drinking guidelines on alcohol consumption in other countries were also collected. In preparing this report, the information from the literature was evaluated with respect to the level, quality, relevance and strength of evidence, in accord with the *NHMRC Guidelines for the development, implementation and evaluation of Clinical Practice Guidelines*. As detailed below, the topics are discussed in three sections: acute versus chronic harms attributable to alcohol use and misuse, and the benefits of alcohol consumption.

The report is organised as follows. First, the methodology used in the review is presented. Then drinking guidelines in other countries are summarised. The evidence concerning the relationships of levels of drinking to various adverse health outcomes is considered next, organised into two major sections on chronic and acute consequences. Chronic consequences include some aspects of cardiovascular disease, cancer, liver cirrhosis and other chronic harms. Acute harms consist primarily of prenatal effects and alcohol-related accidents. The following section concerns potential beneficial effects of

alcohol consumption, specifically ischemic heart disease (IHD), stroke, peripheral vascular disease, diabetes, cholelithiasis and cognitive benefits. Patterns of consumption are then discussed as they relate to both harm and benefits. In the final section the impact of alcohol consumption on total mortality is considered. The report concludes with a discussion of the implications of this review for drinking guidelines in the Australian context, with particular attention to the impact of alcohol consumption on different population groups or in different situations.

This report was prepared for the Commonwealth Department of Health and Family Services, and the Working Party on Drinking Guidelines of the NHMRC in particular. A spring binder containing photocopies of all key studies referred to in the review was provided with it.

2. Methodology

2.1 Search strategy

The search methodology was based on previous in-depth strategies developed and utilised by the project team to review the alcohol consumption literature on several recent occasions (for example, (Ashley et al., 1997; Bondy et al., 1999); Bondy et al., forthcoming). These reviews assessed the implications of the alcohol consumption literature for the development of alcohol policies, guidelines on low risk drinking for individual consumers and for public health strategies that addressed overall consumption in populations.

This review includes evidence from epidemiological, clinical, biochemical, physiological, psychological and sociological research. The retrieval of published literature included searches on Medline, Psychlit, and the NIAAA databases, from the time the previous searches were conducted by the project team beginning in 1996 to the present. Key words and text word entries used in conducting the on-line searches included "guidelines and alcohol", "alcohol drinking and guidelines", "alcohol and morbidity or mortality or disability or disease", "alcohol and accidents or injury or productivity", "alcohol and binge", "binge drinking" and "alcohol and ethnicity". As well, the names of prominent authors in the field were searched from 1996 to the present. Expert informants in this area were also contacted to identify unpublished articles and reports from numerous countries. The reference lists from retrieved articles were examined for citations dated before 1996 that had not been previously reviewed by the project team. Additional searches were also carried out by the members of the project team who took the lead in reviewing the literature regarding specific topics and alcohol-related consequences. These searches typically involved text word searches using alternate forms (for example, "cancer", "carcinogen", "neoplasm" or similar words in conjunction with "alcohol" or "ethanol").

More than 5000 titles were examined for relevance to this project's objectives, and over 800 articles were compiled by the team members for review, in addition to

many articles already in possession of the research team. A bibliography of selected titles, authors and references for key studies is attached as Appendix B.

2.2 Exclusion criteria

This review focused on more recent research. The following criteria were discussed by all authors, and then used as a guide in determining whether to include studies in the review (English et al., 1995):

Reason for exclusion	Explanation and/or examples
Restricted study population	The study was carried out in a population which makes it difficult to generalise to the entire population (for example, a cohort of persons suffering a particular disorder)
Inappropriate comparison group	Control group is contaminated by a high exposure to the risk factor under consideration or other factors related to the condition.
No quantitative exposure measure	Exposure is alcoholism rather than alcohol consumption, or alcohol consumption is undefined or has poorly defined nominal categories (for example, "regular" vs. "non-regular drinkers"), or limited to frequency of consumption (without considering quantity), or measured in a manner not representative of general exposure (for example, with meals or in last 24 hours)
Data too old	As this literature review builds on prior work, unless there is a compelling reason to include it (for example, a high quality study not included in English et al., 1995 or Bondy et al., 1999), studies reported prior to 1996 are generally not included.
Duplication of study	A study is reported in more than one paper, and is already included in the review. A second important way in which a study may be duplicated is when it has already been included in the earlier review conducted by members of the project team—these studies are included in the review but not re-examined in detail.
Sample size too small	Insufficient number of cases ($N < 20$).
Inadequate control for confounding variables	An important confounding variable is not controlled for in the study (for example, smoking not controlled when examining impact on heart disease, or only bivariate relationships and relative risks presented).
No age- or gender- specific data presented	Where this is unacceptable (i.e., where condition under review is strongly related to age or gender)

2.3 Assessing the quality of evidence

The exclusion criteria include some items that involve the assessment of quality of evidence. In order to further assess the quality of evidence regarding particular aspects of this literature review, a standardised assessment form was developed for use by the project team (Appendix A). Time and resources did not permit a complete quantitative analysis of the results of this assessment tool, and the literature review did not require the type of quantitative results that underpin a meta-analysis. But it was considered important that the project team assess studies in a similar manner, and the use of this standardised assessment form improved the comparability of different parts of the review. Because of the wide range of specific issues being addressed (from biological mechanisms to population-level impact), as well as the wide range of disciplines involved and study populations represented in the literature, a fully objective approach was not feasible.

In a meta-analysis, it is common to test inter-observer reliability in assessing the quality of research literatures. While time and resources did not permit a thorough examination, inter-observer reliability of the assessment tool was examined in the following manner. Up to ten of most influential studies in six major categories of conditions related to alcohol use were selected. The six major categories, chosen on the basis of their contribution to overall alcohol-attributed mortality, were: (1) cancer of the lip, oropharyngeal cancer, oesophageal cancer or laryngeal cancer; (2) liver cancer; (3) breast cancer; (4) alcohol dependence syndrome; (5) liver cirrhosis; and (6) motor vehicle accidents. For each of these major disease or trauma categories, two project team members filled out the study assessment forms for each of up to ten of the most influential studies. The results have not been tabulated but there was clearly substantial agreement regarding the assessment of quality of evidence. Disagreement over the quality of evidence was rare and in all instances resolved after discussions within the project team.

There are several instances where only a small number of non-comparable publications were found on specific topics (for example, studies of thresholds for fetal damage in non-heavy drinking women). In such instances we have chosen to discuss the findings, with appropriate caveats, despite the lack of more conclusive evidence. However, the reader should bear in mind that publication biases may exist in such cases and that the conclusions of future reviews may be different.

2.4 Assessment of causality

Following the procedure described in English et al. (English et al., 1995), the evidence of causality between alcohol consumption and physiological effects (including both harmful and protective effects) is assessed in accordance with the following guidelines from IARC (1988), also used in the *NHMRC Guidelines for the development, implementation and evaluation of Clinical Practice Guidelines*:

1. **Sufficient evidence of causality:** In the reviewers' opinion, a causal relationship has been established between alcohol consumption and the disease or injury. The evidence indicates that an association (positive or negative) exists between alcohol consumption and the disease or injury in which chance, confounding variables and other bias can be ruled out with reasonable confidence.
2. **Limited evidence of causality:** An association (positive or negative) has been observed between alcohol consumption and the disease or injury for which a causal interpretation is considered to be credible, but chance, confounding variables or other bias cannot be ruled out with reasonable confidence.
3. **Inadequate evidence of causality:** The available studies are of insufficient quantity, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal connection.

4. Evidence suggesting lack of causality: There are several adequate studies covering the full range of levels of alcohol consumption in the population that show the lack of a relationship (positive or negative) between alcohol consumption and the disease or injury. This assessment is inevitably limited to diseases and injuries, levels of consumption and lengths of observations covered by the available studies, and the possibility of very small risks at the levels of exposure studied can never be excluded.

2.5. General methodological considerations on the epidemiological evidence

Most of the studies reviewed stem from epidemiology, often using a cohort or case-control design. In these designs, the following points generally apply:

- 1) Alcohol is mostly measured by few questions, either separating frequency of drinking and quantity per occasion or combining them into one modified frequency question (Rehm, 1998a; Rehm, 1998b). As a result, data on patterns of drinking and health outcomes are limited, as typical questions in epidemiological surveys cannot be used to measure patterns (see also Rehm, in press). On the other hand studies with good alcohol assessment are mostly cross-sectional, or baseline assessment was very recently so that no longitudinal results can yet be reported. Finally, research has shown that such questions often lead to underestimates of the true consumption.
- 2) The relationship between alcohol consumption and outcome is often based on outcomes assessed at follow-up regressed onto several variables from baseline assessment. These procedures must assume that the baseline variables are stable over time, or that they somehow are good indicators of the postulated theoretical relationship. For example, in assessing the relationship between volume of consumption and liver cirrhosis, it must be assumed that heavy consumption persists after baseline and is a good indicator for overall tissue exposure which is the theoretical determinant. Work on the regression dilution bias has shown that the size of the real effects are often underestimated by such procedures (Clarke et al., 1999), if the exposure is somewhat constant over time.
- 3) The relationship between alcohol consumption and outcomes must be assumed to be fairly constant across cultures if Australian guidelines are to be based on epidemiological studies from other countries. While this may be justified with biologically based relationships, such an assumption is more problematic with accidents and injuries as outcomes, which are much more culturally dependent.

All of these points indicate that the results of our overview of the literature will have limits with regard to the precision of the derived recommendations. For the reasons laid out above, no review will be able to give exact limits in decimals of grams or even grams per week or per occasion.

3. Drinking guidelines in other countries

In 1992, the NHMRC published amended guidelines for safe drinking, recommending that men not exceed 4 units (40 grams) of alcohol per day and that women

limit their consumption to 2 units (20 grams) per day (National Health and Medical Research Council, 1992). The guidelines included the recommendation to avoid binge drinking and individual risks were identified. In addition, special guidelines were detailed for specific situations, such as hazardous situations, when operating machinery or in the context of pregnancy. A summary table of drinking guidelines was included which presented drinking guidelines published by a variety of institutions or authorities from 1870 to the 1980s (NHMRC, 1992: Figure 3). This information is updated in Table 1, which presents recommendations regarding low-risk drinking by various institutions or authorities published in the 1990s. The information was obtained from the literature search as well as from responses to special requests for guidelines sent by the NMHRC to selected organisations and experts in other countries.

It may be seen that throughout the 1990s numerous health agencies, medical associations and individual experts have produced recommendations on low-risk drinking. There is considerable variation in recommended levels of daily drinking. The NHMRC guidelines fall inside the range of levels advocated elsewhere in the world. The volume of alcohol recommended by the NHMRC as low-risk (40 g for males and 20 g for females per day) is lower than the benchmarks promoted in New Zealand (1995: 60g for males; 40g for females) and in the Netherlands (1991: 40g for men and women). The 1992 NHMRC recommendation are similar to those proposed in Italy (1995: 40 g/day for men, less for women) and somewhat higher for men than those currently recommended in the U.K. (1995: 32g for males; 24g for females). On the other hand, the NHMRC currently recommended levels were considerably higher than recommendations in the U.S. (which generally recommend no more than 2 drinks or 24 g/day for men and 1 drink or 12 g/day for women), Canada (1997: 2 drinks or 27 g/day for men and women, with lower weekly limits for women) and Sweden (1997: less than "10 to 20" g/day for men and women).

While there is still some variation in recommended safe levels of daily drinking in different guidelines around the world, it would appear that the range of variation has narrowed somewhat over time. A further general trend is that there appears to be a growing acceptance that moderate drinking (within the recommended guidelines) can lead to lower risk of IHD. There are two notable exceptions where there remains an official reluctance to accept the evidence of a beneficial effect. First, the Swedish Medical Research Council (1997), reviewed the evidence of adverse effects of alcohol in considerable detail but dismissed the evidence of a beneficial impact without citing any studies (p. 373S): "It is possible that a moderate alcohol intake has certain positive medical effects. However, the causal relationships are not sufficiently clear. Complete or almost complete abstention from alcohol can therefore not be considered a risk". Second, the U.S. National Institute on Alcoholism and Alcohol Abuse (National Institute on Alcohol Abuse and Alcoholism), in an official commentary on new dietary guidelines, still considers the evidence of a protective effect against IHD to be inconclusive (Gordis, 1999), although the benefits were recognised in another document from the same agency (National Institute on Alcohol Abuse and Alcoholism, 1992).

Thus, there is still some difference of opinion regarding specific daily consumption levels considered to be low-risk, and with regard to the conclusiveness of a beneficial impact on IHD. Nevertheless, it would appear that there is more convergence than divergence among currently available guidelines on low-risk drinking. The majority of guidelines include these elements:

- specification of the maximum amount of alcohol consumed in one day, ranging from approximately 20 to 60 grams of ethanol, based on considerations of increased risk of acute consequences and tolerance;
- provision of limits on the amount of alcohol consumed over a week, based on considerations of potential long-term health effects in both men and women;
- specific warnings against consuming large amounts per occasion; and
- the identification of specific subgroups and situations in which the risks are greater, and where drinking alcohol is contraindicated.

4. Chronic harms of alcohol consumption

4.1 Cardiovascular Disease

In 1997 cardiovascular disease, that includes both ischemic heart disease and stroke, accounted for more deaths among Australians than any other group of diseases (129,350). However, cancer was the leading single cause of death (35,316), followed by ischemic heart disease (29,051) and stroke (12,133) (Australian Bureau of Statistics, 1999).

The role of alcohol, as both a risk and protective factor for cardiovascular diseases has been studied extensively and reviewed in numerous government reports (United States Department of Health and Human Services, 1990; United States Department of Health and Human Services, 1994; United States Department of Health and Human Services, 1997; UK Inter-Departmental Working Group, 1995; United States Department of Health and Human Services, in press); and review papers (Shaper, 1990b; Shaper, 1990a; Beaglehole and Jackson, 1992; Rimm et al., 1992; Criqui, 1996a; Criqui, 1996b; Hennekens, 1996; Svardsudd, 1998; Waldenstrom, 1998; Rosenqvist, 1998; Rimm and Stampfer, 1995) and a comprehensive research monograph (Zakhari and Wassef, 1996). The role of low (responsible), harmful and hazardous levels of alcohol consumption in hypertension, IHD, cardiac arrhythmia and stroke (cerebrovascular disease) was also examined in a wide-ranging meta-analysis of the health impacts of alcohol (English et al., 1995; Holman et al., 1996). Mechanisms by which alcohol may exert damaging or protective effects on the cardiovascular system also have been reviewed (for example, United States Department of Health and Human Services, 1997; Zakhari and Wassef, 1996; Zakhari, 1997; Freidman, 1998).

The findings concerning IHD are presented in detail in Section 6.1 below. Briefly put, the evidence now supports four key conclusions that must be taken into account in the development of low-risk drinking guidelines for in countries where IHD is a significant cause of death:

1. Alcohol appears to be protective against IHD in middle-aged and older men and women. Although the protective effect extends across the continuum of alcohol consumption, most, if not all, of the reduction in risk is realised with low to moderate levels of consumption (less than 1 oz or 23 g/day of absolute alcohol).
2. In countries where the risk of IHD is high, the protective effect of alcohol against IHD may be limited to certain population subgroups.
3. Most of the protective effect appears to arise from the ethanol component of alcoholic beverages and not from other components. If specific beverages, such as red wine, do confer additional benefit, this effect is small.
4. Pattern of drinking is an important determinant of the risk and protective effects of alcohol with regard to IHD.

It will also be seen that there is evidence that low level alcohol consumption may offer some protection against stroke and peripheral vascular disease, and there is growing evidence of a protective effect against diabetes and cholelithiasis (gallstones).

In this section, the negative effects of alcohol on cerebrovascular disease (stroke), hypertension and other cardiovascular disease are considered.

4.1.1 Cerebrovascular Disease (Stroke): While heavy alcohol consumption is a risk factor for stroke, the weight of evidence suggests that low level alcohol consumption may offer some protection against stroke, particularly ischemic stroke. Therefore, the evidence regarding the relationship of alcohol consumption to cerebrovascular disease (stroke) is presented in Section 6.1.2 below with the discussion of the beneficial effects of alcohol consumption.

4.1.2 Hypertension: Because hypertension is a major risk factor for stroke, as well as for coronary heart disease, it is important to comment on the relationship between alcohol consumption and blood pressure. In Canada a national consensus panel recently conducted an extensive review of the evidence concerning this relationship (Campbell et al., 1999). This panel concluded that observational studies have almost uniformly demonstrated an association between heavy alcohol consumption and increased blood pressure in both men and women. However, with regard to lower levels of alcohol use in comparison with no use, findings are mixed. In many studies either no effect or a small reduction in blood pressure was found, while in others a linear positive relationship was noted across the continuum from no use to heavy alcohol use. In randomised controlled trials to determine the effect of reductions in alcohol consumption on blood pressure in both normotensive and hypertensive persons, the findings consistently indicated that reductions in alcohol consumption were associated with reductions in blood pressure, although not all of these reductions were statistically significant. These findings are consistent with other comprehensive reviews (Camargo and Rimm, 1996b).

In a meta-analysis of five cohort studies and six cross-sectional surveys it was concluded that hazardous and harmful levels of consumption cause hypertension in both men and women (English et al., 1995; Holman et al., 1996). Low (responsible) drinking

was not associated with hypertension in men, while in women it conferred a small protective effect.

It has been suggested that drinking pattern may be an important determinant of blood pressure independent of average consumption. Russell and colleagues showed that in low level alcohol consumers blood pressure was more likely to be influenced by the frequency of use than by the quantity of alcohol consumed (Russell et al., 1991). These investigators pointed out that the standard practice of averaging alcohol consumption may obscure important effects of drinking frequency on health.

In summary, harmful/hazardous drinking increases the risk of hypertension. To reduce blood pressure in the population at large the Canadian Consensus Panel (Campbell et al., 1999) recommended that alcohol consumption be in accordance with the Canadian low-risk drinking guidelines. That is, healthy adults who choose to drink should limit alcohol consumption to 2 or fewer standard drinks per day (27 g or less), with consumption not exceeding 14 standard drinks per week in men and 9 standard drinks per week in women (Bondy et al., 1999).

4.1.3 Other Cardiovascular Disorders: It is well-established that both the acute and chronic consumption of large amounts of alcohol can adversely effect the structure and function of the heart. In alcoholics and heavy drinkers this damage manifests itself in clinical entities such as cardiomyopathy, “holiday heart” syndrome, cardiac arrhythmias, congestive heart failure and sudden death (Regan et al., 1981; Alderman and Coltart, 1982; Greenspon and Schaal, 1983; Lands and Zakhari, 1990; Rubin and Doria, 1990; Arria and Van Thiel, 1992; Shanmugam and Regan, 1996; United States Department of Health and Human Services, 1997; Rosenqvist, 1998; Puddey et al., 1999a; Waldenstrom, 1998; Puddey et al., 1999b). Further, the adverse effects of acute heavy drinking have been demonstrated experimentally. For example, doses of 4 to 6 ounces of spirits over intervals of up to 2 hours were shown to adversely affect contraction of heart muscle and diminish cardiac performance (Regan et al., 1981). These doses resulted in BAC levels around the legal limit (0.08%). The effects were described as “mildly intoxicating”. In another experiment, acute heavy alcohol consumption was shown to increase silent myocardial ischemia in patients with stable angina pectoris (Rossinen et al., 1996). Women may be more sensitive to alcohol than are men with regard to development of both alcoholic cardiomyopathy and other myopathies (Urbano-Marquez et al., 1995). Pattern of drinking may be an important determinant for some clinical outcomes, such as arrhythmias and sudden death (Puddey et al., 1999a).

With regard to moderate drinking, (Freidman, 1998), in an extensive review of the effects of alcohol on the cardiovascular system, concluded that the ingestion of one to two drinks can affect heart rate, blood pressure, cardiac output, myocardial contractibility, and regional blood flow. He noted that although these actions generally are not considered to be clinically important, in the presence of cardiovascular disease they might result in transient unfavourable changes in haemodynamics.

