

Winemakers' Federation of Australia
Submission to
Australia's Future Tax System Review (AFTS)

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1. Introduction

This submission has been prepared by the Winemakers' Federation of Australia (WFA) on behalf of the Australian wine industry.

The Winemakers' Federation of Australia, established in 1990, is the national peak body for the wine industry, representing Australia's wineries on all national and international issues. WFA operates by voluntary membership with specific representation for small, medium and large producers. Current WFA membership collectively accounts for over 90% of wine production in Australia.

WFA provides policy leadership on the issues of business climate, social responsibility, environmental sustainability, innovation, trade, and benchmarking issues that are critical to the enduring viability of Australia's wineries. The Winemakers' Federation of Australia also works closely with Wine Grape Growers Australia (WGGA) on issues of common interest.

Throughout this paper, reference to the "Australia wine sector" is broadly defined to be inclusive of all aspects of the supply chain and production of wine. Therefore winegrape production is encompassed in the analysis.

The WFA is fully committed to the AFTS Review process and accordingly this submission is designed to expand on as well as to summarise the evidence previously provided in the WFA October submission and to respond to issues raised in the April discussion with Review personnel.

This submission is designed to respond specifically to the questions posed on alcohol taxation in the AFTS Consultation paper. For other issues raised in the Consultation paper, refer to the previous WFA submission.

WFA would welcome the opportunity to engage in further discussion on the issues in this submission as the Review process begins to formulate its conclusions.

2. Policy Objectives of Alcohol Taxation

The AFTS Consultation paper identified potentially competing industry assistance, health and revenue raising policy objectives for alcohol taxation.

The Australia's Future Tax System Consultation paper (December 2008) noted that:

"The decision whether to tax some consumption goods more highly than others, and the optimal design of a particular tax, depend on the policy objective it is trying to achieve.

The current tax arrangements for beer, wine, spirits, tobacco and luxury cars reflect a range of competing policy goals. They exist in the context of other forms of regulation and the broader tax-transfer system."

and posed the relevant consultation questions:

"Q11.1 Is it appropriate to use taxes on specific goods or services to influence individual consumption choices, and if so, what principles can be applied in designing the structure and rates of such taxes?"

Q11.2 Can the competing potential objectives of alcohol taxation, including revenue raising, health policy and industry assistance, be resolved? What does this mean for the decision to tax alcohol more than other commodities?"

Industry Assistance

Industry assistance tax policies have not been the driver of the Australian wine industry's remarkable transformation over last 15 years. Most of the growth has been won in export markets against international competition.

Production increase

- Vineyard area from 67,000 to 173,000 hectares
- Grapes from 662,000 to 1,820,000 tonnes
- Wine producers from 802 to 2299
- Wine from 530,534 to 1,239,532 litres

Sales growth

- Domestic and export from \$1,360 million to \$4,800 million
- World wine trade value share from 3.6% to 9.4%

Economic contribution increase

- Employment (direct grape and wine) from 16,000 to 28,000
- Export value from \$260 million to \$2,700 million
- Regional economies viability, 23 substantial (> 10,000 hectares) and 40 significant (> 1,000 hectares) grape producing regions
- Wine tax (WST/WET) from \$260 million to \$661million

Public Health

The WFA supports government initiatives to reduce alcohol abuse that are effective, do not unduly punish responsible consumers, and do not have unintended negative consequences on industries or regional communities supported by those industries.

Measures need to be specifically targeted towards those in the community who are engaging in harmful levels of alcohol consumption, or to underage consumers.

The WFA supports recent comments by Noel Turnbull, adjunct professor in the School of Applied Communications at RMIT University, in which he warns against approaches that "generate widespread community hostility and seek to control the bulk of moderate consumers of alcohol as if they were people with significant alcohol problems. There are alternatives available which treat people as citizens capable of changing behaviour without draconian regulation and punitive taxation". (<http://www.news.com.au/story/0,27574,25396290-421,00.html>)

Using tax to alter price is a blunt social policy tool that does not distinguish between alcohol abuse and responsible drinking – it penalises those who consume responsibly as well as those who are the object of the measure. There is little evidence to demonstrate net population benefits through overall increased alcohol taxation: responsible consumers are likely to reduce or cease consumption depending on the level of increase involved but consumers who abuse alcohol are more likely to either switch products or switch substances.