4.2 Cancer

The first purpose of this section is to define the current status of evidence of a causal association between alcohol use and specific cancers associated with alcohol. The second is to provide a critical discussion of what these data tell us in terms of defining levels and patterns of alcohol intake associated with low risk of cancer.

The potential role of beverage alcohol intake in the development of human cancers has been the subject of structured critical reviews at several points over the last 15 years. Important examples of such overview was the pivotal International Agency for Research on Cancer report of 1988 on the evidence of alcohol carcinogenesis (IARC, 1988), and the overview led by Sir Richard Doll (Doll et al., 1993). English et al. (1995), systematically examined evidence for cancers of the upper aerodigestive system, digestive organs, female breast, female reproductive system, bladder and kidneys. In addition to these, several meta-analyses focusing on individual sites have also appeared (for example, Longnecker, 1994; Smith-Warner et al., 1998). Also, various governments routinely provide overviews and updates to this literature, even if these do not include formal critical appraisal or quantitative summary (United States Department of Health and Human Services, 1997).

This overview updates earlier summary reports, but does not present meta-analytic summaries of the observed associations. Rather, new studies which present relative risk data have been identified where they were located, but preferential attention was given to reports pertaining to moderate drinking, lower thresholds of risk, patterns of drinking, and information on underlying causal mechanisms that might be relevant in identifying patterns of levels of drinking associated with risk.

4.2.1 Oropharyngeal and oesophageal cancer: Specific site of upper aerodigestive tract including the mouth, pharynx, larynx and oesophagus, are among those for which the evidence of a causal association with alcohol is most clear and long-standing. Causal association were concluded by both the 1988 IARC report and Doll (1993). English et al., (1995), similarly concluded there was sufficient evidence for a casual role of alcohol in cancers of the oropharynx and oesophagus. This evidence is strongly supported by research directed toward disentangling the role of potential confounders, notably tobacco use (La Vecchia and Negri, 1989; Doll et al., 1993) as well as dose-response, both in terms of individual consumption and associations with alcoholic beverages of differing strength (Doll et al., 1993) A recent report also shows a positive association between dysplasia of the oral epithelium and beverage types of increasing alcohol concentration (Jaber et al., 1998).

Possible mechanisms for alcohol-related carcinogenesis in the upper digestive system pertain to direct contact of alcohol, or acetaldehyde with local tissues (Doll et al., 1993; Garro and Lieber, 1992; Doll, 1998). Evidence of an association between alcohol-containing mouthwashes and oral cancer also supports possible mechanisms involving direct contact (Doll et al., 1993; Elmore and Horwitz, 1995). Alcohol has been found to have an association with oral epithelial dysplasia that is both independent of and synergistic with tobacco use (Jaber et al., 1998). A recent report by Gronbaek et al.

Examines the effect of different beverages, alone and in combination (Gronbaek et al., 1998). They found an association between alcohol and cancers of the oropharynx and oesophagus within ranges of 'moderate' drinking, but only for beer and spirits, not wine.

Ethanol, although not directly carcinogenic, is cytotoxic (IARC, 1988). Direct contact of cells in the mouth and oesophagus to alcohol may lead to a process of cell death and proliferation which may increase the likelihood of carcinogenic mutations. As well, the production of acetaldehyde through alcohol dehydrogenase activity of bacteria in the mouth and upper digestive system may be important in carcinogenesis. Acetaldehyde is found in the mouth after ethanol is consumed (Homann et al., 1997a). Acetaldehyde applied to the epithelium of the upper digestive system in animals also causes hyperplasia and hyperproliferation (Homann et al., 1997b).

It has been suggested, although not directly demonstrated, that where alcoholic beverages are taken with food (most often noted for wine) the ethanol is prevented from remaining in the mouth, and oesophagus, where it can be acted upon by oral bacteria, thus explaining the lower relative risks associated with wine (Gronbaek et al., 1998) and observed in studies conducted in primarily wine-drinking populations (Garidou et al., 1996).

4.2.2 Cancers of the stomach, pancreas, and liver: These cancer sites are discussed together because each shares a common feature in terms of level of current evidence of a causal relationship with alcohol. For each of these organs, alcohol and heavy drinking are clearly associated with inflammatory changes. This inflammation may precipitate hyperplasia and neoplastic changes, particularly in the presence of co-carcinogens (Garro and Lieber, 1992; Doll et al., 1993). The intermediate link of inflammatory change is more generally accepted for cancer of the liver, but considered only plausible for cancers of the stomach and pancreas (Doll et al., 1993). The effect of alcohol on liver metabolism may also have an indirect effect on cancer risk of the digestive organs, as a result of reduced clearance of other carcinogens for the system (Anderson et al., 1996; Chhabra et al., 1996). The importance of hepatitis B infection as a possible confounder in the association between alcohol and liver cancer has been considered in some studies, with inconsistent results thus far (Thomas, 1995).

IARC (1988) concluded alcohol caused liver cancer based on the consistent, monotonic association, and biologic plausibility. Cirrhosis is a well-documented consequence of chronic heavy drinking and is known to be associated with cancer. English et al. Concluded there was limited evidence of a causal association and noted that alcohol is toxic to liver cells in the absence of cirrhosis, and that alcohol intake has a dose-response relationship with liver cancer in patients without cirrhosis (English et al., 1995).

A thorough review considering whether alcohol has a direct causal role in liver cancer (Farber, 1996) concluded there is no convincing evidence that alcohol is a promoter of liver cancer. It is more likely that it plays an indirect role, through cirrhosis,

as a promoter of tumors, and through possible metabolic effects on clearance of other carcinogens.

Case-control or cohort studies on primary liver cancer, that do not focus on patient cohorts with existing cancer or cirrhosis, and published from 1995 forward, are rare. A cohort study from Nagasaki, Japan, found a slight positive association with total alcohol intake (Goodman et al., 1995).

The link between alcohol use and chronic gastritis is clearly shown, although progression from chronic gastritis to neoplasia is less well understood and probably involves other factors in addition to alcohol (Bode and Bode, 1997; Bode and Bode, 1992). A similar situation may exist for pancreatic cancer. While alcohol is a cause of chronic pancreatitis, the link between alcohol and pancreatic cancer is probable but unproven (Doll et al., 1993).

The meta-analysis of English et al., (1995) identified only one study of alcohol and gastric cancer that controlled for smoking, and concluded that evidence of an association was insufficient to draw conclusions. Another recent case control study (Gammon et al., 1997), including 261 cases of adenocarcinoma of the gastric cardia, found no association with total alcohol intake, or for beer, wine or spirits separately, after controlling for smoking. The interaction between alcohol intake and smoking in the development of gastric cancers is not well understood, and the possibility of a synergistic interaction of these risk factors (possible with diet as well) cannot be dismissed.

With respect to pancreatic cancer, Doll concluded that although alcohol intake is associated with calcifying pancreatitis, a direct role in pancreatic cancer was unlikely (Doll et al., 1993). As well, dose-response relationships between alcohol and pancreatic cancer risk across studies were inconsistent. Recently, a large cohort of American women (Harnack et al., 1997), reported a modest positive (insignificant trend) association between alcohol intake and pancreatic cancer risk, after controlling for age and smoking. An Italian case-control study found no association after adjusting for confounders (Soler et al., 1998).

4.2.3 Cancers of the colon and rectum: Authoritative reviews of studies of alcohol and colorectal cancer have found evidence of a weak but fairly consistent positive association, particularly for rectal cancer (Doll et al., 1993; Longnecker, 1992; Longnecker et al., 1990; Seitz and Poschl, 1997; Seitz et al., 1998a; Seitz et al., 1998b; Simanowski et al., 1995). These reviews tend to agree in their conclusion that a positive dose-response association exists between alcohol intake and colorectal cancer risk, but that there is inadequate evidence of a direct causal role. (IARC, 1988; Doll et al., 1993; Longnecker, 1992; English et al., 1995).

The most recent reports are not entirely consistent in their findings. A recent cohort of Finnish men (Glynn et al., 1996) found a positive trend for alcohol intake within smokers, and an estimated increased risk of 17% with each additional drink. The American Nurse's Health Study showed a positive association for colon cancer

(Giovannucci et al., 1995). A cohort of Japanese-American men also reported a strong positive association for rectal cancer (Chyou et al., 1995). However, an Italian case-cohort study reporting on cancers of colon and rectum by tumour site, failed to show any dose-response relationships (Tavani et al., 1998).

Alcohol may be important as a cofactor in tumours associated with smoking (Yamada et al., 1997) and poor diet, including low folate intake (Boutron-Ruault et al., 1996; Kato et al., 1999). Alcohol has been associated with the formation of adenomatous polyps, a pre-cancerous lesion (Kearney et al., 1995), and may play a role in later stages of tumour growth (Boutron-Ruault et al., 1995). One recent line of work in this area regarding biological mechanisms is focused on the role of acetaldehyde (a first metabolite of ethanol) and its production in the gut by intestinal bacteria (Seitz et al., 1998a).

4.2.4 Cancer of the breast: A rapid expansion of research on the association between alcohol intake and cancer of the female breast has taken place in recent years. Given that breast cancer is the most common cancer among Australian women and a significant cause of mortality, this literature is of great significance in terms of the overall public health impact of alcohol use.

An association between alcohol and breast cancer has been suspected for two decades (Rosenberg et al., 1993; Henderson et al., 1989). Many of the earlier overview, particularly those prior to 1995, concluded that there was insufficient evidence of a causal relationship (IARC, 1988; McPherson et al., 1993; Rosenberg et al., 1993; Schatzkin and Longnecker, 1994).

A series of meta-analyses and other overviews have appeared in recent years. Most have found a modest, but inconsistent and linear association with risk (Longnecker, 1992; Longnecker, 1994) although one such synthesis found a greater association with heavy drinking (Howe et al., 1991). The 1994 meta-analysis by Longnecker indicated a RR of 1.38 associated with 3 drinks per day. English and colleagues reviewed 7 cohort studies and 22 case-control studies and identified a moderately strong and consistent dose-response association between alcohol intake and breast cancer risk (English et al., 1995). In their overview, Hunter and Willett describe the evidence as showing alcohol to be “probably the best-established dietary risk factor for breast cancer” (Hunter and Willett, 1996: 63).

A critical review and meta-analysis involving two of the authors of this report concluded that there is sufficient evidence to consider alcohol a cause of breast cancer (Single et al., 1999). Another recent meta-analysis examined seven prospective studies (Smith-Warner et al., 1998) and included a closer examination of the dose-response curve. In the analysis presented which used alcohol intake as a continuous regression term, the risk of breast cancer increased nearly 10% with each additional 10g of alcohol per day. In a categorical analysis, consumption of from 30 to less than 60g per day was associated with a relative risk of 1.41 (CI: 1.18-1.69) relative to non-drinkers, with limited evidence of a similar relative risk for intakes of 60g per day or more.

Very few recent publications have been identified presenting RR data. Enger and colleagues presented data from two American case-control studies and reported a significant relative risk of 1.7 for drinkers consuming greater than or equal to 27g/day versus less (Enger et al., 1999). Farraroni and colleagues reported data on an Italian case-control study in women described by the authors as relatively light drinkers. They found a significant positive trend with increasing levels of intake (Ferraroni et al., 1998). Zhang and colleagues reported contrasting data in women in the Framingham study, in which the highest category of alcohol quartile of alcohol intake reported on was greater than or equal to 15g/day (Zhang et al., 1999). These authors found no association between alcohol intake and breast cancer incidence.

A number of possible causal mechanisms have been discussed with link ethanol to carcinogenesis in breast tissue (Longnecker, 1995; Longnecker and Enger, 1996; Ringborg, 1998; Seitz et al., 1998b; Singletary, 1997; Thomas, 1995; Wright et al., 1999) although for none of these is there definitive evidence from animal or human data (Singletary, 1997). Nor is there consensus as to the most important mechanisms.

One proposition for causal mechanism for alcohol in breast cancer is through hormonal influences (Longnecker, 1995). Alcohol has been reported to increase estrogen levels and bioavailability of estrogen (Reichman et al., 1993). The hormonal effects of alcohol remain unclear, as is the question of whether alcohol is more closely associated with premenopausal breast cancer (Schatzkin and Longnecker, 1994). Some studies have found no difference in the association between alcohol intake and cancer risk when comparing pre-menopausal and post-menopausal disease. A very recent publication by Enger found alcohol to be most closely associated with estrogen-receptor and progesterone-receptor positive primary tumours in post-menopausal women, and not associated with cancer risk in pre-menopausal women (Enger et al., 1999).

Other evidence corroborating a possible role of alcohol in mediating hormonal effects includes the observation that breast cancer risk associated with postmenopausal estrogen use (hormone replacement therapy) may be increased among alcohol users (Zumoff, 1997; Zumoff, 1998). Such an association was observed in the Women's Health Study (Colditz et al., 1990b) and one other women's cohort (Gapstur et al., 1992), but not in a third (Friedenreich, 1994). Experimental administration of alcohol along with estrogen treatment results in markedly increased estrogen levels (Ginsberg et al., 1996).

Another possible mechanism, not exclusively relevant to breast cancer, pertains to circulating levels of acetaldehyde and the formation of reactive oxygen species chemicals, that could plausibly be associated with the nature of cellular changes seen in breast cancer (Wright et al., 1999).

Epidemiological studies have also focused on the timing of exposure, as this is related to the role of alcohol as an initiator or promoter. Two very recent case-control studies found intensity of drinking to be associated with breast cancer more strongly than duration of exposure (Bowlin et al., 1997; Levi et al., 1996). Alcohol use in later years, closer to the age of diagnosis, also is often found to have the closest association, and it

has been suggested that alcohol may act as a late-stage promoter of breast tumours (Swanson et al., 1997), although method effects (for example, more recent drinking is recalled with less random error) and other possible biases have not been ruled out. Alcohol may also have a complex effect in potentiating various other risk factors (Singletary, 1996; Singletary, 1997).

4.2.5 Summary of conclusions regarding alcohol consumption and risk of cancer across different sites: Even at the outset of this report, sufficient evidence existed to conclude that alcohol consumption is associated with an increased risk of cancer overall (IARC, 1988). Pre-existing authoritative overviews have demonstrated that alcohol has a causal role in cancer, at a minimum for the mouth, pharynx, and oesophagus, and that consistently positive associations are observed for other important cancer sites, including colorectal and breast cancer.

In terms of the shape of the association, a monotonic positive association is observed in most instances of alcohol and cancer. Because of the high incidence of colorectal and breast cancers in Australia, as in most developed countries, evidence of a positive association between alcohol and cancers of the colon and rectum and breast is of clear public significance. The significance of this effect is not diminished by the possibility that alcohol may play a role primarily as a co-carcinogen. In light of these conclusions, and because no cancer preventive effect is indicated for ethanol, it can be concluded that total cancer risk is positively associated with total alcohol intake.

However, the implications of this research for drinking guidelines should be considered carefully. The vast majority of individual studies, as well as formal and critical overviews, have focused exclusively on measures of total dose of exposure. The observation of a monotonic positive association is in fact somewhat tautological, in that such a dose-response relationship is heavily used as a criterion for a causal association (Weed and Gorelic, 1996).

In the setting of research on alcohol-related cancers, evidence of a differential effect attributed to different drinking patterns might serve to reject the null hypothesis of a simple linear dose-response relationship. Zhao, et al. offer what appears to be a rare assessment of models other than a strictly linear association in defining the dose-response relationship between alcohol intake and colon cancer (Zhao et al., 1996).

Most reviews of alcohol and cancer make no mention of patterns of drinking. One discussion on breast cancer (Kohlmeier and Mendez, 1997) states that differences between binge versus regular drinking might be important but that this has not been explored. One might speculate that research on drinking patterns and cancer risk will increase in light of the attention being paid to breast cancer risk. Breast cancer is all too common and there is considerable public interest in primary prevention of this disease. And yet, in contrast to cancers earlier identified as alcohol-related, breast cancer has not been widely identified as a consequence of alcohol consumption and this may have a profound effect on public discussion and the nature of preventive interventions considered.

Research on the significance of different patterns of drinking might be expected to increase as the focus of research in this area shifts to the elucidation of mechanisms. However, unlike the situation seen in cardiovascular disease, the most popular competing hypotheses in carcinogenesis cannot be tested by defining drinking patterns that would favour one pathway compare to another. For example, determination of the role of alcohol as a initiator or promoter of cancer would be determined by the timing of effect. However, different drinking patterns are unlikely to shed light on whether the breast cancer association is attributable to hormonal influences, or to circulating acetaldehyde-associated free radicals, as both would be associated with total dose of intake levels.

Drinking patterns may be more germane in determining the role of alcohol in the development of those cancers for which the most likely causal pathways involve direct tissue injury and metaplasia, or with bacterial production of acetaldehyde, such as may be relevant for cancers of the mouth, oesophagus, stomach, and rectum. The timing of alcohol use in relation to meals, and opportunities for ethanol to remain in contact with oral mucosa have not been explored in detail. The consumption of win with food has been suggested as possible dampening the effect of alcohol intake and cancers of the oropharynx and oesophagus. The consumption of ethanol with meals also reduces the amount of ethanol passing into the gut. (Kalant and Khanna, 1989; Eckardt et al., 1998), and this may reduce the risk of cancers of the lower gastrointestinal system. This supposition, however, does not appear to have been tested directly.

Differences in the degree of association by beverage type have not consistently been found. (Research pertaining to the risk associated with exposure to alcohol beverages which contain known carcinogens in the non-ethanol components of different beverages are not reviewed here). In terms of possible mechanisms, beverage types are more plausibly associated with tumours involving direct contact with alcoholic beverages of different alcohol concentration.

In summary, average alcohol intake can be expected to have a positive and generally monotonic association with total risk of cancer. Elevated risk may occur for relatively moderate levels of drinking (within current guidelines) for cancers of the upper aerodigestive tract and possibly other sites, but there are scarcely any data to indicate a lower limit to dose associated with risk. Similarly, little evidence is available to indicate specific patterns of drinking as representing less risk of cancer than others. The sole exception would be that prolonged direct contact between the upper digestive system and high alcohol-content beverages should be avoided – and this may relate to a lower risk associated to alcohol taken with meals. Beverage difference do not appear to be significant, although quality of diet may modify the levels of risk of cancer associated with different levels

4.3 Liver cirrhosis

4.3.1 Alcohol as a cause of cirrhosis: Alcohol is regarded as the leading cause of cirrhosis (English et al., 1995). However, it is notable that this conclusion is applicable to

industrialised, alcohol-consuming societies similar to those within which the relevant research has been carried out. Also, within the studies that support the causal relation between alcohol and liver cirrhosis, there are observations that bear on the degree to which alcohol is a sufficient and/or a contributing cause of this condition, and of the influence of other factors that may also be both sufficient and/or contributing causes.

There is good evidence that prolonged consumption of beverage alcohol can cause cirrhosis in the absence of other causes. For example, in a cohort study Leibach (Leibach, 1975) found that the risk of developing cirrhosis of the liver in medically fit, 'non-skid-row' men was associated with the prolonged consumption for many years of daily levels of beverage alcohol in excess of 160 g per day. Furthermore, it was found that there was a linear relationship between lifetime consumption and the risk of developing cirrhosis. A diagnosis of alcoholic cirrhosis can be made on the basis of the level of alcohol consumption, the exclusion of other known causes of cirrhosis and the presence of histological evidence of alcoholic liver disease.

Schmidt (Schmidt, 1977) studied the relationship between per capita consumption of alcohol and cirrhosis mortality in Ontario for the period 1932-1974. He found a very close correlation between these variables and concluded that the contribution of alcoholic cirrhosis to total cirrhosis mortality varied with changes in per capita consumption. He estimated that 79% of all cirrhosis deaths in Ontario in 1973 could be attributed to alcohol consumption.

4.3.2 Other causes of cirrhosis: There are other individual factors that acting alone can cause cirrhosis. These include infection with hepatitis B and C, and the genetic disorders haemochromatosis, Wilson's disease and alpha-anti-trypsin deficiency. Cirrhosis caused by these factors can be diagnosed by demonstrating the presence of the causal factor, exclusion of other factors and the presence of characteristic histological changes in liver biopsy specimens.

4.3.3 Unspecified cirrhosis: The third category of liver cirrhosis, unspecified liver cirrhosis, is that in which no specific aetiological factor is either identified or recorded. Since the introduction of percutaneous liver biopsy in the 1950's and the progressive availability of methods to identify specific cirrhogenic factors, diagnostic accuracy has increased. These improvements should reduce the number of cases of liver cirrhosis assigned to the unspecified category.

There are three general reasons why a diagnosis of unspecified liver cirrhosis may be made. They are inadequate investigation, the failure of adequate investigation to determine a cause or causes, or concealment of a recognized cause because of possible negative consequences associated with a specific diagnosis, e.g. alcohol dependence, hepatitis C infection. The first of these is of particular interest, namely failure to identify a specific cause, because it poses the issue of the degree to which cirrhogenic factors can interact as component causes of cirrhosis and, in so-doing, present a clinical and

diagnostic picture in which more than one factor is present and the investigative findings, including liver biopsy, are inconclusive.

4.3.4 Interrelationship between alcohol and other aetiological factors in the development of cirrhosis: Earlier reference was made to Leibach's observation of the high daily levels (in excess of 160 g per day) of prolonged alcohol consumption required for the development of cirrhosis (Leibach, 1975). The results from this study are in contrast with those in which the increased risk of developing cirrhosis occurred at comparatively low levels of daily alcohol consumption over many years (in excess of 40 g per day in men and 20 g per day in women) (Pequignot et al., 1974). This increased risk at low levels of daily consumption suggests the existence of (an)other contributing cause(s).

In a study of cirrhosis deaths in Australia over the period 1905 to 1980, it was proposed that changes in death rate were best explained by alcohol consumption contributing not only to deaths from alcoholic cirrhosis but also from non-alcoholic cirrhosis in which alcohol was a component factor contributing to the etiology, course and outcome. Under these circumstances alcohol consumption may contribute to the development of (a) specific form(s) of cirrhosis, or alternatively contribute to cirrhosis in which the existence of alcohol and other possible causal factors is recognized, and the pathology does not fit a typically recognizable diagnostic pattern (Rankin et al., 1985).

Alcohol and hereditary haemochromatosis: In Australia a recognizable candidate for an interaction between two etiological factors in the development of cirrhosis is hereditary haemochromatosis. This is an inherited disorder of iron metabolism in which the ability of the body to regulate iron absorption is disturbed and, as a result, excess iron is absorbed and deposited in parenchymal cells, in particular the liver, pancreas, heart, pituitary gland, joints and skin. In the liver this deposition causes cirrhosis and hepatic carcinoma. It is the most common inherited liver disease in Caucasian populations and the most common autosomal recessive genetic disorder, affecting approximately 1 in 300 Caucasians (Cullen et al., 1999).

A number of studies of haemochromatosis have reported an incidence of excessive alcohol consumption that was higher than expected. For example, it was found that 20 to 30% of patients with fully developed haemochromatosis consumed greater than 50 g/day of ethanol. It has also been reported that homozygous haemochromatosis patients who consumed excessive amounts of alcohol had a higher prevalence of cirrhosis than those who did not drink heavily. The mechanisms of liver damage caused by excess iron and alcohol are believed to be similar and to result from free radical-mediated toxicity. It is considered likely that these synergistic hepatotoxic processes lead to an increased predisposition to cirrhosis (Fletcher et al., 1999).

The haemochromatosis gene (HFE) is located on the short arm of chromosome 6 in which two mutations have been described, C282Y (a cysteine-to-tyrosine substitution) and H63D (a histidine-to-aspartic-acid substitution). The C282Y mutation is thought to be of Celtic origin. Patients with haemochromatosis are mainly homozygous for C282Y

while a small proportion is homozygous for H63D or heterozygous for both mutations (Cullen et al., 1999). The allele frequency for C282Y in a study of Australian neonates was 14% (Cullen et al., 1999). This is similar to the frequencies reported in Irish (14%) (Ryan et al., 1998) and New Zealand populations (13.2%) (Burt et al., 1998). In a recent study of a Western Australian community the homozygous C282Y mutation was detected in 1 in 200 (Olynyk et al., 1999).

Diagnosis of hereditary haemochromatosis: In the past there has been disagreement and confusion about the distinction of hereditary haemochromatosis from cirrhosis with iron deposition occurring in alcoholic subjects. This problem was not resolved until the mid-1970's when the genetic basis of hereditary haemochromatosis was established (Simon et al., 1976). However, despite a greater awareness of hereditary haemochromatosis and the availability of specific diagnostic techniques, cases of this condition still go unrecognized and the associated cirrhosis is misdiagnosed as either non-specific or alcoholic in origin.

4.3.5 Liver disease and drinking guidelines: Evidence on the relationship between alcohol consumption and the risk of cirrhosis supports *a general recommendation* that the average daily consumption of alcohol should not exceed 40 g per day in men and 20 g per day in women. However, it also supports *a specific caution* that those who are homozygous for the C282Y mutation for hereditary haemochromatosis are at particular risk if they exceed moderate levels of consumption (Fletcher, 1988).

In the presence of active liver disease and established cirrhosis the following clinical guidelines are considered applicable:

1. *Acute hepatitis:* Individuals with acute hepatitis are advised to abstain from alcohol. In practice the patient's symptomatology usually mitigates against alcohol use.
2. *Chronic hepatitis:* Individuals with chronic hepatitis without scarring are advised limit their weekly intake to no more than seven standard drinks. Eligibility to receive interferon for the treatment of chronic active hepatitis B and C under the Highly Specialised Drugs Program of the Australian Pharmaceutical Benefits Scheme requires individuals to limit their alcohol intake to no more than seven standard drinks per week (Pharmaceutical Benefits Advisory Committee, 1996 and 1998).
3. *Cirrhosis:* Individuals with established cirrhosis are advised to abstain from alcohol.

In sum:

1. Alcohol alone can cause liver cirrhosis.
2. Alcohol can contribute to the development of at least one other form of cirrhosis for which there are is a known cause, namely haemochromatosis.
3. The possibility remains that, in combination with other factors, alcohol may contribute to the development of cirrhosis in which the aetiological diagnosis is uncertain.

4. The levels of alcohol consumption at which the risk of cirrhosis occurs are relevant to the establishment of drinking guidelines.
5. There are clinical recommendations on alcohol consumption for individuals with established liver diseases that are relevant to the establishment of drinking guidelines.

4.4 Other chronic conditions

Another risk of alcohol consumption is the potential to become alcohol dependent (or, in the language of International Classification of Diseases (ICD), being classified as under the categories of alcohol dependence or alcohol abuse). The toll of alcohol dependence is considerable—in Australia, about half of bed days involve diagnoses of alcoholic psychosis, alcohol dependence or alcohol abuse, three conditions that are very closely related to the dependence syndrome (Room, 1998). In Canada, based on the cost study (Single et al., 1998; Rehm, 1999) estimated that about 50% of the total costs involve people who could be classified as alcohol dependent (for example, under the categories of alcohol dependence or alcohol abuse). How is addiction related to amount of drinking?

Trivially, lifetime abstainers have a risk of 0 for developing alcohol dependence. For moderate drinkers (those consuming within existing guidelines), this risk is hard to quantify, as it depends mainly on interactions with other factors, most notably genetic vulnerability (for example, Johnson and Leff, 1999). Such an evaluation is further complicated by the fact that many definitions of moderate drinking have used the absence of dependence as a criterion (for example, see discussion of Eckardt et al., 1998). Alcohol drinking has rewarding and reinforcing effects and these effects may explain part of the progression from moderate to harmful use in individuals. It has also been shown that genetically predisposed persons on average feel these effects stronger and at lower levels of drinking (Schuckit et al., 1997). This is one reason given why sons of alcohol dependent persons are more at risk for becoming alcohol dependent themselves and why many low-risk drinking guidelines specify precautions for this group (see Section 3). However, this does not exclude the risk for others to progress from moderate drinking to alcohol dependence. Given the current state of knowledge, this risk cannot be quantified. As individual drinkers in many cases do not know their genetic predisposition, they should be aware of the potential of a risk to become dependent.

Drinking more heavily imposes a higher risk for dependence. The functional form of this risk is unfortunately not very well understood, as almost all of the information comes from survey studies where amount of consumption and alcohol dependence are both measured at the same time. However, in terms of developing low risk drinking guidelines, it suffices to know that moderate drinking (within existing guidelines) implies some risks, and heavier drinking implies higher risks. Future research should address this problem with priority.

5. Acute adverse consequences of alcohol consumption

5.1 Effects of prenatal alcohol exposure

Alcohol use during pregnancy has been associated with varying degrees of toxic effects on the fetus, the most severe of which include gross congenital anomalies, and a defined syndrome- the Fetal Alcohol syndrome (FAS)- which includes characteristic physical anomalies, growth retardation and neurological dysfunction with developmental delay. Alcohol has been associated with a variety of more subtle developmental effects as well. The effects of prenatal alcohol exposure on the physical and neurologic development of the fetus, and on neurobehavioural development in the child have received a great deal of attention during the past 15 years. In reviewing this material, a number of substantial overview reports were identified. Many of these were produced, directly or indirectly, for the United States government, where the issue of prevention of alcohol-related birth defects is a highly charged political issue.

The purpose of this report is not to repeat these comprehensive overviews. Rather, a general summary is provided of the evidence of a causal link between prenatal alcohol exposure and identified effects in the fetus, particularly in relation to heavy drinking. The emphasis here will be placed on research directed at moderate alcohol intake during pregnancy, evidence of the lower limits of alcohol intake that are associated with meaningful developmental effects, and on research which addresses drinking patterns in relation to fetal harm.

5.1.1 Summary of previous important overviews: There have been many summary reports which have attempted to draw conclusions about the nature and extent of risk associated with prenatal drinking (for example, Knupfer, 1991; Larroque, 1992; English et al., 1995; Stratton et al., 1996). Major reports produced for the U.S. Federal Government agencies include two overview reports to the Congress on alcohol and health. The first of these (United States Department of Health and Human Services, 1993) discussed six large prospective studies of prenatal exposure and incorporated other literature such as animal data and overviews about mechanisms of fetal damage. The subsequent report updated this evidence and provided a very thorough examination of dose-response evidence, a discussion of mechanisms of fetal damage and reviews evidence to date on drinking patterns (United States Department of Health and Human Services, 1997). A series of special reports published by the U.S. National Institute on Alcohol Abuse and Alcoholism in a special thematic issue of *Alcohol Health & Research World* (1994: volume 18, issue 1) also provided relevant discussion of specific aspects of the evidence for alcohol-related fetal effects.

Another report reflecting a comprehensive review and summary of available evidence is that prepared by the Committee to Study Fetal Alcohol Syndrome established through the Institute of Medicine and National Academy of Sciences, as mandated by the U.S. Congress (Stratton et al., 1996). However, this report does not focus on moderate and low volume intake during pregnancy, nor does it attempt to define low-risk levels of intake. More recently, the individual contributions of a report of a French symposium,

published in April, 1998, provide some current and significant reviews (see (Riley, 1998). Another overview of 20 years of research on neurobehavioural effects of prenatal exposure was published recently by Mattson and Riley (Mattson and Riley, 1998).

5.1.2 Potential mechanisms of alcohol-related fetal damage: Alcohol was shown to be a teratogen in mice shortly after the syndrome of FAS was defined clinically (for example, Chernoff, 1977); United States Department of Health and Human Services, 1997). Considerable animal research now exists showing neurologic and behavioural effects similar to those seen in humans (United States Department of Health and Human Services, 1997; Hannigan et al., 1995). Alcohol affects the development of specific brain structures in animals which are functionally related to the behavioural and memory dysfunctions found in both animals and humans (Guerri, 1998). Specific biochemical processes have also been identified to describe the toxic effects of alcohol on developing cells of the central nervous system (Guerri, 1998; Michaelis and Michaelis, 1994). Ethanol permeates fetal cells and may lead to reduced fetal cell growth through the inhibition of growth hormone production and diminution of the action of growth factors on nerve cell development. It may also adversely affect oxygen perfusion to fetal cells either through restriction of blood flow through the placenta or locally through increased prostaglandin activity. Also, ethanol may affect the migration and adhesion of developing neural cells and disrupt the formation of brain structures (Guerri, 1998; Michaelis and Michaelis, 1994). Prenatal alcohol exposure may also affect later neurotransmitter functions, which could in turn be associated with impaired neuronal maturation and with observed behavioural effects (United States Department of Health and Human Services, 1997).

The timing of exposure is critical in determining risk and the nature of the associated damage (United States Department of Health and Human Services, 1997; Hannigan et al., 1995; Coles, 1994; Maier et al., 1997). Because physical anomalies may be more sensitive to teratogens acting in the first months of pregnancy, alcohol intake in the earliest days of pregnancy (often before it is recognised) may be most relevant here. Animal studies and limited epidemiological evidence in humans tend to support such a conclusions (Coles, 1994). However, neurological development and physical growth continue throughout pregnancy, and so exposure during the rest of pregnancy is of relevance to weight at birth and to neurological and cognitive effects. Because it is most common for women to decrease their intake over the course of pregnancy (Day, 1992), it is difficult to separate effects of early exposure from later exposure. However, cessation in the third trimester has been associated with improvement in fetal size at birth (Coles, 1994).

Jacobson and Jacobson discuss four domains of fetal injury that are associated with different thresholds for toxic doses: fetal death; congenital malformation; growth retardation; and, functional neurobehavioural deficits (Jacobson and Jacobson, 1994). The greater the toxic dose, the greater the likelihood of injury and the larger the number of fetuses expressing progressively more severe forms of damage. Fetal death in utero is most likely associated with toxicity at the highest levels of intake. The toxic effects most likely to be sensitive to lower doses of exposure are functional teratogenesis, and

neurobehaviour problems that are subtle, and not associated with immediately recognisable physical anomalies. Because these outcome classes are expected to be increasingly sensitive to the effects of lower doses of alcohol, the four domains will be considered in relation to moderate alcohol intake in this order.

5.1.3 Spontaneous abortion: English et al. (1995) concluded there was insufficient evidence of fetal damage below a limit in the order of 2 to 3 Australian drinks daily. A more recent review of this topic by Abel provided an intriguing critical discussion of the available evidence (Abel, 1997), including 16 epidemiological studies. He identified a potential geographical bias, in which North American studies are the only ones to present significant positive associations, and several of these are criticised for failure to account for important confounders such as maternal body weight and social class. Two case-control studies not available to English et al. (Parazzini et al., 1994; Dominguez-Rojas et al., 1994), were reviewed by Abel, neither of which found a significant association (Abel, 1997). Abel also extrapolates from animal studies of acute alcohol administration and induced spontaneous abortion and concludes that the equivalent blood alcohol dose in a human mother would be approximately equal to 200 mg/dl.

More recently, a very large prospective study found a statistically significant association between alcohol intake and fetal death in the order of an additional 1% risk of fetal death in association with each additional drink per week, after controlling for smoking and other relevant confounders (Faden et al., 1997).

5.1.4 Fetal alcohol syndrome: One conclusion that may be drawn from the major reviews cited above, is that the identified syndrome of Fetal Alcohol Syndrome (FAS) is not a consequence of light or moderate drinking, however defined (Knupfer, 1991; Stratton et al., 1996; United States Department of Health and Human Services, 1994). (For discussions on clinical diagnosis of FAS, see Stratton et al., 1996; United States Department of Health and Human Services, 1997). Furthermore, alcohol intake consistent with alcohol dependence or alcoholism is not sufficient to cause FAS. In fact, one study found just 7% of children born to alcohol dependent women to have FAS (Polygenis et al., 1998). Maternal characteristics, measured or unmeasured, have a large influence on risk (Day, 1992).

Most of the earlier reports cited have made some attempt to consider lower thresholds of risk, or levels of drinking associated with damage; however, most were unable, or otherwise failed to make definitive statements about thresholds of risk for FAS. The committee of the (U.S.) Institute of Medicine reported.....

“...The committee did not establish precise lower limits of alcohol exposure associated with significant increased risk of FAS. Some researchers have attempted such calculations, but the committee felt that it is premature to make such a statement. Maternal factors such as parity, age, history of heavy drinking, and general health status all influence how much alcohol exposure is necessary for FAS. The level of alcohol exposure is generally very high and likely found in only a small percentage of women who do drink while pregnant” (p. 7).

Subsequently, Sokol has estimated the threshold for FAS at approximately 21 ounces (535g) of absolute alcohol per week (Sokol et al., 1988).

FAS, as a clinical syndrome, therefore will not be considered further in this report. However, many of the individual clinical signs which contribute to a clinical diagnosis of FAS will be considered individually: namely growth retardation and evidence of central nervous system deficits or neurodevelopmental abnormalities.

5.1.5 Other alcohol-related defects (ARBD): The Institute of Medicine provided a list of congenital anomalies associated with prenatal alcohol exposure, and which are not exclusively associated with FAS or very heavy alcohol exposure in utero. Identified alcohol-related birth defects (ARBD) include cardiac, skeletal, renal, ocular and auditory anomalies as well as the characteristic facial dysmorphism associated with FAS (Stratton et al., 1996).

English and his colleagues reviewed the effects of alcohol on fetal damage because of the lack of identified admissions or deaths identified by the appropriate ICD code for fetal damage caused by other conditions in the mother, and found that there was insufficient evidence to derive an etiologic fraction for birth defects, aside from FAS which was assigned an AR of 1 (English et al., 1995).

A recent meta-analysis of studies of fetal malformations and alcohol exposure (Polygenis et al., 1998) included studies of moderate drinking mothers. All studies selected, on the basis of maternal intake range and quality ratings, were published before 1993. Moderate use was defined as greater than two drinks per week and up to 2 drinks per day in the first trimester. This level of use was contrasted against use of less than 2 drinks per week. A pooled OR of 1.01 (95% confidence interval: 0.94-1.08) indicated no significant effect of moderate drinking, so defined, on birth defects associated with alcohol exposure.

The evidence to date of an association between moderate drinking and growth deficits, although limited, suggests it is unlikely there is a significant effect at intake levels less than 2 drinks per day. However, no study was found which attempted to detect a threshold effect in continuously reported prenatal exposure.

5.1.6 Intrauterine growth retardation and low birthweight: English et al. (1995) reviewed 11 relevant studies (up to 1993) of the association between maternal intake and outcomes related to low fetal growth. These authors concluded there was insufficient evidence of an association for low to moderate drinking, and assigned etiologic fractions only to hazardous and harmful drinking. The Ninth report to U.S. Congress, discussed only one additional study published later than those considered by English and his colleagues.

A prospective study in Pennsylvania and New York (Shu et al., 1995) found a reduction in birthweight, adjusted for smoking and other factors, of 280g in association with a maternal intake in the first trimester of 2 drinks per week. A California case-

control study did find an association between growth indicators and alcohol intake in the first 20 weeks gestation (Windham et al., 1995). moderate drinking (less than 2 drinks daily and at least 3 drinks per week) was associated with a significant increase in the risk of low birthweight, relative to less than 3 drinks per week (OR = 2.6 after adjusting for smoking and other confounders, although not gestational age). A significant association was also found in relation to IUGR (lowest tenth percentile on weight for gestational age) with an OR of 2.3.

A large prospective study reported by Lundsberg et al. found a curvilinear association between alcohol intake in the first month of pregnancy and rates of intra-uterine growth retardation (Lundsberg et al., 1997). Light drinking (less than 0.1 oz. or 2.7 g of absolute alcohol per day) was associated with a slight, but statistically significant decrease in risk relative to non-drinkers. Consumption at higher levels (greater than 0.1 oz. or 2.7 g of absolute alcohol per day) was associated with increased risk of IUGR in a dose-response manner.