Alcohol is complex and studies show price is not the only determinant of consumption choices. Significant reductions in sales have been observed in response to price increases but these reductions were mitigated by significant substitutions between beverages types or qualities (Gruenewald et al. 2006).

The taxation regime that generates the socially optimal level of consumption **will not** eliminate all negative alcohol impacts on society. Those negatives cannot be resolved through general taxation measures without causing a substantial welfare loss to all alcohol consumers, the overwhelming majority of whom are responsible consumers.

Non tax policies more appropriate to target alcohol abuse

Taxation has not proven to be an effective policy to reduce alcohol abuse.

- *“Perhaps the most compelling evidence against taxation as an effective policy measure against abuse comes from countries where taxation rates have traditionally been high. In many of these, such as the Nordic countries or those in Eastern Europe, alcohol consumption and harmful drinking patterns remain high.”* (International Center for Alcohol Policies (ICAP), ICAP Reports 18, May 2006)

These Nordic countries have also been found to have relatively high levels of home distilling and brewing in comparison to other countries with lower taxation thresholds. This has also opened them up to 'entrepreneurs' who sell home made alcohol products on the black market and to the illegal importation of alcoholic products.

- Focussing specifically on wine, ACIL Consulting concluded:
"the case for a general health-related (public social cost) tax on wine is weak due to the favourable differences in wine consumption patterns and the recognised health benefits of moderate wine consumption." (ACIL Consulting, *Pathways to Profitability for Small and Medium Wineries*, October 2002)

These arguments all add up to a compelling case against a general increase in taxation on wine and strong support for specific policies that target the specific behaviours, attitudes and groups of wine consumers who impair public health outcomes.

Rose (Rose G, 1985, Sick Individuals and Sick Populations, *International Journal of Epidemiology*, International Epidemiological Association 1985, Vol. 14, No. 1) found the following benefits in pursuing individual (targets high-risk consumers) strategies.

- Intervention appropriate to the individual
- Subject motivation
- Physician/health professional motivation
- Cost-effective use of resources

The following disadvantages were linked to a population-based strategy

- Small benefit to individual (prevention paradox)
- Poor motivation of subject
- Poor motivation physician/health professional

The other significant disadvantage of a population-based strategy is the possibility of substantial welfare loss to the majority of consumers. Evidence shows that specific occasions of heavy consumption, usually by people who generally consume moderate amounts of alcohol in low risk ways, result in most alcohol-related harm (Single and Rohl 1997).

Accordingly, drinking pattern is often a better predictor of alcohol-related harm than just the amount consumed (Rehm et al. 2001a). Correspondingly, a greater reduction in harm may be achieved through the prevention of heavy high-risk consumption occasions rather than by a reduction in the mean level of consumption.

The Australian wine sector believes strategies should be implemented to target those groups that are engaging in risky consumption with a view to changing that behaviour. It will continue to support population-based programs that educate consumers about the health implications of drinking at risky levels and the benefits of responsible consumption to bring about long-term, sustained cultural change.

Bringing about cultural change is a primary objective of DrinkWise Australia (<http://www.drinkwise.com.au>) an initiative supported by winemakers.

Revenue Raising

Historically revenue raising has been a policy objective for taxing alcohol at higher rates than other goods and services.

However revenue raising as a stand alone objective is not a valid rationale for taxing alcohol more than other commodities, since economic principles of efficiency and equity would dictate that revenue is raised from the broadest possible tax base – namely consumption of all goods and services.

Australia is the highest taxing country among new world wine-exporters for wine above \$11 retail per 750ml bottles. Even for non premium wine selling for the equivalent of \$2.63 per 750ml bottle, only Canada and New Zealand have higher tax rates than Australia. (Anderson 2008).

Access Economics, in its review of the 2008 Collins and Lapsley report *The costs of tobacco, alcohol and illicit drug abuse to Australian society in 2004/2005*, pointed out that “**Alcohol taxes thus pay more than the social costs of alcohol abuse, by a considerable margin**, each year.” (Access Economics, *Collins and Lapsley report review: social costs*, 28 November 2008)

3. Tax Change Implications

Implications of a change to a volumetric tax at the packaged beer rate of \$40.82 per Litre of Alcohol (LAL).

Wine sector impact

- 95% of wine would increase in price, reducing sales volume by 34%
- Reduction in grape supply requirement of 192,000 tonnes
- Reduced wine producer competitiveness in all markets, including export, due to increased cost base resulting from lower scale.

Employment impact

- Job losses nationally estimated through economic modeling to be 5,300
- In addition large numbers, of the order of 700, small wine producers (WFA estimate), with Victoria most affected, forced out of business due to loss of WET rebate. Consequential job loss is estimated at 2,700.

Regions impact

- Adverse grapegrower impact concentrated on inland irrigation regions in South Australia, Victoria and New South Wales
- Region specific economic impacts modeled for the 6 wine zones/regions of South West WA, North West Victoria, NSW Riverina, SA Riverland, SA Limestone Coast, SA Barossa, indicate a combined employment loss of 1038. However this is likely to be substantially under estimated because modeling assumptions assume, contrary to the current situation, that all grape and wine businesses in these regions are profitable and hence are capable of absorbing some of the loss of business in reduced profits.
- \$457 million loss of Gross Regional Product in just 6 key wine regions.

Individual producer impact

- Cash flow stress on all wine producers due to changes in timing of tax payments
- Substantial compliance and business disruption costs would be incurred due to necessary revisions in computer software, warehousing logistics, record keeping and security.

Community impacts

- Higher wine prices impacting disproportionately on lower income and older consumers
- No significant reduction in risky alcohol behaviours

Government impacts

- Tax collection increase of \$630 million
- However the \$457 million loss of Gross Regional Product in just 6 key wine regions alone is almost equivalent to the \$630 million projected revenue yield from the tax increase.
- An increase in Government compliance and regulatory burden due to the addition of 2,200 wine manufacturers' to the existing 300 (approx) alcohol manufacturers' operating under the complex volumetric collection scheme

Tax change on top of the current challenges would devastate the Australian wine industry

- In the Australian market, locally produced wine is losing share to imports.
- In export markets, Australian wine is suffering volume and margin declines in its largest markets of the UK and the USA that is not being offset by growth in its newer markets of China, Hong Kong, and Denmark.
- Consequently, the demand outlook offers little prospect of relieving the endemic grape oversupply resulting from the speculative winegrape plantings of the late 1990's - necessitating restructuring strategies by the industry.
- The further loss of 34% of wine sales volume due to a tax change would precipitate an industry collapse.

4. Wine – Profile of Difference

Wine is different from other alcohol in its demand structure; consumption; health impacts; production; economic contribution; and regional location.

Wine is different due to the structure of market demand

Wine demand spans a vast price range but only a small proportion of the market commands prices above \$20 AUD equivalent .

Price segments in the world wine market (Rabobank, Nielson)

Segment name	Volume market share, %		Price range, AUD, 750ml bottle
	Australia	International	
Basic	21	50	< 7
Popular premium	58	34	7 - 15
Premium	17	8	15 - 20
Super premium	3	5	20 - 30
Ultra premium	0.7	2	30 - 50
Icon	0.2	1	>50

Glass bottles maintain the dominant share as the preferred wine package despite the lower cost, dispensing convenience and environmental advantage of soft pack (casks).

Wine sales, Australian market % volume by type of package (ABS)

Wine container type	Volume share % 2007-08 Australian sales in Australian market
Bottled	45.7
Soft pack, 2 litres or less	14.2
Soft pack, more than 2 litres	26.3
Flagon and bulk	2.5
Container unspecified	11.3

Wine is different due to consumption patterns

Wine consumption generates lower social costs than alcohol generally

- older age consumers
- place of consumption is predominantly in the home or restaurants
- occasions of consumption especially association with food (more than 90%) and with water (30 - 50%).