In a very large U.S. prospective study on maternal and infant health (including over 18,000 pregnancies), maternal alcohol intake was not associated with birthweight after controlling for confounders in linear regression models. However, it was statistically significant in logistic models using low birthweight as the outcome (Faden et al., 1997). The effect was described as small relative to the other risk factors included.

One report from a prospective study over 10,000 women addressed binge drinking in relation to infant birthweight (Passaro et al., 1996). This study used complex measures of alcohol intake. 'Binges' were defined as episodes of having at least 40 to 45g of absolute alcohol in one day. Early pregnancy drinking was associated with birthweight reductions (adjusted for confounders, including smoking and gestational age) only for mothers who drank daily and at least 3 drinks per day. Taking binge drinking into account did not affect the results.

Generally, there is some information in favour of an effect of moderate alcohol use on reduced birthweight. The effect of alcohol, where clearly found and separated from tobacco and other risk factors, is not large in magnitude. The identification of thresholds of effect may be related to sample size. Larger studies may be required to detect more subtle effects at lower intake levels, and the clinical significance of the observed reduction in weight should be considered.

5.1.7 Neurodevelopmental deficits: A series of neurobehavioural signs have been associated with prenatal alcohol exposure in infants who do not meet criteria for fetal alcohol syndrome. Commonly cited attributes in the neonate include reduced attention, irritability and distractibility, as well as poor physical coordination and development, while later behavioural problems associated with prenatal alcohol exposure include hyperactivity, irritability, perseveration behaviours, as well as continued deficits in memory, cognitive processing and learning (Larroque, 1992; Mattson and Riley, 1998; Allebeck and Olsen, 1998; Forrest et al., 1992). Standardized tests of neonatal and early

childhood development have been used across several studies, such as the Bayley series of assessment indices (Mattson and Riley, 1998; Jacobson and Jacobson, 1996).

Although evidence of fetal damage at heavy levels of intake is clear, several reviewers writing in the early 1990s expressed the opinion that there was insufficient evidence of fetal effects at low to moderate levels of intake to warrant recommendations of abstinence during pregnancy (for example, (Knupfer, 1991; Larroque, 1992).

Contributors to the EUROMAC study concluded that the lowest levels of prenatal alcohol intake that had been associated with altered child development was 150 g of alcohol per week (Forrest et al., 1992). Others tended to support abstinence on the basis that lower limits of effects were not defined; thus, the most conservative approach (abstinence) was warranted. As an example, the Eighth report to the U.S. Congress concluded that insufficient evidence existed to define thresholds of risk for relevant indicators of neurologic damage or behavioural effects.

“Because an enormous range of defects can result from prenatal alcohol exposure, it is not unreasonable to assume that different aspect of development will be found to be sensitive to different levels of exposure.”

As expressed by Clarren et al.:

“It is probably that there is no single dose-response relationship for ethanol teratogenesis, but rather than each abnormal outcome in brain structure or function, morphology, and growth has its own dose-response and gestational timing parameters.” (Clarren et al., 1987).

Relatively few authors have attempted to formally define dose-response associations and thresholds of exposure associated with neurological and behavioural deficits. Those that have specifically addressed this have appeared quite recently.

Jacobson and Jacobson (1994) assess thresholds of effect of alcohol intake on various outcome measures for neurological and behavioural effects reported in a Seattle cohort (Streissguth et al., 1980; Streissguth et al., 1983) and their own study of African American women in Detroit (Jacobson et al., 1993). For most of the various neurobehavioural outcomes reported across the two studies, thresholds of effect were observed at levels of intake ranging from 1 to 3 standard drinks per day (also cited as equivalent to approximately 0.5 to 1.5 ounces of absolute alcohol per day (United States Department of Health and Human Services, 1997). However, some of the measure showed no threshold effect to indicate other than a monotonic dose-response relationship (small but measurable differences in reaction time and information processing speed and more impulsive behaviour) (Jacobson and Jacobson, 1994). The authors also note that the significance of these measurable difference in terms of the child’s true functional status was unclear.

In a more recent publication from the same Detroit study (Jacobson et al., 1998), the authors used nonparametric modeling and hockey stick curve fitting to determine if the dose-response effect is linear or indicates a threshold. These techniques identified thresholds of effect for the various outcome measures ranging from 0.4 ounces of absolute alcohol per day to 1.5 ounces of absolute alcohol per day, with a median

threshold of 0.5 oz. of absolute alcohol per day (corresponding to 12 g of absolute alcohol/day). They also found that the effect was much more marked in the offspring of older mothers (30 years of age or older) than in children of younger women.

Larroque et al. reported on a prospective study of French women and their children up to 4 1/2 years, although nearly 50% were lost to follow-up (Larroque et al., 1995). Measurable deficits in child development were observed, and described as being consistent with the Seattle study findings. An effect was identified at a level of 1 to 1.5 ounces of absolute alcohol daily. Below this no consistent associations were found.

A threshold effect was also found in a study of prenatal exposure in relation to academic achievement by age six (Goldschmidt et al., 1996). These authors reported a significant negative correlation between alcohol exposure in the second trimester and subsequent scores on spelling, reading and math. Through non-linear model fitting, they also found a threshold effect at approximately one drink per day in reading and spelling scores, but no threshold effect for arithmetic scores.

5.1.8 Drinking patterns and neurobehavioural deficits: Drinking patterns may also be important in determining the effects on structural brain development. Calls have been made for some time to capture episodes of heavy drinking in studies of prenatal alcohol exposure, in addition to total doses consumed at different phases of the pregnancy (United States Department of Health and Human Services, 1997; Jacobson and Jacobson, 1994). High blood alcohol levels achieved during episodes of heavy drinking may represent heightened risk, and do appear to influence teratogenic effects seen in experimental animals (Maier et al., 1997; West and Goodlett, 1990; Bonthius and West, 1990).

Jacobson and colleagues (1998), again using data from the Detroit cohort, examined the associations between the three variables indicating drinking patterns and the same neurobehavioural outcome measures reported previously. These pattern variables were: frequency of drinking, amount consumed on drinking days (less than five drinks versus five or more drinks), and the Michigan alcohol Screening Test (indicating a history of alcohol abuse). Of these, the authors concluded that dose per drinking day made the largest contribution to determining functionally significant effects on neurobehavioural development. These authors also noted that their results corresponded with those of Streissguth (1983); cited in (Jacobson et al., 1998) in finding a drinking pattern of at least five to seven drinks, on one to two occasions per week, as being associated with functional deficits in the child consistent with significant impairment.

5.1.9 Summary of evidence of fetal damage in relation to moderate intake and drinking patterns: The evidence reviewed above indicates that FAS and spontaneous abortions are unlikely consequences of moderate drinking in early to mid pregnancy. Similarly, evidence of an association between moderate alcohol use in pregnancy and congenital physical anomalies is very limited. Some evidence in favour of an effect of growth retardation in association with moderate drinking is found, but the potential effect is likely to be small – requiring large sample size to detect. At levels of

maternal intake consistent with typical low-risk drinking guidelines for non-pregnant women, it has not been shown that a reduction in birthweight would be clinically meaningful. This evidence does not clearly point to a threshold of effect, and it is worth noting that the observed size of the effect of alcohol was much smaller than other known risk factors such as smoking or inadequate prenatal nutrition.

There is considerable evidence to show that prenatal alcohol exposure can result in preventable neurological deficits in offspring, even at intake levels that would be considered moderate. Several studies now exist which have attempted to define inflexion points in dose-response curves. Threshold for effect in the order of one drink per day are typical, where thresholds are found.

Much of the evidence on relevant drinking patterns has results from experimental data with animal models. While there is strong concordance between the physiologic, performance and behavioural effects observed in animal models and humans, the non-human research does not permit direct extrapolation of dose-response effects. Binge drinking has been shown in animal models to increase the risk of neurologic damage, but only a few studies in humans support this. Episodic drinking in the order of 5 to 7 drinks has been associated with fetal damage in humans, but the studies showing this were not designed to measure the relationship between

5.2 Alcohol-related traumatic injury

In general terms, alcohol use has been associated with increased risk of injury in a wide variety of settings including vehicular crashes, bicycling accidents, incidents involving pedestrians, falls, fires, injuries related to sports and recreational activities, and injuries resulting from interpersonal violence (Cherpitel, 1992; Hingson and Howland, 1987; Hingson and Howland, 1993; United States Department of Health and Human Services 1997; Martin, 1982; Martin and Bachman, 1997; Freedland et al., 1993; Hurst et al., 1994). There is also some evidence that the presence of alcohol in the body at the time of injury may be associated with greater severity of injury and less positive outcomes (Fuller, 1995; Li et al., 1997). Overall, mortality and morbidity from traumatic injury is by large the most important health consequence of alcohol (Single et al., 1999).

This section will not reproduce the material compiled in extensive reviews on the subject, but will attempt to highlight research findings relevant to establishing dose-response data, and information on drinking patterns and lower levels of intake associated with an increasing risk of injury. Several areas of research are particularly relevant to this task: studies of usual drinking patterns in populations in relation to individual risk of injury; retrospective studies of the association between BAC levels and injury; and, experimental research on the association between alcohol doses and psychomotor effects relevant in avoiding accidents and injuries.

Studies relating usual drinking patterns or levels to risk of injury have found the risk of injury to be positively related to increasing average intake levels, and to increase at relatively low volumes of intake (for example, Cherpitel et al., 1995). Two studies of

injury among older adults reported a U-shaped relationship between alcohol use and occupational injury (Zwerling et al., 1996) and traumatic deaths (Ross et al., 1990). However, abstinence could be related to existing health problems or cognitive deficits that are, in turn, related to accident risk (Zwerling et al., 1996).

Studies of usual drinking habits have also highlighted the importance of specific parameters of drinking pattern in modifying the association between total intake and injury risk. Frequent heavy drinking and frequent subjective drunkenness are both associated with injury, particularly injury resulting from violence (Cherpitel, 1996). Frequency of heavy drinking has also been associated with a greater likelihood of death due to injury, relative to other causes (Li et al., 1994). One important line of research in this area has empirically defined a parameter of usual drinking pattern that is most closely associated with the risk of injury and drunk driving behaviour after adjusting for other drinking pattern variables and characteristics of the drinker (Gruenewald and Nephew, 1994; Gruenewald et al., 1996; Gruenewald et al., 1996; Treno and Holder, 1997b; Treno et al., 1997a). Greatest risk is found to be associated with variance in drinking, or approximately the statistical variance in the amount consumed by an individual across different drinking occasions for that individual. This variance term reaches its highest value in individuals who consume relatively large amounts on some occasions, and whose highest amounts are markedly greater than their average amount per occasion. Overall, the available literature relating usual drinking patterns to risk of injury indicates a positive association with total dose without information provided to demonstrate a threshold effect, and a stronger association with occasions of relatively heavy drinking.

A long series of retrospective studies have involved comparison of BAC levels in individuals who have experienced a collision or trauma in comparison with selected individuals not involved in trauma, using a case-control design (Cherpitel, 1992; Freedland et al., 1993; Fuller, 1995; Stoduto et al., 1993; United States Department of Health and Human Services, 1997; Hurst et al., 1994). One of the most influential case-control series was the Grand Rapids study of 5,985 collisions (Borkenstein et al., 1964; Hurst et al., 1994). Proper analysis of the Grand Rapids study indicates that all levels of BAC are associated with an increased risk of crashes, relative to a BAC of zero, and an accelerating slope in which the risk of injury increases markedly with high BACs (Hurst et al., 1994). Other analyses of risk of injury in relation to alcohol use prior to the event have found drinking alcohol in the previous 6 hours to be associated with injury risk in a dose-response fashion, without any evidence of a threshold effect (Vinson et al., 1995). Another case-control study combined data from a United States fatal accident reporting system with time-matched data from a roadside breathalyser survey (Zador, 1991). This study reported a relative risk of nearly 2 for a BAC of 20mg% (relative to zero) and a relative risk of 9 for a BAC in the range of 50 to 90mg%. Related lines of research include studies of the BAC among patients seen in emergency rooms, and the reports of coroners (United States Department of Health and Human Services, 1994; United States Department of Health and Human Services, 1997). Although there are considerable differences in the prevalence of positive BACs in injured individuals across settings, this literature generally reveals a positive correlation between trauma risk and BAC with no clear indication of a threshold effect.

Moderate doses of alcohol (less than two drinks or 23 g/day) have been demonstrated in controlled experimental studies to have cognitive and psychomotor effects that are relevant to the risk of injury, such as reaction time, cognitive processing, co-ordination and vigilance (Moskowitz and Robinson, 1988; United States Department of Health and Human Services, 1997; Kruger et al., 1993; Eckardt, 1998). Several reviews were identified of the effects of low to moderate doses of alcohol on psychomotor skills relevant for driving (Moskowitz and Robinson, 1988; Starmer et al., 1989; Nixon, 1995; Kruger et al., 1993; Eckardt et al., 1998). A common purpose behind many of these reviews is an assessment of evidence relevant to establishing legal limits on BAC for drink-driving legislation (Mann et al., 1998).

An older report (Moskowitz and Robinson, 1988) reviewed 41 studies of reaction time in relation to doses of ethanol. Fourteen of these studies showed performance deficits at BACs of 50mg% or less and only 2 failed to show an effect at BACs of 60mg% or more. Generally, cognitive impairment, such as performance on divided attention tasks showed effects starting variably around the range of 50mg% through 80mg% (Moskowitz and Robinson, 1988). More recently, Krüger reviewed 220 experiments on the effects of alcohol administration on psychophysical functions (including vision, psychomotor function, etc.), automatic processing and control actions (Kruger et al., 1993). This author found subtle effects on vision at very low doses, around 30mg%, while visual skills needed to assess depth and motion were affected at doses above 50mg%. Automatic processing deficits typically showed a threshold at approximately 50mg% and rising steadily thereafter. The review by Eckardt and colleagues concluded that the threshold dose for negative effects on psychomotor tasks is generally found around 40 to 50 mg% and also stated, 'injury can occur as a result of alcohol's disruption of psychomotor function in individuals at BACs of approximately 10 mM' (Eckardt et al., 1998 p. 1015), which is equal to a little less than a BAC of 50 mg%.

The extent of psychomotor impairment does vary according to the experience level of the individual and learning dampens the adverse impact on performance (Preusser et al., 1978). Also, dose-response effects of risk of crash-related injuries in relation to BAC exist for all age groups, younger drivers have much higher relative risks at the same BAC level than older drivers not only because they have less tolerance to alcohol, but also because of their relative inexperience in driving (Mayhew et al., 1985; Mayhew et al., 1986; Zador, 1991).

Dose response-curves observed in experimental data are not always monotonic. For example, a recent experimental study with human subjects (Lloyd and Rogers, 1997) assessed the effects of low doses of alcohol given with a meal and found that an 8 g (absolute alcohol) bolus resulted in improved complex cognitive task performance, relative to no alcohol, although 24g of alcohol produced impaired performance. Such J-shaped or U-shaped effects of low ethanol doses on task-specific performance are explicable by pharmacological effects (Eckardt et al., 1998). Ethanol not only interacts with several distinct neurotransmitter systems, but it also has different thresholds of effect with these variations systems, and may have a qualitatively different effect on

different individuals at different doses (for a more thorough discussion, see (Eckardt et al., 1998). This might explain why the effect of ethanol on psychomotor performance tasks may be qualitatively different at different doses, and differ according to whether blood alcohol level is rising or falling. Psychomotor responses that are most sensitive to the lowest doses of alcohol include a stimulatory effects, and subtle euphoric effects; while high doses are associated with sedative effects. These subtle stimulant effects or elevated mood may explain small performance improvements, while the BAC level is still rising, which are replaced with performance deficits thereafter. It should also be noted that expectancies influence psychomotor effects as well, and expectation of enhanced or impaired performance can result in actual subtle changes in performance (Eckardt et al., 1998).

The blood alcohol level that will be attained by an individual during a single episode of drinking will be determined not only by the amount consumed and time over which it is consumed, but also by body size and constitution, (such as the volume of water in the body) as well as by drinking experience, and whether or not the alcohol was taken with food (Kalant and Khanna, 1989; Eckardt et al., 1998; United States Department of Health and Human Services, 1997). Two- to three-fold differences also exist in how rapidly different individuals metabolize and eliminate comparable doses of alcohol (Eckardt et al., 1998). One report determined that genetic differences accounted for a much greater proportion of individual differences in peak BAC and alcohol-clearance rate than other factors such as body size (Martin et al., 1985). Because of these factors, estimation of BAC only from number of drinks and timing alone can only be approximate.

The relationship between alcohol intake at moderate levels (within drinking guidelines) and increased risk of non-skill related injuries such as those associated with interpersonal violence have not been studied as closely as the relationship between alcohol use and traffic injuries. Alcohol use increases the risk of these other types of injuries by the above mechanisms, and by increasing the likelihood of, and escalation of aggressive behaviour (Cherpitel, 1994; Martin, 1982; Martin and Bachman, 1997; Norton and Morgan, 1989; Zhang et al., 1997). Alcohol appears to interact with personality characteristics and other factors related to a personal propensity for violence, such as impulsivity (Lang and Martin, 1993; Zhang et al., 1997). Violence-related trauma may also be more closely linked to alcohol dependence symptoms than other types of alcohol-related injury (Cherpitel, 1997).

Obviously, the setting or environment has a huge influence on the degree of risk associated with the psychomotor effects caused by moderate alcohol use. Settings in which physical hazards are present will heighten risk, and circumstances requiring more highly complex reasoning and psychomotor skills will be most sensitive to risk associated with alcohol-related impairments (Eckardt et al., 1998).

In summary, the evidence reviewed above indicates that the amount consumed per occasion, and more specifically blood alcohol content, is the critical feature in determining risk of injury. Dose-response relationships are also evident regarding acute

alcohol intake. Blood alcohol concentrations as low as 40 to 50 mg% may cause psychomotor impairments relevant to increased risk of injury in circumstances such as driving. However, significant individual differences make it difficult to exactly calculate BAC from number of drinks and time taken to consume them. The degree of risk will also depend upon the setting, the requirements of the situation for high-order psychomotor skills, and the experience of the individual with the tasks being undertaken. In the important setting of drink-driving, younger, less experienced drivers are likely to have lower risk thresholds for meaningful impairment at the same BAC levels compared to older drivers.

6. Benefits of alcohol consumption

6.1 Cardiovascular and other health benefits

6.1.1 Ischemic heart disease: The evidence now supports four key conclusions that must be taken into account in the development of low-risk drinking guidelines for a country, such as Australia, where IHD is the foremost cause of death.

(1) First, alcohol appears to be protective against IHD in middle-aged and older men and women. Although the protective effect extends across the continuum of alcohol consumption, most, if not all of the reduction in risk is realised with low to moderate levels of consumption.

The evidence for this conclusion stems from many epidemiological reviews published over the last three decades indicating that drinking alcohol is protective against IHD mortality and morbidity in middle-aged and older populations (Ashley, 1982; Beaglehole and Jackson, 1992; Jackson, 1994; English et al., 1995; Holman et al., 1996; Klatsky, 1996; Svardsudd, 1998; Doll, 1998). Relatively few studies have failed to find this association in men (English et al., 1995; Hart et al., 1999) or women (Coate, 1993; Maskarinec et al., 1998; Murray and Lopez, 1999).

From a comprehensive review and meta-analysis of 19 cohort studies and six case-control studies it was concluded that the protective effect of alcohol is fully realised in association with low (responsible) levels of consumption, although the risk of death from IHD is reduced across the continuum of alcohol consumption ((English et al., 1995; Holman et al., 1996). This finding is consistent with that from an earlier meta-analysis showing no additional IHD benefit with increased alcohol consumption beyond a modest level of a drink a day (Maclure, 1993).