The 2007 National Drug Strategy Household Survey reports on alcohol consumption patterns of Australians aged 14 years or older. The following broad conclusions can be drawn from the data collected:

- The proportion of the population consuming alcohol fell between 2004 and 2007 but consumption patterns remain stable;
- Males are twice as likely as females to consume alcohol daily with the proportion doing so trending down;
- Indigenous Australians are more likely to abstain from alcohol but those that do consume are more likely to do so at risky levels;
- Underage groups consume at very low levels on a daily or weekly basis;
- Between the ages of 14-29 is the stage of life when consumers are most likely to drink at risk of short and long term harm;
- Wine is not the main beverage of choice for consumers until around the age of 30 years;
- Those aged between 14-19 drinking at levels considered high risk prefer bottled spirits and liqueurs;
- Bottled wine is preferred over cask wine for all age groups, but there is a significant number of consumers over 55 who drink cask wine as well as bottled wine;
- Around 91% of recent drinkers had taken steps to reduce alcohol consumption with those drinking at low risk levels being less likely to take steps to reduce their consumption than those drinking at risky levels;
- 53% of wine is consumed in the consumer's own home. In total almost 90% of wine is consumed either in a private home or in a restaurant; and
- The majority of wine consumption is combined with food - 90% of bottled wine and 93% of red cask wine.

Wine is less implicated in the incidence of "risky drinking" than other types of alcohol

Wine as a product in general is consumed differently to other alcohol beverages: it is consumed with food, in moderation, by older consumers at home or in restaurants.

The greatest percentage of the population who drink at risky levels is proportionally found amongst 14 - 29 year old groups.

The below table outlining the type of alcohol usually consumed, recent drinkers aged 14 years or older, by long term risk status, demonstrates that wine is not the preferred beverage of choice for these high-risk age groups.

MALES		
	"Low Risk"	"Risky" or "High Risk"
14-19	Pre-mixed spirits in a can (52.8%)	Regular strength beer (74.3%)
20-29	Regular strength beer (65.8%)	Regular strength beer (78.6%)
30-39	Regular strength beer (59.0%)	Regular strength beer (77.0%)
40+	Bottled wine (54.3%)	Regular strength beer (61.5%)

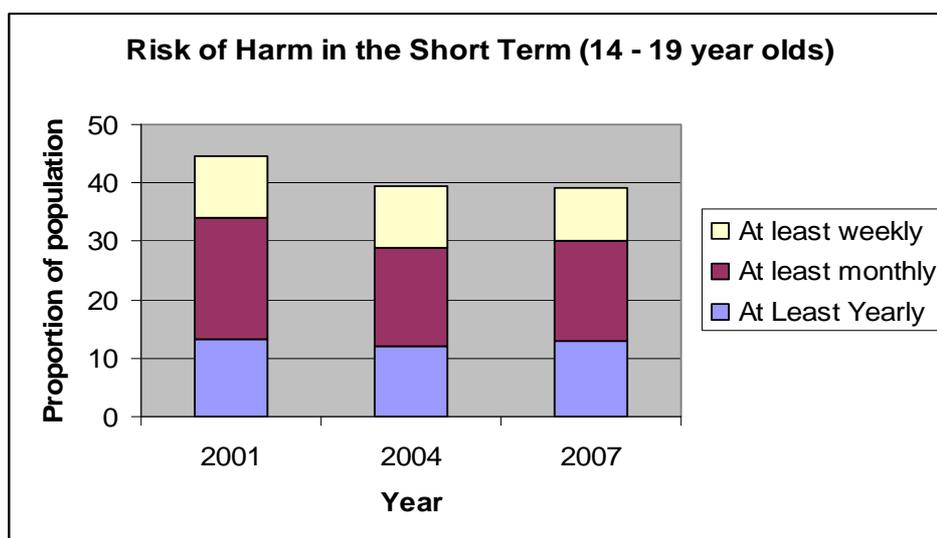
FEMALES		
	"Low Risk"	"Risky" or "High Risk"
14-19	Pre-mixed spirits in a can (64.2%)	Bottled spirits and liqueurs (84.9%)
20-29	Regular strength beer (58.8%)	Bottled spirits and liqueurs (67.6%)
30-39	Regular strength beer (68.9%)	Bottled wine (69.7%)
40+	Bottled wine (69.9%)	Bottled wine (72.2%)

From the above two charts it can be seen that in 2007 neither cask nor bottled wine was a significant product of choice for young and underage consumers.

Bottled wine became more popular with females as they matured, although other beverages were still the preferred product for females under the age of 30.

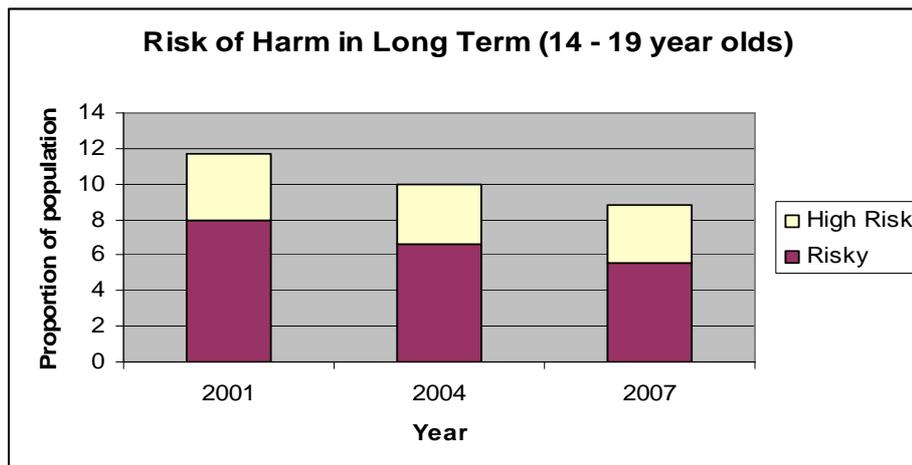
Again, we must draw attention to the bigger picture.

It is important to note that overall levels of underage consumption, and risky consumption by younger people, have remained largely unchanged and have actually declined, as demonstrated in the below graphs.



[Notes to Graph: Short Term Risk - Alcohol consumption, risk of harm in the short term: proportion of the population aged 14 - 19 years, Australia, 2001, 2004 and 2007. Level of risk is determined as follows: For males, the consumption of 7 or more standard drinks on any one day. For females, the consumption of 5 or more standard drinks on any one day.

Sources: 2001, 2004 and 2007 National Drug Strategy Household Survey]



[Notes to Graph: Long Term Harm - Alcohol consumption, risk of harm in the long term: proportion of the population aged 14 - 19 years, Australia 2001, 2004 and 2007. Level of risk is determined as follows: For males, the consumption of up to 28 standard drinks per week is considered 'Low risk', 29 to 42 per week 'Risky', and 43 or more per week 'High Risk'. For females, the consumption of up to 14 standard drinks per week is considered 'Low risk', 15 to 28 per week 'Risky', and 29 or more per week 'High Risk'.

Sources: 2001, 2004, and 2007 National Drug Strategy Household Survey]

There is little evidence of an explosion in youth binge drinking that warrants a change to a higher taxation level on alcohol, and especially on wine.

Consumption: Wine casks – the evidence challenges the stereotype

Wine casks are perceived to be consumed in a risky manner and this perception has entrenched a stereotype of wine casks as a predominant source of abusive alcohol consumption. The evidence doesn't support this stereotype.

Consumers tend to drink more from glass bottles on average than from casks. However this does not tell the whole story (Wine Intelligence 2009); there are some very different groups among the cask-buying population:

- **Frequent large cask users** (15% of Australian regular wine drinkers)
 - Drink an average of 3 glasses per session and drink at least 3-4 times per week
 - Tend to be older (half are aged 55+) and from lower income brackets
- **Occasional cask users** (both small and large casks)
 - Drink less often from casks, but use casks for moderate consumption
 - Tend to drink fewer glasses on average when using casks than for their overall consumption
- **Those who use *small casks* frequently have consumption patterns closer to frequent glass bottle users than to frequent large cask users.**

Consumption: Evidence that cheap alcohol price is not the driver of risky consumption choices