That the risk of death from IHD is reduced across the continuum of alcohol consumption has also been reported in other large prospective studies, for example, of men in the United Kingdom (Doll et al., 1994), Germany (Keil et al., 1997), and Japan (Kitamura et al., 1998) and the United States (Camargo et al., 1997; Rehm et al., 1997; Maskarinec et al., 1998), and among women in the United States (Fuchs et al., 1995) (Rehm et al., 1997; Rehm et al., 1997). These studies clearly show that most if not all of protection is found in association with light to moderate levels of drinking. Little is

gained from drinking more. Indeed, among women consuming more than 28 drinks a week, an upturn in risk has been demonstrated (Rehm et al., 1997).

With regard to IHD morbidity evidence concerning the protective effect of alcohol across the continuum of consumption is more limited. In an analysis of cross-sectional morbidity data from large numbers of men and women who took part in the 1988 U.S. National Health Interview Survey, it was concluded that protection against heart disease of all forms is confined to lower levels of drinking (Hanna et al., 1997). However, in a smaller study of Hispanic and non-Hispanic white elderly men and women in the United States, it was shown that the protective effect of alcohol consumption against IHD was not limited to the lower levels of consumption (Lindeman et al., 1999).

The epidemiological evidence that moderate alcohol consumption protects against IHD is strengthened by growing and, in some instances, substantial evidence concerning the biological mechanisms by which a protective effect could be mediated (Renaud et al., 1993; Rankin, 1994; Svardsudd, 1998). First, moderate alcohol intake has been clearly linked to favourable lipid profiles (Baraona and Lieber, 1998). It has been estimated that as much as 40%-50% of the protective effect may be attributable to this mechanism (Criqui et al., 1987; Suh et al., 1992; Criqui, 1994). Second, moderate alcohol intake favourably affects coagulation profiles (Baraona and Lieber, 1998), in particular, through its effects on platelet aggregation (McKenzie and Eisenberg, 1996) and fibrinolysis (Reeder et al., 1996). Third, low to moderate consumption of alcohol has been shown to favourably affect insulin resistance (Rankin, 1994; Kiechl et al., 1996; Lazarus et al., 1997). Fourth, it has been postulated that alcohol could protect against IHD through its effect on hormonal profiles, in particular, its estrogenic effects (Svardsudd, 1998). Fifth, the alcohol metabolite acetate has been postulated to protect against IHD by promoting vasodilatation (United States Department of Health and Human Services, 1997). Sixth, it is possible that some of the effect is mediated through the anti-oxidative constituents of alcohol beverages, especially wine (Reinke and McCay, 1996). However, as discussed below, most of the protective effect appears to be linked to ethanol, per se.

(2) Second, even in countries where the risk of IHD is high, the protective effect of alcohol against IHD may be limited to certain population subgroups.

Although the protective effect of alcohol consumption against IHD have been demonstrated across the adult lifespan, it appears to be of primary importance in those age groups in which IHD is an important cause of death (Jackson, 1994; Anderson, 1995; Thakker, 1998). In the Australian population this begins to occur at about 40-45 years in men and 45-50 years in women. In a cohort of young men followed up over 15 years, (Andreasson et al., 1988) showed that any cardiovascular mortality benefit was more than balanced off by alcohol-related increased risks of other causes of death, notably trauma. In younger women Fuchs and his colleagues failed to find any mortality benefit from light-to-moderate drinking (Fuchs et al., 1995). Nor has it been shown that drinking in younger years necessarily leads to a cardiovascular benefit in middle or old age, although it is reasonable to postulate that the atherogenic process might be retarded by alcohol consumption at any point in time. Further, the benefit may be limited to certain other

population subgroups, for example, those with insulin resistance (Heim et al., 1993; Rankin, 1994).

Some studies suggest that the benefit is either largely limited to or most advantageous to persons in middle and older age groups for whom the risk of IHD is higher than the population average. Fuchs and colleagues found that the benefit from light-to-moderate drinking was most apparent among women with risk factors for IHD (Fuchs et al., 1995). An analysis of data from the 9-year follow-up of 490,000 Americans enrolled in the Cancer Prevention Study II showed that both men and women who consumed alcohol were at lower risk than abstainers of death from all cardiovascular disease with little relation to the amount consumed (Thun et al., 1997). A reduction in risk of death from IHD was also clear, and it was particularly marked among men and women with pre-existing disease. Shaper and colleagues (Shaper et al., 1994) also found that the risk of major IHD events was most reduced among men who had symptomatic IHD. However, Muntwyler compared the subsequent cardiovascular mortality experiences (mostly due to IHD) of U.S. male physicians who had and had not had previous myocardial infarctions and found no difference between the groups in the substantial (about 20% in men who drank weekly or more often) and sustained reduction of risk across the consumption continuum (Muntwyler et al., 1998).

It also must be pointed out that most epidemiological studies from which much of the evidence is derived have involved middle-aged or older persons in stable social situations. This has to do with the fact that many large cohorts have been selected based on the criterion that persons should be easily traceable. It cannot be automatically assumed that the findings in these age-and social groups necessarily apply to younger drinkers or to other social groups.

(3) A third conclusion regarding the relationship between alcohol consumption and IHD is that much, if not all, of the protective effect arises from the ethanol component of alcoholic beverages and not from other components.

Some have argued that particular protection against IHD may be conferred by the consumption of wine (Goldberg et al., 1995). However, in an extensive review of the literature, it was concluded that a substantial portion of the benefit is derived from alcohol rather than other components of each type of drink (Rimm et al., 1996). Recent laboratory studies (for reviews, see Chadwick and Goode, 1998; Goldberg et al., 1995; Puddey and Croft, 1997) have found mixed results concerning the favourable effects of wines in modulating plasma lipid and lipoprotein concentrations, partly by comparisons with grape juices or with wines where the ethanol content was removed.

On the epidemiological level, the issue of beverages differences was recently examined in the context of overall mortality in a large group of Chinese men among whom the consumption of wine, predominantly fermented from rice, was prevalent (Yuan et al., 1997). No extra benefit from such consumption was observed. Most recently, Wannamethee and Shaper found that regular drinkers of all beverage types experienced a lower risk of major IHD events in a 16.8-year follow-up of men in the

British Regional Heart Study (Shaper and Wannamethee, 1999). Although wine drinkers had a substantially lower rate of these events compared to drinkers of spirits and beer, they also had a substantially lower risk of mortality from all causes, suggesting that as a group they had other characteristics that might contribute to the greater degree of protection experienced. Indeed, when the advantageous social and life-style characteristics of the wine drinkers were taken into account, the protection differential was markedly reduced to the point where it was no longer statistically significant. Overall, the question of potential additional effects of some alcoholic beverages is not fully settled yet and papers purporting particular health benefit from wine continue to appear. It can be concluded that any additional effect from wine is very small compared to the ethanol effect, and may not be relevant on a public health level (Klatsky et al., 1997; Rimm et al., 1996).

Doll also concluded that no specific benefit is associated with a particular beverage, but that any benefit arises from ethanol, *per se* (Doll, 1997). He pointed out that the extra health benefit associated with drinking wine that has been found in some studies (Gronbaek et al., 1995; Klatsky and Armstrong, 1993) can be accounted for by differences in the pattern of drinking, wine being usually consumed in small amounts on most days rather than in large amounts on only one or two days a week. Poikolainen and Vartiainen found that self-reported subjective good health was associated with moderate wine drinking in a general population sample of Finns (Poikolainen and Vartiainen, 1999). They also suggested that the beverage association might reflect drinking patterns, in particular the lesser tendency of wine drinkers to drink to intoxication.

(4) Finally, pattern of drinking is an important determinant of the risk and protective effects of alcohol with regard to IHD. This evidence is reviewed in Section 7 below.

In summary, the consumption of alcohol may confer protection against IHD among older adults. It remains unclear if low level drinking among young adults confers cardiovascular benefits later in life. It is important to emphasise that the protection is realised with the consumption of small to moderate amounts of alcohol (within current drinking guidelines) and that little, if any, additional benefit is derived from drinking larger amounts. The IHD benefit is largely, if not wholly, attributable to ethanol *per se*, and not to other constituents of particular beverages. Protection is most closely associated with a consistent pattern of drinking small amounts of alcohol. More variable drinking patterns, especially involving large amounts of alcohol, may actually increase the risk of IHD and death due to cardiovascular causes.

6.1.2 Cerebrovascular Disease (Stroke): Cerebrovascular disease refers to conditions giving rise to inadequate blood supply to the brain (United States Department of Health and Human Services, 1997). Stroke results from the sudden, severe disruption of cerebral blood supply, due either to blockage of a blood vessel (ischemic stroke), by far the predominant type of stroke, or rupture of a blood vessel (haemorrhagic stroke). The relationship between alcohol consumption and stroke is complicated by the disparate actions on these different pathologic processes of some of the biological mechanisms by

which alcohol use might influence the risk of cerebrovascular disease. For example, although alcohol-related hypertension may increase the risk of both forms of stroke, the antiatherogenic effects of alcohol consumption may decrease the risk of ischemic stroke, while the antihemostatic effects may increase the risk of haemorrhagic stroke and decrease the risk of ischemic stroke (Hillbom and Juvela, 1996).

The relationship of alcohol consumption to stroke was investigated in a comprehensive meta-analysis (English et al., 1995; Holman et al., 1996). The risks of ischemic and haemorrhagic stroke associated with alcohol consumption were compared and found to be similar. Evidence concerning a protective effect of low levels of alcohol against stroke was inconsistent, although the pooled estimates of 15 case-control and six cohort indicated a protective effect at low (responsible) levels of consumption in men, and at low (responsible) to hazardous levels in women. There was clear evidence that heavy drinking was associated with increased risk, particularly in women. In an extensive review of 12 case-control and 14 cohort studies, it was concluded that while there is substantial evidence that moderate drinking (defined as up to two drinks a day for men and one drink a day for women) does not increase the risk of ischemic stroke, evidence is divided on the question of a protective association of moderate consumption for ischemic stroke (Camargo, 1996a). Also, evidence from two cohort studies was cited, indicating that even moderate consumption may increase the risk of haemorrhagic stroke.

Other recently reported studies fail to offer clear evidence of a protective effect against stroke of moderate drinking, while further evidence of increased risk of stroke with heavy drinking has emerged. In the analysis of cohort data on British middle-aged men it was concluded that heavy drinking is associated with an increased risk of total stroke that is largely mediated through blood pressure (Wannamethee and Shaper, 1996). The role of alcohol as a risk factor for hypertension has been considered above. However, in comparison to occasional drinking there was no convincing evidence that light to moderate drinking was associated with a reduced risk of stroke. In an analysis of cohort data from the Busselton study in Australia, Knuiman and Vu concluded that the association between moderate alcohol consumption and stroke requires more study (Knuiman and Vu, 1996). In a prospective follow-up of more than 18,000 middle-aged men in Shanghai, light to moderate drinking (less than 1 oz or 23 g/day) offered no protection against death from stroke, the leading cause of non-cancer deaths in this population, while heavy drinking was associated with a 70% increase in mortality from this cause (Yuan et al., 1997). Most recently, in a 21 years follow-up of middle aged men, (Hart et al., 1999) demonstrated that risk of stroke increases steadily as alcohol consumption increases.

In contrast, in an analysis of data from the 9-year follow-up of 490,000 U.S. adults, Thun and colleagues found that less than daily drinking and daily drinking of 1, 2-3, and 4 or more drinks were all associated with a significant decrease in the risk of stroke death in men. In women, the protective effect was only significant among those in the two lowest consumption categories (Thun et al., 1997). In a case-control study, (Sacco et al., 1999) found that moderate drinking protected against ischemic stroke, but that heavy consumption increased the risk. As noted earlier, some of the same

mechanisms that underlie a protective effect of moderate drinking against IHD, notably the anti-atherogenic effects of alcohol, would also be expected to provide some protection against ischemic stroke (Hillbom and Juvela, 1996).

Long-term heavy alcohol consumption has been identified as an important risk factor for stroke in young people (You et al., 1997). Very recent alcohol drinking, particularly drinking to intoxication, also has been associated with a significant independent increase in the risk of cerebral infarction in both men and women ages 16-40 years (Hillbom et al., 1995). Haapaniemi and colleagues reported that recent drinking of alcohol was primarily associated with the onset of stroke during weekends and holidays in young people, possibly reflecting stroke-triggering events associated with heavy drinking (Haapaniemi et al., 1996).

In summary, it seems clear that heavy alcohol consumption is a risk factor for stroke. Evidence concerning the effect of more moderate consumption is less consistent. The weight of evidence suggests that low level alcohol consumption may offer some protection against stroke, apparently by reducing the risk of ischemic stroke. However, some studies have shown either no effect or a direct risk association. Drinking pattern may be an important determinant of stroke risk.

6.1.3 Peripheral Vascular Disease: Because of the now strong evidence concerning the protective effect of alcohol against IHD, it is logical to hypothesise that alcohol may be protective against peripheral vascular disease, another manifestation of atherosclerosis. In an earlier analysis of cohort data from the Framingham study alcohol was not found to have a significant relationship, either risk or protective, with peripheral vascular disease (Kannel and McGee, 1985). Other previous analyses of case-control or cross-sectional data have either failed to find a significant relationship between alcohol consumption and peripheral vascular disease, or weak and inconsistent inverse relationships were noted (Camargo et al., 1997). For example, in a cross-sectional study of middle-aged and older men and women conducted in Edinburgh, Scotland, it was found that increasing alcohol consumption was inversely associated with the prevalence of peripheral vascular disease in men, but not in women (Jepson et al., 1995). However, in a prevalence study of non-insulin dependent diabetics, a negative association was reported between alcohol consumption and peripheral vascular disease in women, but not in men (Mingardi et al., 1997). In a case-control study conducted in Greece, a pattern consistent with a "U" shaped risk curve was found, but the reduction in risk with low consumption was minimal and the increase in risk at high level was unusually large (Skalkidis et al., 1988).

More recently, in an analysis of the 11-year follow-up of more than 22,000 men enrolled in the Physicians' Health Study that controlled for the effects of smoking, exercise, diabetes and parental history of myocardial infarction, Camargo and colleagues found that daily drinkers of 7 or more drinks per week had a substantially reduced risk (relative risk 0.74) of peripheral vascular disease (Camargo et al., 1997). Further, in a recently reported prevalence study of peripheral vascular disease in 4,549 American Indians current alcohol consumption was negatively associated with the risk of this

disease in both men and women (Fabsitz et al., 1999). This analysis suggested that at least part of the protective effect was mediated through increased HDL levels, a well-established effect of alcohol on blood lipids (Zakhari and Wassef, 1996).

In summary, the relationship of alcohol consumption to peripheral vascular disease warrants further study.

6.1.4 Diabetes: In the Australian meta-analysis two cohort studies were identified that met the criteria for inclusion (English et al., 1995). It was concluded that there was some evidence that alcohol may protect against the onset of diabetes. Since then, the findings from a cohort of more than 40,000 male health professionals showed that moderate alcohol consumption may decrease the risk of diabetes, perhaps through the effects of alcohol on insulin sensitivity (Rimm et al., 1995). These effects have also been postulated to play a role in the protective effect of alcohol against ischemic heart disease (Heim et al., 1993; Rankin, 1994). Also, findings from another large cohort (the British Regional Heart Study) indicated a protective effect (Perry et al., 1995). Further, in a recently reported follow-up of the men enrolled in the U.S. Physicians Study a strong negative association of incident diabetes with alcohol consumption was shown. Men drinking one or more drinks per day had a 40% reduction in risk (Ajani et al., 1999). However, Kao and colleagues (Kao, 1998), in a three-year follow-up of middle aged men and women enrolled in the Atherosclerosis Risk in Communities Study (ARIC), found a statistically significant gender difference in the relationship between alcohol consumption and diabetes. In women but not in men, there was evidence (based on small numbers) of an inverse relationship between alcohol consumption and the risk of diabetes. Indeed, men consuming more than 21 drinks per week were at increased risk of diabetes. Lastly, in three prevalence surveys in high risk populations no association between alcohol consumption and diabetes was found (Hodge et al., 1993).

In summary, there is growing evidence from cohort studies that moderate alcohol consumption reduces the risk of diabetes.

6.1.5 Cholelithiasis: In the comprehensive Australian meta-analysis it was concluded that there was some evidence that alcohol protects against gallstones, which was supported by laboratory evidence concerning alcohol's role in cholesterol metabolism and the formation of bile acids (English et al., 1995; Holman et al., 1996). However, others attributed this association to protopathic bias, that is, people with gallstones reduce their alcohol consumption (Thijs et al., 1991).

An inverse relationship between alcohol consumption and the risk of gallstones has been found in three cohort studies from the United States, two of which were included in the Australian meta-analysis, that is, the Framingham Study (Friedman et al., 1966) and the Nurses Health Study (Colditz, 1990a; Maclure et al., 1989). Most recently, (Leitzmann et al., 1998) reported on the follow-up in 1994 of a cohort of 46,006 U.S. men aged 40-75 years who were free of gallbladder disease in 1986. Daily alcohol intake and number of drinking days was inversely related to the risk of gallstones, effects that persisted when 5,945 current non-drinkers were excluded from the analysis. Compared to

abstainers, men who consumed 45 grams or more of alcohol on 5 to 7 days had more than a 50% reduction in risk. These authors recommended that protection against gallstone disease be taken into account in formulating guidelines on moderate drinking. However, recent prevalence studies have failed to find any relationship, namely, findings from blood donors in Germany (Kratzer et al., 1997) and from male college alumni in the United States (Sahi et al., 1998). These differences may be explained once we measure patterns as well as volume of drinking and can relate outcomes to patterns. Leitzmann et al. (1999) showed that frequent moderate intake of alcohol decreases the risk of symptomatic gallstones, whereas infrequent or episodic intake had no such effect (Leitzmann et al., 1999).

In summary, the conclusion of the Australian meta-analysis (English et al., 1995) is further strengthened by recently reported findings from a large cohort that frequent and moderate alcohol consumption provides protection against gallstones.

6.1.6 Cognitive Benefits: The effects of moderate drinking on the brain's ability to perform cognitive tasks—including remembering, reasoning, and thinking—are largely unexplored (United States Department of Health and Human Services, in press). Although the relationship of heavy alcohol consumption (Parsons and Nixon, 1998), or alcohol abuse or dependence on cognitive impairment is well established (Williams and Skinner, 1990), much less attention has been paid to whether moderate drinking affects cognitive performance.

Before we go into details to answer this question, we would like to summarise the Parsons and Nixon overview with respect to quantity of drinking and cognitive functioning in social drinkers (Parsons and Nixon, 1998). Overall, the research since 1986 reviewed by these authors supports a threshold hypothesis for alcohol. Persons drinking five or six U.S. standard drinks per day over extended periods of time manifested some cognitive inefficiencies, persons drinking from seven to nine drinks per day manifested mild cognitive deficits, and 10 drinks or more per day resulted in moderate cognitive deficits equivalent to those found in persons diagnosed as alcohol dependent.

Most studies of the relationship of moderate alcohol consumption to dementia, notably Alzheimer's disease have failed to find statistically significant associations (for a summary, see (Tyas, 1996); for more recent research, see (Broe et al., 1998; Leibovici et al., 1999; Hebert et al., 1992). This should not take away from the fact that there is an established diagnosis for alcohol-related dementia that seems to constitute a substantial part of all dementias in long-term care facilities (Carlen et al., 1994).

However, several recent studies suggest that moderate alcohol consumption may have a positive benefit on cognitive function (for the most recent overview, see (Chick, 1998). In an analysis of baseline data (i.e., data collected at the beginning of a study) of persons aged 59 to 71 who were enrolled in the Epidemiology of Vascular Aging Study in France, moderate alcohol consumption was associated with higher cognitive

functioning among women, but not men, after controlling for a number of possible confounding variables (Dufouil et al., 1997).

Another study, that followed 3,777 community residents in France who drank primarily wine, found a markedly reduced risk of the incidence of dementia among moderate drinkers compared with abstainers (Orgogozo et al., 1997). This analysis controlled for age, sex, education, occupation, and baseline cognitive functioning. The investigators suggested several mechanisms by which alcohol might exert a protective effect against declining cognition with aging. One proposed mechanism is that alcohol may have a beneficial effect on the blood vessels in the brain. This mechanism would be consistent with observations from at least one study showing that the relationship between higher cognitive functioning and moderate drinking was confined to men with cardiovascular disease or diabetes, both of which are associated with impaired circulation (Launer et al., 1996).

Hendrie and colleagues also found a small but significant dose effect of drinking for cognitive performance in an urban sample of older black Americans, with subjects in the lightest drinking category scoring best (Hendrie et al., 1996). The curve can be described as J-shaped, but the differences in cognitive performance between drinking categories were rather small. Very similar findings of a small protective effect of past moderate alcohol intake on cognitive function was reported in aging Caucasian men (Christian et al., 1995).

On the other hand, Australian investigators found no associations, linear or non-linear, between alcohol consumption in 1982 and the results of any neuropsychological tests to measure a range of intellectual functions in 1991 in a random sample of Australian soldiers who served in the Second World War (Dent et al., 1997). Also, Edelstein and colleagues found no consistent effects of moderate social drinking on cognitive functioning on five standardised cognitive function tests (Edelstein et al., 1998). Elwood and colleagues also failed to find an association between alcohol consumption and cognitive functioning in a cross-sectional study of older men, although ex-drinkers had markedly lower test scores than either current drinkers or men who had never consumed alcohol (Elwood et al., 1999).

Trying to weigh the evidence together, one may tentatively conclude, that cognitive decline in older people may be reduced by light to moderate drinking (up to two drinks or 23 g per day; see also (Chick, 1998), who came to a similar conclusion). However, better control for confounders like education or social adjustment is necessary before coming to more definitive conclusions. A recommendation such as that by Chick to introduce alcohol consumption at “social hours” in institutions to achieve such benefits should be tested in more controlled settings before being implemented (Chick, 1998).

6.1.7 Stress reduction and mood elevation: Relaxation and the lessening of the symptoms of stress are among the most commonly cited benefits of moderate drinking, not only by popular accounts but also by scientific writers (Wilson et al., 1982; Wilson et al., 1988; Baum-Baicker, 1985a; Hauge and Irgens-Jensen, 1990). However, perceived

stress-reduction has also long been associated with alcohol dependence, particularly within individuals with high levels of anxiety (Wilson et al., 1988; United States Department of Health and Human Services, 1997; Eckardt et al., 1998). Psychological distress and reliance on alcohol for the relief of such symptoms are also predictive of the development of alcohol abuse and dependence; and are considered to be important clinical signs of an existing problem (Kessler et al., 1996; Kessler et al., 1997).

This overview will not address stress-reduction of heavier drinking or in dependence. It is also beyond the scope of this report to provide a critical review of pharmacological research in this area, much of which involves experimental studies of humans and laboratory animals. However, even moderate amounts of alcohol are not recommended for patients with existing mood and anxiety disorders (see Section 10.2) because of the potential for adverse drug-interactions, as well as the likelihood of worsening of symptoms (Castaneda et al., 1996; Castaneda et al., 1998).

The effects of alcohol on the central nervous system are extremely complex, in part because alcohol interacts with many different neurotransmitter systems, and also because the effects on these systems may be variable (Kalant and Khanna, 1989). The interaction of ethanol on several of these systems may produce an effect of reduced or heightened anxiety (United States Department of Health and Human Services, 1997; Eckardt et al., 1998; Pohorecky, 1991; Eckardt et al., 1998). Two relevant reviews (Pohorecky, 1991; Eckardt et al., 1998) have concluded that there is evidence that ethanol has an anxiolytic effect in mice and rats, particularly as mediated by the GABA_A – Benzodiazepine receptor complex; but other receptors may also be involved. In mice, the anxiolytic effect is found only at fairly high levels of blood alcohol (Eckardt et al., 1998). There is also some evidence that greater anxiety levels might play a role in certain strains of animals bred specifically for their preference for alcohol.

The situation in human subjects is further complicated by issues such as previous drinking experiences and tolerance but also, and significantly, by expectancies and beliefs about the effects of ethanol which can have an effect as strong as the pharmacological properties (Leigh and Stacy, 1991; Eckardt et al., 1998). Because of the significance of expectancy effects, experimental studies able to control for these effects provide more relevant data than non-experimental studies based on self-reports. Reviews of the experimental studies of stress-reduction in humans, however, have concluded that this evidence is highly inconsistent (Pohorecky, 1991; Eckardt et al., 1998; Castaneda et al., 1998). Whether physiologic measures of reduced stress response are found in the predicted direction varies according to the type of physiologic response measured, the stressful stimulus used, the dose used, and whether the blood alcohol level was rising or falling (Stritzke et al., 1996; Wilson et al., 1982; Eckardt et al., 1998). Several, but not all, studies have also found anxiolytic responses to be more likely, or stronger, in individuals with higher anxiety levels, such as phobic patients and those with anxiety disorder (Pohorecky, 1991; Eckardt et al., 1998). One frequently cited paper reported that some subjects have exhibited increased anxiety as measured by physiologic changes, while perceived anxiety has been reduced (Pohorecky, 1991). Withdrawal from alcohol,

in humans, has also been shown to result in depressive symptoms and excitability (Castaneda et al., 1996).

Sufficient evidence exists to show that moderate alcohol use is associated with perceived reduction of stress in individuals with positive expectancies about its stress-reducing properties. However, objectively measured stress-reduction is highly unpredictable, and no meaningful statement may be made about the amount of alcohol required by most individuals to achieve such an effect. Although it has not been conclusively shown that anxiety-reduction plays a meaningful role in reinforcement of alcohol use that lead to alcohol dependence, this is a plausible mechanism at least for individuals with high prior anxiety levels. Therefore, it cannot be concluded that stress-reduction is a predictable outcome of moderate drinking. At this time, it would also be irresponsible to advise alcohol use for stress-reduction, given the possible link between this strategy and addiction. Further, the use of alcohol for this purpose may lead to adverse effects such as worsening mood and anxiety problems and aggravate sleep-disorders (Castaneda et al., 1998)

Another benefit popularly attributed to alcohol is as a sleep aid (for review, see (Castaneda et al., 1998). Although moderate alcohol may induce sleep, it also leads to increased wakefulness and arousal, several hours later and so is well-documented as having aggravating effect is sleep disorders.

6.2 Magnitude of benefits

There is an increasing body of evidence that alcohol consumption has a protective effect against IHD and, probably, ischemic stroke (Maclure, 1993; English et al., 1995; Poikolainen, 1995; see also the literature cited above). The amount of consumption required to obtain a beneficial effect remains at issue, with some studies showing a beneficial impact for as much as six drinks per day, but it is clear that relatively low levels of consumption are associated with lower rates of cardiovascular disease. However, it was well known that alcohol conveys a wide variety of subjective benefits to the drinker long before there was any evidence that low level drinking provides objective physiological benefits. These more subjective psychological benefits include an improved sense of well-being and quality of life, as well as evidence of potential cognitive effects in enhancing creativity and therapeutic impacts in times of stress (Baum-Baicker, 1985b; Makela and Mustonen, 1988; Midanik, 1995; Poikolainen et al., 1996; Poikolainen and Vartiainen, 1999). Peele maintains that it is critical in terms of understanding alcohol use to recognise that alcohol accompanies, encourages, and in some sense leads to good times, sociability, shared experiences, and personal enjoyment and well-being (Peele, 1997). Ironically, these benefits are so widely accepted as to be somewhat invisible (Roche et al., forthcoming).

Although research is a long way from quantifying these subjective benefits of alcohol at the population level, it is possible to derive estimates of the number of deaths and hospitalisations prevented by alcohol use.¹ Scientific awareness of the cardiovascular benefits of alcohol consumption is still relatively new, and estimates of the number of

lives saved by alcohol use have only been reported in Australia (English et al., 1995), New Zealand (Scragg, 1995), Canada (Single et al., 1999) and in Finland (Makela et al., 1997).²

English and colleagues presented estimates of alcohol attributed mortality for 1986 with and without including the effect on IHD (English et al., 1995 Table 3.23). It may be seen that 3129 deaths were attributed to alcohol before considering the positive impact of alcohol consumption on IHD. After including IHD the net number is –1323 which corresponds to 4452 deaths prevented from IHD. The number of deaths averted by the use of alcohol is therefore greater than the number of deaths caused by alcohol use. The same finding appears to be true for Canada. The Canadian estimates were conducted as part of a study to estimate the costs of substance abuse, including alcohol misuse (Single et al., 1998; Single et al., 1999). It was estimated that alcohol prevented 7,401 deaths in 1992 (5,162 males and 2,239 females). This includes deaths due to IHD (4,205 deaths prevented), stroke (2,965 deaths prevented), heart failure and ill-defined heart conditions (183 deaths prevented), and from various other causes (47 deaths prevented).

However, the Canadian study also found that alcohol-related mortality frequently involves young adults while the benefits of low level consumption in preventing cardiovascular disease generally involves preventing the loss of life among older adults. Thus, the years of potential life lost due to alcohol (186,257) is more than twice as large as the number of years of potential life saved by the beneficial effects of alcohol (88,656). A very similar pattern was found in New Zealand, resulting in a net effect of years of life lost of 9,525 (Scragg, 1995). With regard to morbidity, while alcohol accounts for approximately 86,000 hospitalisations in 1992, it is estimated that 45,414 hospitalisations (31,270 for males and 14,114 for females) were prevented by alcohol use in the same year. These were mainly due to the benefits of drinking to IHD (18,705), stroke (16,138), cholelithiasis (7,722), and heart failure and ill-defined heart conditions (2,312). Therefore, the number of hospitalisations caused by alcohol far outnumbers the number prevented by alcohol use.

The Finnish study (Makela et al., 1997) found that the number of deaths from IHD prevented by alcohol use was nearly equal to the number of deaths caused by alcohol in older age groups, but the overall number saved was much smaller than the number of deaths caused by alcohol use. This finding contrasts with that of the Australian, New Zealand and Canadian studies where it was found that the number of lives saved were higher than the number of deaths caused by alcohol use. However, as noted above, in the Canadian study, the years of life lost and hospitalisations caused by alcohol were much greater than the years of life and hospitalisations saved. Further, it should be noted that even relatively low levels of consumption carry some risks, particularly alcohol-related trauma arising from intoxication because low-level consumers tend to be naïve drinkers with low tolerance and few social mechanisms to avoid problems when intoxicated.

7. Patterns of consumption as they relate to both harm and benefits

Prospective and case control studies on the risk of cardiovascular disease and other consequences of alcohol consumption generally examine an individual's average drinking level without taking drinking patterns into account. Thus, the estimates of mortality and morbidity caused or prevented by alcohol use must necessarily rely on a summary measure of an individual's overall level of drinking to assess risk. The major epidemiological studies encompassed in meta-analyses such as English and colleagues (English et al., 1995) do little to inform us on the role of drinking patterns³ (vs. drinking level) in influencing the harmful or beneficial effects of alcohol consumption. Despite the limited nature of the evidence, there are indications that drinking pattern has a significant impact not only on the nature and magnitude of adverse consequences, but also on the benefits of alcohol consumption (Puddey et al., 1999a).

Many studies clearly indicate that pattern of drinking is an important determinant of both risk and protection with regard to cardiovascular disease, IHD and cardiovascular risk factors (Poikolainen, 1998; Puddey et al., 1999a). Some years ago, in a clinical study of coronary occlusion in 526 male patients who had had coronary arteriography, lower levels of coronary occlusion were found in regular drinkers whose drinking patterns were relatively consistent, compared to drinkers whose patterns were more variable (Gruchow et al., 1982). More recently, in comparison to abstainers, a pattern of moderate regular consumption was associated with a reduction in the risk of a major coronary event (acute myocardial infarction or coronary death) whereas 'binge' drinkers had an increased risk of experiencing such an event (McElduff and Dobson, 1997). Further, an acute protective effect was evident in regular drinkers of both sexes in relation to alcohol consumption in the preceding 24 hours.⁴

In a comprehensive review, Bondy concluded that a pattern of frequent drinking may confer some protection against IHD; further, large amounts are not needed to achieve a beneficial effect (Bondy, 1996). Small amounts may be particularly helpful if taken with meals, because alcohol with meals reduced high levels of blood lipids found after eating (Criqui, 1994; Criqui and Ringel, 1994; Veenstra et al., 1990). Recent experiments by Dutch investigators confirm the beneficial effect on blood lipids of moderate alcohol consumption (40 grams ethanol) with dinner (vanTol et al., 1998). Further, these effects are similar for beer, wine, and spirits (Hendriks et al., 1998). Finally, it has been shown that the anti-hemostatic benefit conferred by moderate alcohol use is only present while the person is drinking (Rubin and Rand, 1994).

In contrast, the acute heavy consumption of alcohol appears to increase the risk of a cardiovascular event. For example, a pattern of beer bingeing (consuming six or more bottles per drinking session) was found to markedly increase the risk of acute myocardial infarction (Kauhanen et al., 1997b). As well, in a follow-up study of middle-aged men in Finland that took into account age and total alcohol consumption, men who had frequent hangovers were found to have more than twice the risk of cardiovascular death compared to men who drank but had fewer hangovers (Kauhanen et al., 1997a). Binge drinking has been implicated as an important cause of sudden cardiac death in Russia, where this

pattern of drinking prevails (Chenet et al., 1998). The adverse effect of acute heavy consumption with regard to IHD found epidemiologically has been confirmed experimentally in patients with stable angina pectoris (Rossinen et al., 1996).

There is relatively little evidence on patterns for other chronic disease. An exception concerns gallstones. The above cited Leitzmann et al. study found that only frequent drinking occasions and not episodic drinking were protective (Leitzmann et al., 1999). This scarcity of results does not indicate that no relationship between patterns and chronic disease outcomes other than IHD exist. It may just be a reflection of the current methods used in medical epidemiology, where only volume is measured (see remarks in Sections 2.5 and 4.2 above).

With respect to acute outcomes it goes without saying that patterns including heavy drinking episodes are detrimental. In fact it has been found that most acute consequences in established market societies were caused by average moderate drinkers after they had heavy drinking occasions (Kreitman, 1986; Stockwell et al., 1996; Skog, 1999).

Further evidence of an impact of drinking pattern stems from the findings in Australia, New Zealand, Canada and Finland regarding the numbers of deaths prevented by alcohol use. As noted earlier, in Australia, New Zealand and Canada, it was found that many more lives were saved by low-level use (English et al., 1995; Scragg, 1995; Single et al., 1999) while in Finland more deaths were caused than prevented by alcohol use in Finland (Makela et al., 1997). Although the overall rate of consumption in Finland was slightly below that in Canada, New Zealand and Australia, it is likely that the well documented Finnish pattern of drinking (Makela et al., 1983) may also account for at least part of these divergent results. A Finn who drinks 7 drinks a week often does so at one sitting, while a Canadian who averages 7 drinks a week tends to have one or two drinks on several days of the week. Given the manner in which Finns drink, even an average of one drink per day is often not 'moderate' at all. Thus the more sporadic, binge drinking patterns among Finns may be an important reason why they appear to obtain fewer cardiovascular benefits from drinking compared with Canadians. This evidence is only suggestive however, due to differences in overall consumption and study methods employed.

The finding of a much lower cardiovascular benefit in Finland compared to Australia, New Zealand and Canada strongly suggests that it may be important to consider more than the average ethanol intake in future studies. The binge drinking pattern common in Finland may result not only in greater alcohol problems, particularly acute problems arising from intoxication, but it may also greatly limit the benefits of low-level drinking. Thus, drinking patterns are not only important in predicting adverse consequences, they may also be also important in determining the magnitude of the benefits from drinking.

Finally, there is one further aspect of drinking patterns that should be noted. The setting in which drinking takes place can have an influence on the likelihood of alcohol-

related trauma. General population surveys have found a strong association between high consumption levels and the proportion of consumption that occurs in particular venues (Single and Wortley, 1994). Heavy drinkers report a higher proportion of their alcohol consumption in bars and taverns. Tavern studies have identified five major sets of situational determinants of drinking behaviour: temporal variations, characteristics of the drinking group, the length of time spent on one drinking occasion, the characteristics of the physical environment and price differentials (Single and Storm, 1985). In particular, drinking to intoxication is related to drinking in large groups and with exclusively male drinking confederates.

8. The impact of alcohol consumption on total mortality

The overall impact of alcohol consumption on mortality can be assessed in several ways (Rehm and Bondy, 1998):

- 1) by combining risk for various alcohol-caused diseases with weights derived from the prevalence or incidence of the respective disease;
- 2) by conducting meta-analyses using individual-level epidemiological studies that examine all causes contributing to mortality; and/or
- 3) by conducting meta-analyses based on aggregate level studies between per capita consumption and mortality.

The first approach has rarely been used mainly due to the fact that alcohol has been found to be related to more than 20 different diseases (see Single et al., 1999)). A simpler model based on two relationships was used in the Global Burden of Disease (GBD) study : (1) the deleterious effects of alcohol on injuries and disease, and (2) the beneficial effect of alcohol on IHD (Murray and Lopez, 1996). No alcohol consumption distribution risk curves for different regions were included in the first GBD study but the GBD 2000 study will use this distributional approach (Murray and Lopez, 1999).

The meta-analytic approach to assessing overall mortality was used by English and colleagues English et al., (1995) to summarise the results of 16 studies, 10 of which were conducted in the United States. In this analysis, researchers found the relationship between alcohol intake and mortality for both men and women to be J-shaped curves: the lowest observed risk for overall mortality was associated with an intake of one to two drinks (10-19 grams of alcohol) per day for men and somewhat less for women (English et al., 1995: Table 3.2). An intake of 2-3 drinks (20-29 grams of alcohol) per day for women was associated with a significantly increased risk of death compared with abstainers. The risk for women continued to rise with increased consumption and was 50 percent higher among those consuming 40 grams of alcohol per day or more, when compared with abstainers. Men who averaged 3-4 drinks (30-39 grams of alcohol) per day had the same mortality as abstainers, whereas a significant increase in mortality was found for those consuming at least 4 drinks (40 grams of alcohol) per day. The study team pointed out that these results should be applied only to industrialised countries.

The confidence intervals around these estimates were rather small, suggesting that the J-shaped curve was very stable. And indeed, most recent studies, not yet included in the meta-analysis, have confirmed such a relationship (Brenner et al., 1997; Camargo et al., 1997; Doll et al., 1994; Fuchs et al., 1995; Keil et al., 1997; Renaud and Gueguen, 1998; Thun et al., 1997; Yuan et al., 1997).

It is true that some studies did not confirm this J-shape, either by finding no protective effect for light to moderate drinking (less than 1 oz or 23 g/day; see Leino et al., 1998; Middleton Fillmore et al., 1998; Hart et al., 1999) or by finding protective effects for all drinking categories (Berberian et al., 1994) but significantly only for CVD deaths). But overall, the basic J-shape of the curve persisted in the vast majority of studies (Gaziano and Buring, 1998), even after:

- controlling for the *sick quitter hypothesis* (Shaper, 1990b; Shaper, 1990a; Shaper et al., 1988); for an example of persistence by comparing to lifetime abstainers see (Rehm and Sempos, 1995b),
- *adjusting for diet* (Artaud-Wild et al., 1993); for an example of persistence after controlling for BMI and cholesterol see (Rehm and Sempos, 1995a), and
- *adjusting for social isolation* (Skog, 1996); for an example of persistence of the beneficial effect of alcohol after controlling for different aspects of social variation (see Murray et al., in press).

It should be noted that the J-shape results mainly from the beneficial effects of moderate consumption on ischemic cardiovascular conditions and the detrimental effects of all kinds of drinking on other health conditions. The risk curves of the latter may vary between linear, exponential or threshold effects, but they seem to be always monotonic: the more consumption, the higher the disease-specific mortality risk (Rehm et al., 1996a). This also means that the J-shaped curve should not be expected and cannot be found in populations with no or few IHD deaths (for example, in some developing countries, (Murray and Lopez, 1996); or in younger age groups, (Andreasson et al., 1988; Andreasson et al., 1991; Rehm and Sempos, 1995b).