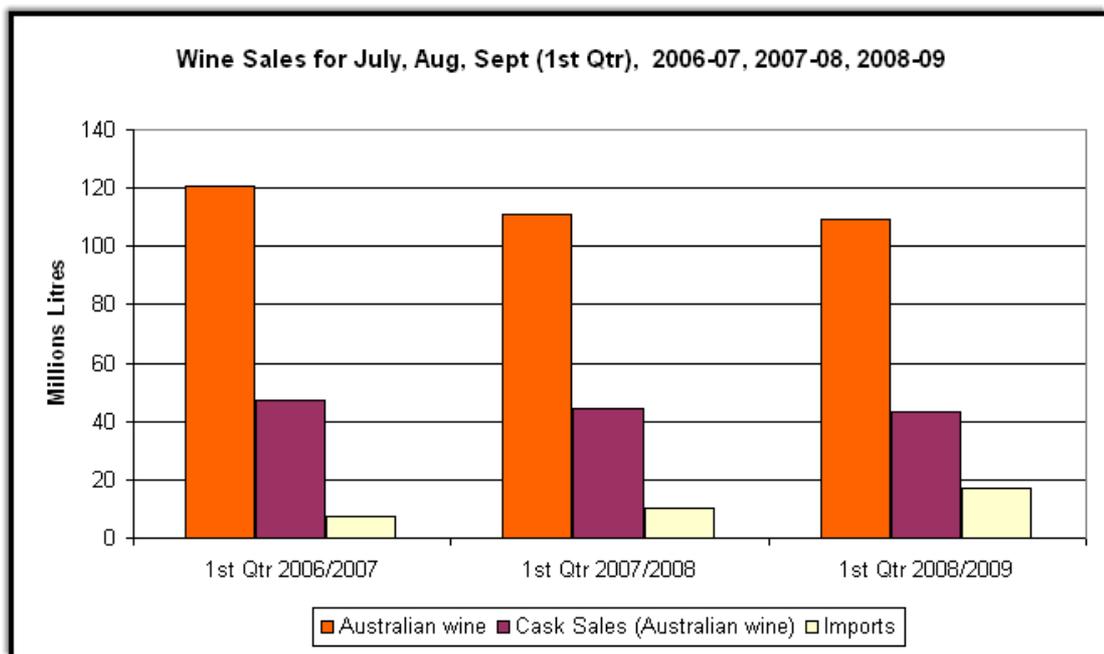
RTD tax increase showed no substitution to wine and zero to casks.

The WFA has analysed publicly available data on wine sales following the tax increase on RTDs to evaluate the extent of any substitution effect from RTDs in favour of wine. Please note that wine consumption data by sex, age and alcohol beverage for the period after the introduction of the increased RTD excise in April 2008 is not currently available. However, data is available on winery depletions (sales) which is a useful proxy for consumption.

The data shows that despite the higher price point for pre-mixed spirits, there was not a consumer substitution to a lower-price point alcoholic beverage – namely wine or cask wine in particular.

Further to our earlier evidence, this demonstrates that alcohol is a complex good. Universal taxation increases will not result in changes to “risky” consumption choices.

Chart 1



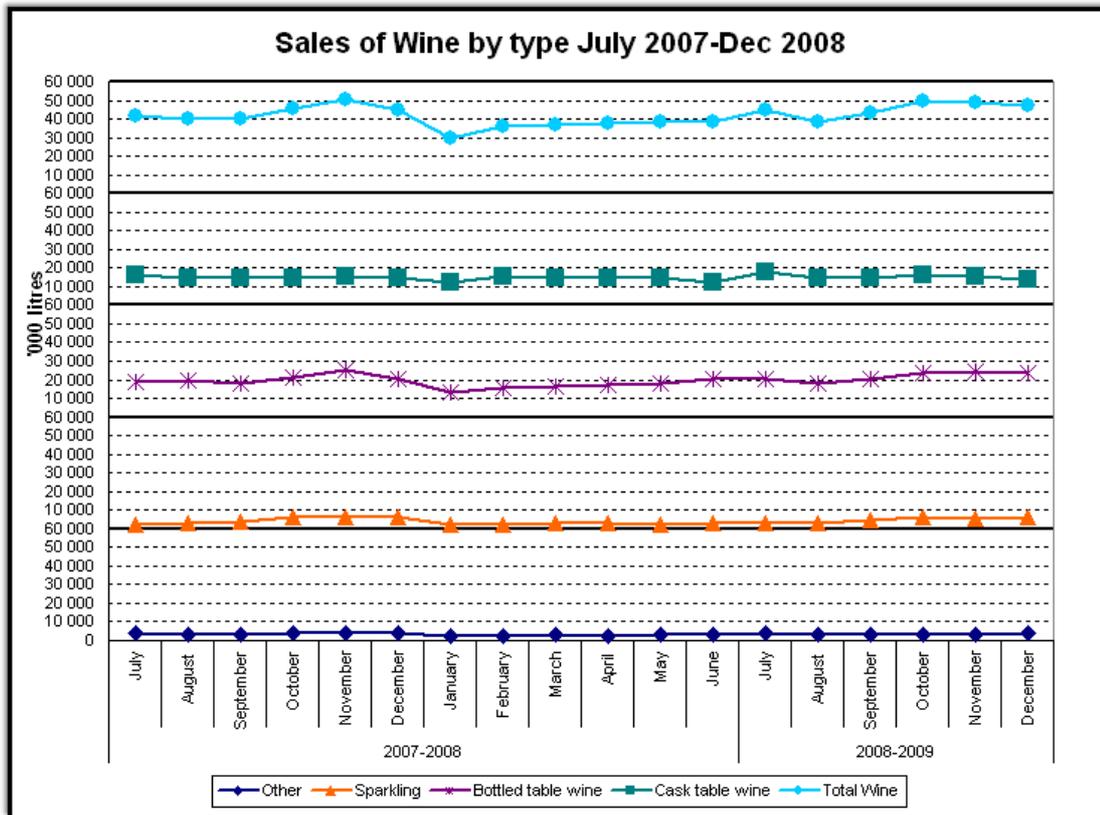
Source: ABS Catalogue No. 85.04. Sales of Australian wine & Brandy by Winemakers