Biological experimental research supports both the beneficial effect of moderate consumption on IHD, as well as the detrimental effects (see the various contributions *in Alcohol Health and Research World*, 1997 (Chadwick and Goode, 1998); specifically for IHD, see (Klatsky, 1994; Renaud et al., 1993) and Section 6.1.1, thus strengthening our belief in causality according to standard epidemiological criteria (Rothman and Greenland, 1998)).

Thus, it seems fair to say that the J-shaped curve has persisted in the years since English et al. (English et al., 1995). The following points should be considered, however, before transforming epidemiological results into public health programming:

- While recent research has more often confirmed the J-shape than not, the optimal level of consumption (for example, the level of consumption associated with minimal risk) seems to vary quite dramatically as a factor of culture. Thus, studies from

cultures with high consumption levels also found the optimal level to be much higher. For example, the following studies all found higher optimal levels than those calculated by English and colleagues (English et al., 1995; Brenner et al., 1997; Farchi et al., 1992; Keil et al., 1997; Renaud and Gueguen, 1998). While this variety of results, indicating levels of lowest mortality associated with average alcohol consumption from 0 g (Hart et al., 1999) to 30 g or more of pure alcohol per day in the German or French cohorts (Keil et al., 1997; Renaud and Gueguen, 1998) does not contradict the J-shaped curve, it casts doubt on the assumption that *only* or *mainly* biologically-based mechanisms result in beneficial effects. Other mechanisms must be working in addition to biological ones, and since the results vary systematically by drinking culture, this variable is suggested as another additional determinant of the level of minimum mortality risk. Suggesting that drinking culture is an important factor in the relationship between consumption levels and mortality does not suggest the exact mechanisms that can explain this relationship. Such mechanisms could be as simple as similarity amongst the composition of the abstainer groups in different cultures (Shaper and Wannamethee, 1998). These considerations also lead to the conclusion that, based on current research, an optimal level of average consumption for Australia cannot be easily given.

- Many studies have traditionally been carried out in medical epidemiology, based on questionnaires that included only a few questions or, in the extreme cases, only one question on alcohol consumption. While such questionnaires are likely to give a reliable indication on overall volume (Willett et al., 1985; Willett et al., 1987; Willett et al., 1988; Rimm et al., 1992), they tend to concentrate on this parameter and disregard patterns of drinking (Rehm and Bondy, 1998). As a result, non-chronic disease-related mortality and other mortality linked more to patterns than to volume of drinking may be underestimated (Rehm et al., 1996b). Again, this would not necessarily change the overall pattern of the J-curve, but it adds a new dimension which cannot be easily reduced into the average volume of consumption axis. It should also be mentioned that in order to start a program of research on drinking patterns, the field needs reliable (test-retest) and validated instruments to measure consumption patterns (Rehm, 1998a; Rehm, 1998b).⁵
- There may be several mechanisms working at the same time. On the one hand, *specific* health benefits and risks may be related to biological mechanisms. On the other hand, *generalised* health risks, or a general susceptibility, may be present in addition to the specific risks. Such risks would be related to problems of adjustment or deviant behaviour. Generalised health risks would be over-represented among abstainers and heavy drinkers (see Andreasson et al., 1988), who does not include the biologically-based benefits into his hypothesis; see also (Skog, 1996), for similar argumentation). Again, this may not change the basic J-shape, but adjusting for social mechanisms by subtracting the generalised effects from both abstainer and heavy drinkers would render the curvilinear section of the curve much flatter.
- Aggregate level studies using time series methodologies have not found any curvilinearity between per capita alcohol consumption and all-cause mortality. A

recent study of data from 25 European countries pertaining to the years 1982 to 1990 estimated that increases or decreases in per capita consumption of one litre of pure alcohol were associated with corresponding increases or decreases of about 1 percent in all-cause mortality rates (Her and Rehm, 1998). Another analysis of European data from the turn of the century (Norstrom, 1996) indicated similar findings. These results may be explained by the fact that the optimal level for aggregate consumption is different from the optimal level for individual consumption (Skog, 1996; Rehm et al., 1997), and that the analyses have only detected the right hand part of the J-curve that could be modeled as a straight linear effect. Clearly, we need more studies of this kind before coming to any conclusions on this issue (see also Rehm et al., 1996).

In summary, we have identified four areas, where further work on the J-shaped curve between alcohol consumption and mortality seems necessary. However, while such research is likely to result in different J-shapes than the one described in the meta-analysis of English et al. (English et al., 1995), the basic form of curvilinearity should hold for average volume of drinking. However, for alcohol policy recommendations or low-risk drinking guidelines these refinements are crucial. It makes a huge difference if the level of optimal consumption is 0 g, 10 g, 30 g or even more of average per day. As well, such guidelines should have recommendations on patterns of drinking to cover more acute consequences (Bondy et al., 1999).

9. Alcohol consumption in different population groups

Australian drinking patterns—relevant surveys: Five National Drug Strategy Household Surveys (NDSHS) of the general community were carried out in the period 1988-1998. The Australian Bureau of Statistics conducted the first four, the combined results being reported in the monograph, *Patterns of Drug Use in Australia* (Makkai and McAllister, 1998). The fifth survey was conducted in 1998 by the Australian Institute of Health and Welfare (Australian Institute of Health and Welfare, 1999; Australian Institute of Health and Welfare, 1999). In addition, the Australian Bureau of Statistics carried out a survey of Urban Aboriginal and Torres Islander Peoples in 1994 (Commonwealth Department of Human and Human Services, 1996).

In *Patterns of Drug Use in Australia* Makkai and McAllister classified drinking behaviours by combining information on quantity and frequency of consumption as follows (Makkai and McAllister, 1998):

- Harmful/hazardous-drinking = males: 5+ drinks 7 days per week, 7+ drinks 4-6 days per week or > 12 drinks 2-3 days per week; females: 3+ drinks 4+ days per week, 5+ drinks 2-3 days per week or > 6 drinks 2+ days per week;
- Binge drinking = males: >7 drinks no more than 1 day per week; females: >5 drinks no more than 1 day per week);
- Heavy drinking = males: usually drinks 5+ drinks; females: usually drinks 3+ drinks;
- Moderate drinking = less than the above amounts;

- Non-drinkers = never tried alcohol as well as ex-drinkers.

A 1998 NDSHS release (Australian Institute of Health and Welfare, 1999) included information on the proportion of recent drinkers aged 14 years and older, by consumption risk level, age and sex. The categorisation was based on NHMRC guidelines for daily intake and the response to the question, 'On a day that you have an alcoholic drink, how many standard drinks do you usually have?' (Low risk = males <5, females <3; hazardous = males 5-6, females 3-4; harmful = males >6, females > 4.). With this categorisation that is based on a usual drinking day, it is to be expected that the reported frequency of harmful and hazardous drinking will be higher than those in the earlier surveys that classified drinking behaviour by combining daily levels and frequency.

In the subsequent publication, *1998 National Drug Strategy Household Survey. First Results* (Australian Institute of Health and Welfare, 1999), additional information was provided on the quantity of alcohol consumed and frequency of consumption for recent alcohol drinkers aged 14 years and over, by sex. However, the manner in which this information is reported does not enable comparisons to be made with the proportions of moderate, heavy, binge and hazardous/harmful drinkers in the report on consumption patterns for the period 1988-95.

Selected findings are presented in Table 2 (Types of Drinkers by Gender, 1988-1995), Table 3 (Types of Drinkers, excluding non-drinkers, by Gender, 1988-95) and Table 4 (Drinking Patterns Among Adolescents, 1988-1995).

1988-1995 Household Surveys-Adult drinking patterns: Over the period 1988-95 there was evidence of some favourable changes in the drinking patterns of Australian adults. These changes affect the abstinent, moderate and heavy-drinking categories. Since 1998, abstinence and moderate drinking among drinkers have increased, while high volume drinking, heavy drinking sessions and binge drinking among moderate drinkers have decreased.

Women were more likely than men to be non-drinkers and conversely men were more likely than women to be moderate drinkers. However, if these two categories are combined there appears to be no significant gender difference. Over the period 1988-1995 the combined prevalence of non-drinking and moderate drinking appears to have increased (Table 2).

If one includes non-drinkers, there is no significant gender difference in the prevalence of the combined categories of heavy, binge and harmful/hazardous drinking in 1995 (Table 2). However, if only drinkers are included, there appears to be a gender difference with a consistent preponderance in women in all survey years (Table 3).

In recent years the relationship between the nature and circumstances of drinking episodes to acute alcohol-caused problems has been well described and has led to the development of prevention strategies. These studies have produced an appreciation that a significant proportion of alcohol-related burden occurs as a result of occasional heavy drinking sessions in individuals who otherwise fit the category of moderate drinkers (Kreitman, 1986; Skog, 1999). In the 1993 survey moderate drinkers made up 30% of those who reported consuming 8-12 drinks on one or more than one session in the last two weeks and 17% of those who reported their intention to get drunk during these sessions. In the 1995 survey a significant decline was observed in heavy drinking and binge sessions in moderate drinkers, few of who reported their intention to get drunk during their last heavy drinking session. Such improvements were not observed among binge and harmful/hazardous drinkers.

1988-1995 Household Surveys-Adolescent drinking patterns: The major difference in drinking patterns between the general urban community 20 years and older and adolescents aged 14-19 years, is the much higher prevalence of heavy and binge drinking among the latter. The results from the 1988-1995 surveys indicate an increase in the prevalence of those who report non-drinking and a slight decline in harmful/hazardous drinking. Young men are more likely to be moderate drinkers than young women with the latter reporting more binge and heavy drinking (Table 4).

1998 Household Survey--Drinking patterns: Eighty-one per cent of Australians aged 14 years and older were recent drinkers (i.e., consumed alcohol at least once in the last year) and of these approximately 50% were regular drinkers (i.e., consumed alcohol at least one day per week). Of those aged 14 to 19 years, more than two-thirds were recent drinkers and 30% were regular drinkers. Males in all age groups were more likely to be regular drinkers.

Among recent drinkers (i.e., consumption within the last 12 months) harmful/hazardous drinking, defined on the basis of the usual level of daily consumption when drinking occurred, was most prevalent in those aged 14-19 years (67%) and progressively declined in each succeeding decade to 15% in those aged 60 years and older. Hazardous/harmful drinking was much more prevalent in females than in males from the age 14 to 39 years, was slightly greater in males than in females in the decades 40-49 and 50-59, and then became more prevalent in females than in males aged 60 years and older. Overall harmful/hazardous drinking prevalence was greater in females (38%) than in males (33%).

Changes between 1995 and 1998: The following changes have been noted in the drinking status of Australians aged 14 years and older between the 1995 and 1998 surveys:

- The proportion that consumed alcohol regularly (i.e., at least one day per week) increased from 44% in 1995 to 49% in 1998. In 1998 males were more likely than females to drink regularly (59 versus 39%).

- The proportion that consumed alcohol occasionally (i.e., less than one day per week) decreased from 34% in 1995 to 32% in 1998. In 1998 females were more likely than males to drink occasionally (39 versus 25%).
- The proportion of ex-drinkers remained constant at about 10% between 1995 and 1998.
- The proportion that had never consumed a full glass of alcohol declined from 12% to 10%.

Aborigines and Torres Strait Islanders: In comparison with the general urban adult community, urban Aborigines and Torres Strait Islanders were more likely to be non-drinkers (38% vs. 28%) and to drink less frequently. However, current indigenous drinkers were more likely to drink in a harmful/hazardous manner than the urban community (82% vs. 28%). Most of the difference in the prevalence of non-drinkers between these two groups is accounted for by the much higher prevalence of ex-drinkers in the indigenous group (22%) compared with the general urban community (9%) (Commonwealth Department of Human and Human Services, 1996).

Available evidence supports the view that high-risk drinking among Indigenous Australians is an expression of their severe socio-economic disadvantage and, as such, is part of a cycle in which "alcohol has had a major, and generally damaging impact on Aboriginal traditional life, family structure, health and capacity for self-determination" (Hunter et al., 1991).

It is noteworthy that Indigenous adults are more likely than non-Indigenous adults to be exposed to more than one of three risk factors—high risk drinking, smoking and obesity—that are interactive in their effects on the aetiology, course and outcome of disease (McLennan and Madden, 1999).

Immigrants: Sample sizes limit interpretation of data on drinking among non-English speaking immigrants. However, the data suggest that members of this group are more likely to be abstainers than English speaking citizens (Makkai and McAllister, 1998).

Per Capita Consumption of Alcoholic Beverages: In the six-year period 1992/93 to 1997/98 the annual per capita consumption of alcoholic beverages in litres of absolute alcohol has fluctuated between a low of 7.57 in 1992/93 to a high of 7.79 in 1993/94. In 1997/98 the value was 7.77 litres (Australian Bureau of Statistics, 1999). These values compare with a peak value of 9.8 litres in 1980 (Health and Welfare Canada, 1984).

10. Implications to drinking guidelines

The major purpose of the foregoing review is to provide an evidentiary basis for the development of new drinking guidelines in Australia. In going from research findings to drinking guidelines, one inevitably moves into areas of uncertainty and judgment. The evidentiary basis of guidelines necessarily suffers from certain gaps in our research knowledge. In particular, there is a need for improved standardisation of measures of

drinking. For example, there is no universal standard for what constitutes a "standard drink" in epidemiological studies. There is also a need for more research into the impact of different drinking patterns on the relative risk of various causes of disease and death.

Bearing these caveats in mind, the following levels of drinking considered to be low-risk could be specified, based on existing evidence of overall mortality. For chronic disease consequences the low-risk levels should be different for females and males. For females the average daily intake should not exceed a level between 15g and 25g of pure alcohol per day. For males, the average daily intake should not exceed a level between 25g and 45g per day. These values were determined from the meta-analysis of English and colleagues (English et al., 1995), taking into account the subsequent studies on overall mortality cited above. Some of these studies, especially in countries with relatively high per capita consumption, found higher drinking levels for males than English et al., which were still protective. As indicated below, these levels should be supplemented with guidelines of maximum intake per occasion based on acute consequences.

Alcohol as an exposure may have different consequences in different populations because of two reasons:

1. Alcohol consumption may be different (for example, overall consumption or prevalence of heavy drinking or patterns of drinking) in the populations under consideration leading to different consequences.
2. The relationships between consumption of a certain level and consequences may differ between populations.

Consider the first case, which is by far the more frequent one. It assumes that normally the risk relationships between alcohol consumption and consequences are stable. In other words, a consumption of 8 drinks a day on average for a prolonged time has the same elevated risk for liver cirrhosis, no matter what population the drinker stems from. Such an assumption is underlying the meta-analysis of English and colleagues (English et al., 1995) and in effect is underlying this review to a certain degree. If risk relations were not relatively stable across populations, we could not infer from research in the U.S. or Europe to build recommendations in Australia. Implicitly underlying this inference process is the assumption that most relationships between alcohol consumption and health outcomes are invariable because they are biologically determined, that is, that intake of alcohol is invariably associated with certain biological processes which in turn lead to the health outcome under consideration.

There is some evidence to support such an assumption for cancers, the mental health and cardiovascular disease conditions (both for the beneficial and the detrimental effects, see (Zakhari, 1997)). However, the evidence is by no way complete in the sense that we could specify exact mechanisms for all of the relationships between alcohol-related variables and health outcomes.

Note that even universal biological mechanisms may lead to different burdens for the same alcohol intake when other circumstances are quite different. For example, the

predisposition to alcohol effects that can lead to cirrhosis is related to a higher prevalence of the gene for hemochromatosis in the Australian population, as noted earlier. Also, in very poor populations, where the general health state is already inferior for various reasons (such as inadequate nutrition, poor health care, etc.), the same intake may lead to more severe detrimental consequences. This seems to be the case in Russia today (Leon et al., 1997; Chenet et al., 1998). However, different drinking patterns in Russia (specifically, binge drinking), which are clearly related to mortality but usually not measured in epidemiological studies, may be an alternative explanation (see above and (McKee and Britton, 1998) for physiological underpinnings).

Most of the time, however, it seems a reasonable assumption that the relationships between alcohol intake and health consequences are fairly stable for cancer, mental and cardiovascular conditions. This means that different burdens in different populations could be attributed to different alcohol intake, overall consumption or patterns of drinking. Following this reasoning this also means that preventive actions could be specified to change the alcohol intake in order to reduce disease burden.

For accidents and injuries, the relationship between alcohol intake and outcome seems to be more socially driven. For example, the links between consumption and acute problems are often quite weak, and culturally mediated by norms about how to behave after drinking. This mediation can be seen by inspecting the different forms of relationship between aggregate consumption and homicide in different Nordic countries (see (Lenke, 1990), for comparative time-series analyses).

What does this mean for guidelines in special populations? For the most part, such guidelines should be formulated to identify specific detrimental patterns of drinking and to advise against them. Usually, low risk drinking guidelines need not be changed for this reason, if they already include advice both for chronic and acute consequences of drinking (Bondy et al., 1999). Only if there is evidence that the population under consideration has different risk relationships for the same alcohol intake is it necessary to formulate specific guidelines. Here are some populations for which specific guidelines are indicated:

1. Women: As discussed in the sections about chronic conditions and all-cause mortality, there is enough evidence to indicate a differential effect for men and women. Consequently, guidelines intended to deal with these consequences (for example, weekly limits) should be specific for males and females. Thus, for example, the Canadian guidelines for weekly intake are lower for women than men (9 drinks or 122.4 g/week vs. 14 drinks or 190.4 g/week) because the risk of overall mortality increased at an earlier point in the J-shaped curve. Suggested ranges for low risk drinking resulting from this review were given in the section on overall mortality above (average daily drinking: maximally 15g – 25g pure alcohol for females and 25g - 45g pure alcohol for males).

2. Persons with genetic predisposition for alcohol dependence/abuse or with known alcohol problems: Persons with a genetic predisposition to alcohol dependence would not increase their risk of dependence if they drink within the low-risk drinking

guidelines. However, starting drinking may put them at risk to become alcohol dependent, as they disproportionately are not able to restrict their drinking to moderate levels. The same reasoning applies to persons who are recovering from alcohol dependence where research has shown that in many cases the resumption of drinking may not be controlled.⁶ It should be noted that few individuals have knowledge of a biological predisposition. While guidelines should generally represent a low risk of dependence for all members of the population, additional caution may be required for individuals with a predisposition to alcohol dependence. For some individuals, low-risk guidelines might be abandoned in favour of a recommendation of abstinence.

3. Elderly: With age, the volume of total body water decreases, and as ethyl alcohol is distributed in total body water, an alcohol dose identical to that administered to a similar-sized individual of the same gender produces a higher blood alcohol concentration in an older individual. It should also be taken into consideration that elderly often take regular medication, which may interact with alcohol. Consequently, the definition of moderate drinking needs to be revised downward for older individuals (Dufour et al., 1992; Dufour and Fuller, 1995; National Institute on Alcohol Abuse and Alcoholism, 1998).

4. People experiencing problems with mood, anxiety and sleep disturbances: As already stated, even moderate amounts of alcohol are not recommended for anyone with existing mood or anxiety disorders because of the potential for adverse drug-interactions, as well as the likelihood of worsening of symptoms (Castaneda et al., 1996; Castaneda et al., 1998). Individuals with specific conditions, such as bipolar affective disorders, may be at a significantly increased risk of alcohol dependence, and even moderate drinking may worsen the course of the condition (Castaneda et al., 1998).

5. Pregnant women, women trying to conceive and lactating women: Pregnancy represents a special circumstance worth noting. Guidelines intended to protect the mother from alcohol-related harm continue to be valid. However, the biological susceptibility to harm for the fetus and infant is quite different and this should also be considered. For example, during breastfeeding, alcohol can pass from mother to the child - who has a limited ability to metabolize the alcohol. Poor feeding, irritability and sleep-disturbances have been noted in young children exposed to alcohol where the blood alcohol level was not sufficient to greatly affect the mother. Such considerations might be sufficient reason for abstinence until the end of breastfeeding.

The weight of the evidence reviewed above (see Section 5.1) indicates that the most devastating alcohol-related birth defects are unlikely to occur in a woman whose pre-pregnancy drinking is in keeping with low-risk drinking guidelines. The evidence showed that drinking less than one drink per day, without heavier drinking episodes, has been found to have no measurable impact on several validated indicators of development and performance. However, there is also no guarantee that neurodevelopmental effects will not occur – effects which are measurable at the aggregate level, even if they are of uncertain significance to the actual mental and behavioural performance of the child. Women planning to become pregnant, or who have discovered they are pregnant, would

be wise to avoid frequent drinking and heavier drinking occasions, and may choose to abstain out of caution, especially if other risk factors are present, such as advanced maternal age, or poor maternal health or nutrition.

6. Children and adolescents: Children cannot be expected to have the same vulnerability to alcohol-related harm as adults. Lack of experience with effects and lower tolerance may be important in determining risk. The associations between alcohol and health consequences discussed in this report have rarely been assessed on anything other than adult populations and, typically, at middle age or greater, where chronic disease outcomes are more immediate. It is also worth noting that discussions of the special risk to children and adolescents are highly influenced by cultural beliefs about the appropriateness of drinking at earlier ages and the prevailing norms in terms of style of drinking seen in youth and young adults.

However, it should be noted that surveys found relatively high rates of alcohol-related problems in adolescents in countries where alcohol is officially not available to people of that age. (Adlaf et al., 1999) found for the year 1998 that 11% of the students in grades 7 to 13 (13 to 19 years of age) scored above 11 points on the AUDIT, a standardized WHO screening instrument for alcohol problems, and 6% were over the cut-off for the CAGE, a short screening instrument for alcohol abuse and dependency. It seems that many of these problems are transitory in the life course. Both the level and pattern of problems, as well as best policy measures, seemed to be strongly correlated with cultural beliefs.

7. Aborigines and Torres Strait Islanders: As specified above, the health-related outcomes of alcohol consumption for Aborigine and Torres Strait Islander people stem from their volume and patterns of drinking that are largely an expression of and further contribute to their severe socio-economic disadvantages. The adverse effects of high-risk drinking are further aggravated by smoking, poor nutrition, obesity, poor living conditions, exposure to violence and environmental hazards, and limited access to and use of health and social services.

The cumulative impact of all of these factors is reflected in a life expectancy for Indigenous People at birth that is almost 20 years less than that of all Australians. The life expectancy for Indigenous males born in 1991-96 is 56.9 years and 61.7 years for Indigenous females, compared with a life expectancy of 75.2 years for all Australian males and 81.1 years for all Australian females (Australian Bureau of Statistics, 1999).

Indigenous Australians' awareness of the severe problems related to their alcohol use has led to initiatives to encourage non-harmful use, to limit access to alcohol and to establish "dry" areas. These initiatives are only one very small part of major efforts by Indigenous People to improve their social and economic circumstances.

Because of the extent of hazardous/harmful drinking among those indigenous people who do consume alcohol, communicating the principles of drinking guidelines, 'safe drinking' and standard drinks has not been easy. The difficulty has been exacerbated

by an overall focus on primary and tertiary prevention for indigenous people, with little emphasis until very recently on secondary prevention (Brady, 1999).

8. Abstainers: It should not be recommended that abstainers start drinking alcohol for health reasons except in very limited conditions. The beneficial health consequences of alcohol can in most cases be obtained with less risk from other behaviours like quitting smoking, physical exercise or aspirin.

9. Persons taking certain medications: It is well-established that alcohol can interact with a wide range of prescribed, over-the-counter, and herbal medications, thereby altering the effect of alcohol and/or the medication (Zakhari, 1994; Patel and Regan, 1996; Lieber, 1996; Weathermon and Crabb, 1999). Some of these interactions can occur at moderate levels of alcohol consumption, resulting in decreased effectiveness of the medication, or other harms to the drinker resulting from enhancement of the effects of alcohol or the medication, or both. As a rule, persons taking these substances should read product warning labels to determine if interactions exist, and health care providers should be aware of the possibility of interactions and attentive to their implications with regard to alcohol consumption. Limited consumption or abstinence may be indicated in certain instances.

10. Persons with established liver disease: Alcohol is contra-indicated in individuals with either acute liver disease or cirrhosis. In addition, those with chronic hepatitis without scarring should limit their alcohol intake to no more than seven standard drinks per week.

11. Persons engaged in activities requiring skill and care: There are also special situations (rather than special populations) which should be taken into account in drinking guidelines. Due to its intoxicating effects, alcohol consumption is counter-indicated in situations requiring care and skill such as when operating complex machinery or having others in one's care. This is the rationale for the prohibition of alcohol consumption by airline pilots within 24 hours of flying and for legal driving limits under impaired driving legislation.⁷

Table 1: Recommended upper limits of drinking in guidelines, policy statements, journal editorials and statements by leading experts, 1990-1997*

Author/organization (and reference)	Country	Date	Level	Rationale/comments
1. Journal of the American Medical Association (Hwang et al., 1999)	US	1999	"moderate drinking" defined as 1-2 drinks (14-28 g)/day for men and 1 drink/day for women	This is a 1-page fact sheet as part of JAMA's Patient Page. It notes "moderate use can have some health benefits".
2. NIAAA recommended year 2000 alcohol guidelines (Gordis, 1999)	US	1999	<2 drinks (28 g)/day for men under 65; <1 drink(14 g)/day for women and men over 65	In an official comment on US Dietary guidelines, the Director of the NIAAA, Enoch Gordis, advocates informing the public that: <ul style="list-style-type: none"> • Causality regarding CHD risk reduction is not conclusive • Studies show CHD reduction at levels below moderate • Very serious health consequences quickly accrue at levels of consumption above moderate
3. Israel Society for the Prevention of Alcoholism (Weiss, 1999)	Israel	1999	Not specified	15 guidelines are presented on drinking, including avoidance of intoxication, dilution of high alcohol content drinks, drinking with food, drink slowly, women being more "careful in drinking" than men, avoidance of drinking when pregnant or taking medications
4. The John Hopkins White Papers (John Hopkins Medical Institutions, 1998)	US	1998	1-2 drinks(14-28 g)/day for men and 7 drinks/week for women if no heart disease or other risk (otherwise 1 drink(14 g)/day)	Nutrition experts from John Hopkins University note "undeniable" health benefits to moderate alcohol consumption, but they also write that alcohol adds extra calories, can interfere with medication, can cause some types of heart disease, carries the potential for abuse and may increase breast cancer risk for women. They also recommends that if you don't drink, don't start.
5. National Stroke Association (NSA, 1998)	US	1998	Not specified	NSA's Prevention Advisory Board's Stroke Prevention Guideline # 4: "If you drink alcohol, do so in moderation...one drink each day may actually lower your risk for stroke (provided there is no other medical reason you should avoid alcohol)."
6. Centre for Addiction and Mental Health/ Canadian Centre on Substance Abuse (Bondy et al., 1999)	Canada	1997	2 drinks (27 g)/day for men and women; 14 drinks(190 g)/week for men and 9 drinks(122 g)/week for women	These guidelines also stipulate various situations or special populations where alcohol consumption should be minimised or avoided altogether.

* Ordered by date beginning with the most recent statements.

Table 1: Recommended upper limits of drinking in guidelines, policy statements, journal editorials and statements by leading experts, 1990-1997 (continued)

Author/organization (and reference)	Country	Date	Level	Rationale/comments
7. Medical Research Council of Sweden (MRC, 1997)	Sweden	1997	"intake should be kept below 10 to 20 g/day"	"It is possible that a moderate alcohol intake has certain positive medical effects. However, the causal relationship are not sufficiently clear. Complete or almost complete abstention from alcohol can therefore not be considered a risk".
8. Harvard University Cancer Prevention Center (HUCPC, 1997)	US	1997	"moderate drinking"=2 or less drinks (28 g)/(day for men; 1 drink (14 g)/day for women	"Recommendations for alcohol intake are complicated by strong evidence that 1 or 2 drinks per day is protective against cardiovascular disease."
9. National Heart, Lung and Blood Institute (NHLBI, 1997)	US	1997	30 ml of ethanol/day for men, 15 ml for women and lighter weight persons	"Such amounts do not raise blood pressure and have been associated with a lower risk for CHD."
10. Invited British Medical Journal editorial (Doll, 1997)	UK	1997	Up to 4 drinks (32 g)/day	Consumption of small and moderate amounts of alcohol reduces mortality from vascular disease by about one third. Minimum mortality occurs with 2 to 3 drinks/day.
11. American Cancer Society (ACS, 1996)	US	1996	2 drinks(28 g)/day	"Cancer risk increases with the amount of alcohol consumed and may start to rise with intake as few as two drinks a day...Moderate intake of alcoholic beverages has been shown to decrease the risk of CHD in middle-aged adults."
12. American Heart Association (Pearson, 1996)	US	1996	1 or 2 drinks(14-28 g)/day	The article notes that 80,000 deaths are prevented each year due to moderate intake of alcohol. Other recommendations include consulting with physician to tailor risks to benefits and not drinking when operating machinery or motor vehicles.
13. Pearson and Fuster, 1996 (Pearson, 1996)	US	1996	Not specified: recommends reducing alcohol consumption to a "moderate" level	Includes decision flow chart for general practitioners on management of vascular disease in which alcohol moderation included in management of blood pressure.
14. Centre Alcologico Integrato	Italy	1996	< 40 g/day for men, less for women	Although the threshold for low risk drinking is defined in terms of grams per day, the equivalent number of drinks is not stated.

Table 1: Recommended upper limits of drinking in guidelines, policy statements, journal editorials and statements by leading experts, 1990-1997 (continued)

Author/organization (and reference)	Country	Date	Level	Rationale/comments
15. American College of Cardiology (ACC, 1996)	US	1996	Moderate consumption=1-3 drinks(14-42 g)/day	Moderate drinkers (1-3 drinks/day) "have a 40% to 50% reduction in coronary artery disease risk compared with individuals who are abstinent." No alcohol consumption included as a CHD risk factor.
16. National Institute on Alcoholism and Alcohol Abuse (DHHS, 1995)	US	1995	Not more than 2 drinks(28 g)/day	Recommends physicians advise patients who drink to do so in moderation and to abstain under certain circumstances.
17. United States Dietary Association (USDA and DHHS, 1995)	US	1995	2 drinks(28 g)/day for men and 1 drink(14 g)/day for women	The guidelines state "if you drink alcoholic beverages, do so in moderation, with meals and when consumption does not put your or others at risk."
18. Royal College of Physicians, Psychiatrists and General Practitioners (Royal College, 1995)	UK	1995	21 units (210 g)/week for men, 14 units(140 g)/week for women (unit=10 grams of ethanol in this case)	While not recommending that people increase drinking to reduce risk of CHD, the report concludes that moderate drinkers have lower CHD risk.
19. UK Dept. of Health (UK Dept of Health, 1995)	UK	1995	21 units(210 g)/week for men, 14 units (140 g)/week for women (unit=10 grams of ethanol)	This UK report on "Sensible Drinking" notes a significant health benefit from moderate drinking for men over 40 and postmenopausal women, including lower risk of CHD, ischemic stroke and gallstones. A maximal advantage is at 1-2 units/day for men and significant health risk "will not accrue" up to 4 units/day for men and 3 units/day for women.
20. Alcohol Advisory Council of New Zealand, (AACNZ 1995)	New Zealand	1995	<60g/day and 210g/ week for men and <40 g/day and <140 g/week for women	Alcohol-free days recommended and special circumstances are noted when lower limits or abstention is advisable.
21. Invited editorial in Am J of Public Health (Klatsky and Friedman, 1995)	US	1995	Not specified.	Light drinkers have 30% to 40% lower CHD risk and 10% lower mortality risk. However, concern about the risks of heavier drinking "makes it inappropriate to indiscriminately advise nondrinkers to start drinking."
22. Letter to the editor of JAMA (Gordis, 1995)	US	1995	Not specified	In response to the JAMA editorial by Pearson and Terry (below), Enoch Gordis, Director of the NIAAA, cautions against advising abstinent and infrequent drinkers to increase alcohol consumption.

Table 1: Recommended upper limits of drinking in guidelines, policy statements, journal editorials and statements by leading experts, 1990-1997 (concluded)

Author/organization (and reference)	Country	Date	Level	Rationale/comments
23. Canadian Centre on Substance Abuse and the Addiction Research Foundation (Ashley et al., 1997)	Canada	1994	Men and Women: No more than 2 drinks(27.2g)/day with one day of abstention per week	Lower limits also appropriate for persons with low body weight and for inexperienced drinkers. Those who drink less than every day should not increase their consumption and those whose drinking exceeds two drinks in any day should reduce their consumption of alcohol. All persons who consume alcohol should avoid drinking to intoxication.
24. Invited editorial in JAMA (Pearson and Terry, 1994)	US	1994	More than "1 to 2" ounces/day of ethanol associated with increased health risk	Giving patients advice on drinking is described as a "conundrum", requiring balancing risk of adverse consequences with potential benefits from moderate consumption.
25. Simon, 1994	US	1994	"Low dose" not specified.	The author notes that there are circumstances when "physicians might reasonably prescribe alcohol for responsible people with low HDL cholesterol levels or other major CAD risk factors that have failed to respond to lifestyle interventions."
26. Friedman and Klatsky, 1993	US	1993	Not specified: moderate amounts depend on individual characteristics but 3+ drinks/day is undesirable	Some people (those with high risk for CHD but low risk for problem drinking) might benefit from taking up drinking, but this should not be recommended indiscriminately.
27. NMHRC, 1992	Australia	1992	<40 g/day for men and <20 day for women	Also recommends to avoid binge drinking and individual risk were identified. In addition, special guidelines were detailed for specific situations, such as hazardous situations, when operating machinery or in the context of pregnancy.
28. Stichting Verantwoord Alcoholgebruik (1991)	Netherlands	1991	<40 g/day for men and women	Abstinence promoted among pregnant women, adolescents, those driving or operating machinery and those who are working or studying. Women and those with low body weight are advised to drink less than the recommended levels.
29. Editorial in Epidemiology (Ellison, 1990)	US	1990	Cautions against a specific amount due to individual differences	This editorial, aptly entitled "Cheers!", cites evidence of CHD reduction from moderate drinking and cautions against the risks of heavier drinking. It concludes that a male without a bleeding tendency or risk of alcohol abuse "might consider the advantages of washing down his aspirin with a glass of claret."

Table 2: Types of Drinkers, including non-drinkers, by Gender, 1988-1995 ^(a, b)

Drinking Status	(Percent)			
	1988	1991	1993	1995
Non-drinker				
Male	12	14	19	17
Female	22	23	31	27
Moderate drinking				
Male	62	66	63	61
Female	51	54	50	52
Heavy drinking				
Male	14	11	10	11
Female	15	13	11	11
Binge drinking				
Male	4	3	4	4
Female	6	4	4	6
Harmful/hazardous drinking				
Male	7	6	4	6
Female	6	6	4	4

(a) Adapted from (Makkai and McAllister, 1998).

(b) Estimates are for respondents aged 20 years and more.

Table 3: Types of Drinkers, excluding non-drinkers) by Gender), 1988-95^(a, b)

Drinking Status	(Percent)			
	1988	1991	1993	1995
Moderate drinking				
Male	70	77	78	74
Female	65	70	72	71
Heavy drinking				
Male	16	13	12	13
Female	19	17	16	15
Binge drinking				
Male	5	3	5	5
Female	8	5	6	8
Harmful/hazardous drinking				
Male	8	7	5	7
Female	8	8	6	5

(a) Adapted from (Makkai and McAllister, 1998).

(b) Estimates are for respondents aged 20 years and more.

Table 4: Drinking Patterns Among Adolescents, 1988-1995 ^(a, b)

Drinking Status	(Percent)			
	1988	1991	1993	1995
Non-drinker				
Male	25	27	33	36
Female	29	28	42	36
Moderate drinking				
Male	41	42	42	37
Female	26	29	23	20
Heavy drinking				
Male	19	19	12	15
Female	19	19	17	26
Binge drinking				
Male	13	10	12	10
Female	20	15	13	16
Harmful/hazardous drinking				
Male	-	-	-	-
Female	6	9	-	-

(a) Adapted from (Makkai and McAllister, 1998).

(b) Estimates are for respondents aged 14-19 years.

Appendix A: Critical Review Form for Prognostic Studies

I) Are the Results Valid?

1. Was there a representative sample of subjects at a well-defined point in the course of the disease or condition?
2. Was follow-up sufficiently long and complete?
3. Were objective and unbiased outcome criteria used?
4. Were important prognostic factors adjusted for?

II) What are the Results?

1. How large is the likelihood of the outcome events in a specified period of time?
2. How precise are the estimates of likelihood?

III) Will the results help me in determining safe drinking guidelines?

1. Was the study carried out on subjects who are not typical of normal drinkers in the Australian population (e.g., a cohort of persons suffering from a particular disorder)?
2. Do the results help set cut-off points for average weekly drinking?
3. Do the results help set cut-off points for daily drinking?
4. Do the results help specify exclusions (e.g., women of child-bearing age) or special circumstances (e.g. when engaging in tasks requiring skill and care) that should be taken into account in determining safe levels of consumption?

Overall assessment:

On a scale from 1 to 10: ____

In words (optional):

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Endnotes:

¹ However, the reader is warned that comparing the costs and benefits of alcohol use to population health is *not* a zero-sum game where the object is to achieve parity between the two sets of figures. There is little purpose in "balancing" the number of deaths caused by alcohol with the number of deaths prevented by alcohol. The objective of alcohol prevention is to reduce deaths, hospitalisations and other adverse consequences of alcohol misuse, regardless of the number of lives and hospitalizations prevented by moderate use.

² In the U.S., crude estimates have been made which indicate approximately 100,000 lives lost per year due to alcohol use, compared with 80,000 deaths averted due to the beneficial impact on ischaemic heart disease (cited in (Gordis, 1999). However, the estimates of alcohol attributed mortality are based on somewhat dubious methods which use the same aetiologic fractions for men and women for most causes and which fail to take age into account. It is likely that the estimates of alcohol attributed mortality would be much lower if derived by the same methodology used by English et al. (English et al., 1995) in Australia or Single et al. (Single et al., 1999) in Canada.

³ Patterns of drinking may refer to several aspects of drinking behaviour, including temporal variations in drinking, the number and characteristics of heavy drinking occasions, the settings where drinking takes place, the activities associated with drinking, the personal characteristics of drinkers and their drinking confederates (e.g., drinking in large, exclusively male groups), the types of beverages consumed and clusters of drinking norms and behaviours often referred to as drinking cultures. How much one drinks may also be thought of as part of a person's drinking pattern. In this report, however, we use the term drinking pattern to refer to aspects of drinking behaviour other than the overall level of alcohol consumption.

⁴ As noted elsewhere in this report, the cardiovascular benefits of low level drinking must be weighed against risks. Even low level drinking may carry increased risk of trauma from alcohol-related accidents and certain forms of cancer.

⁵ There is an additional point regarding the reliability and validity of consumption measures. In the studies cited, reliability has usually been measured as test-retest and validity by regression or correlation techniques. Both techniques do not yield correct absolute volume as they routinely underestimate it but allow satisfactory stable rankings, at least for the short term (Feunekes et al., 1999). Long-term stability, one of the prerequisites of conducting epidemiological analysis, has been much less demonstrated (Rehm and Bondy, 1998).

⁶ This recommendation does not imply that controlled drinking is not achievable for some persons with alcohol problems.

⁷ Although it is beyond the scope of this paper to consider the appropriate Blood Alcohol Concentration (BAC) limits for operating a motor vehicle, it is noteworthy that intoxicating effects of alcohol begin to appear in experimental conditions at BAC's as low as 0.015. There exists no clear standard to assess when intoxicating effects represent impairment but most drinkers who consume alcohol within current NMHRC guidelines would not be in violation of impaired driving laws, even in jurisdictions with a BAC limit of 0.05.