It can be observed from the above chart that for the first quarter of 2008-09 (July, August, September 2008) after the introduction of the increased RTD excise;

- sales of Australian produced wine decreased,
- sales of cask wine also decreased, and
- sales of imported wine increased marginally, due to the increased popularity of NZ Sauvignon Blanc.

Chart 2 covers an 18 month period showing sales by type of wine and by total wine. Seasonal trends can be clearly seen. **This graph demonstrates that there are no obvious increases resulting from the RTD excise increase, and in the case of cask wine a declining trend is clearly evident. Consequently there is no evidence of wine being substituted for RTDs.**

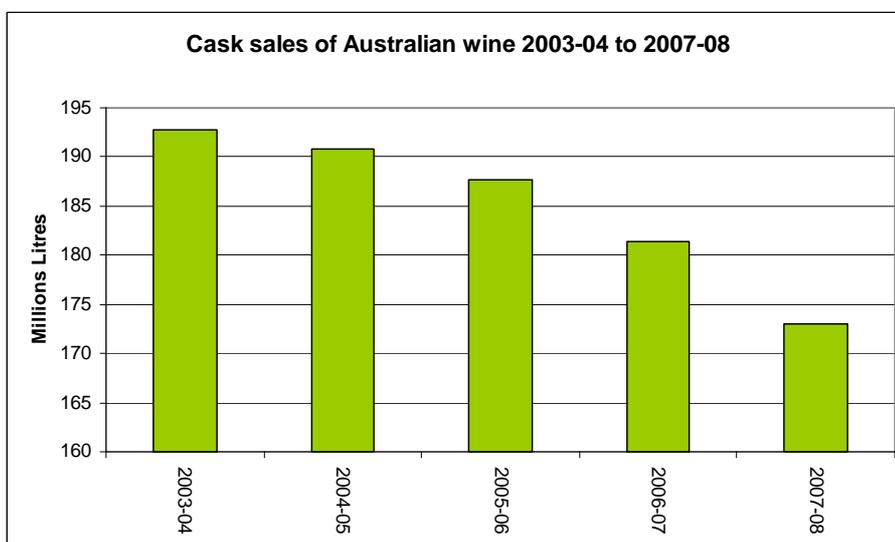
Chart 2



Source: ABS Catalogue No. 85.04. Sales of Australian wine & Brandy by Winemakers

Chart 3 highlights cask wine sales steadily reducing over the past five years. There is no evidence that consumers seek the lowest price point of alcohol. **This demonstrates that price-points are not substitutable across alcohol categories despite cask wines price advantage.**

Chart 3



Wine is different due to production features

Wine production has less flexibility and higher risk than most manufacturing business

- grape growing is hostage to seasonal weather fluctuations
- only one grape harvest per year (inventory costs), 3 to 4 year supply lag
- very limited scope to substitute between grape colour, grape types or to vary alcohol levels
- full utilisation of the grape supply resource and achievement of economies of scale and scope requires production of cask wine as the destination for the lowest ranked wine quality

And the financial structure of wine businesses is out of alignment with the tax system

- capital intensive long life assets
- high inventory with slow stock turn
- high working capital requirements

Resulting in higher vulnerability to tax changes and a more disruptive impact.

Further analysis through Deloitte's benchmarking reveals some of the unique financial features of wine businesses namely:

- Wine businesses are very asset intensive, with total assets representing up to 240% of sales for a \$5 to \$10 million revenue business
- Wine businesses have low inventory turnover, with a ratio of around 0.7 for a less than \$5 million revenue business
- Wine businesses have high inventory requirements, with a working capital to COGS ratio around 2.0 for a less than \$5 million revenue business
- Wine businesses have high working capital requirements, with a ratio of 1.13 to 1.22 times the value of sales for a less than \$5 million revenue business

The interaction of the tax system with these intrinsic structural features of the wine industry **result in differential impacts and outcomes on wine businesses relative to business generally.**

Wine is different due to economic contribution

- **Value added**
 - High degree of value adding to an agricultural product
- **Exports**
 - 62 % of production is exported
- **Tourism**
 - Creates tourism destinations and visitation motivation
- **Employment in non metropolitan regional economies**
 - 63 regional economies have a substantial or significant dependency on the wine sector. Refer to map in the Appendices.

Wine is different due to regional location

The wine sector's contribution to regional economies is more transformational than most other rural industries due to:

- High degree of local value adding
- Supplier demand creates a critical mass of infrastructure and business services
- Business leadership
- Connects the region directly to specific international markets
- Skills base
- Tourism attractions and infrastructure

5. Wine and Health

Evidence of disease risk reduction attributable specifically to moderate wine consumption

Cardiovascular disease – approximate 30% reduced risk of disease associated with consumption of 1 or 2 glass/day of wine compared with lifelong abstainers, and is approximately 10-20% greater compared with beer and spirit consumption

Certain cancers –reduced risk for Non-Hodgkin’s Lymphoma, aero-digestive tract and lung cancers (by approximately 20-40%), as well as colorectal cancer at three subsites [proximal colon, distal colon, and rectum] (by approximately 20%) associated with consumption of 1 or 2 glass/day of wine compared with abstainers; in contrast, ethanol is associated with an increased risk of aero-digestive tract, colorectal and liver cancers

Diabetes mellitus – approximate 30-40% reduced risk of disease associated with consumption of 1 or 2 glass/day of wine compared with lifelong abstainers

Dementia and Alzheimer’s disease –up to 50% reduced risk of disease associated with consumption of 1 or 2 glass/day of wine compared with abstainers

Cognitive function – approximate 20% reduced risk of decline associated with consumption of 1 or 2 glass/day of wine compared with abstainers

Total mortality – approximate 10% reduced risk of death from all-causes associated with consumption of 1 or 2 glass/day of wine compared with lifelong abstainers

Phenolic compounds unique to wine have therapeutic benefits

Phenolic compounds are present in the fruit and vegetable core components of a Mediterranean-style diet, which has been associated with a reduced risk of both cardiovascular disease (CVD) and cancer compared with a low fruit and vegetable (low phenolic) and high fat diet.

Both ethanol (common to all alcoholic beverages) and the wine-derived phenolic compounds improve the blood ratio of HDL to LDL cholesterol and reduce blood clotting associated with a reduced risk of CVD.

Only the wine-derived phenolic compounds, however, have a beneficial effect on endothelial function and inflammation associated with a reduced risk of cardiovascular disease.

The endothelium plays a crucial role in regulating peripheral blood flow and oxygen supply to organs and tissues through the production of nitric oxide. Reduced endothelial function (dysfunction) has been shown to be an independent predictor of CVD even after adjusting for traditional risk factors, such as hypertension and hypercholesterolaemia, which are characterized by an impairment of endothelium-dependent vasodilatation. Reduced endothelial function (dysfunction) and inflammation occur in the early phases of atherosclerosis leading to CVD. Wine-derived phenolic compounds thus provide protection against the progression of atherosclerosis leading to CVD.

Furthermore, the primary wine-derived phenolic compounds of catechin, quercetin and resveratrol have measurable effects on the blood cholesterol ratio and blood clotting at a lower concentration than ethanol, and also have measurable effects on inflammation and endothelial function in test tube, animal and limited human studies.

Therefore improving endothelial function by means such as 1 or 2 glass/day of wine consumed with food might represent an important therapeutic target.

Ethanol (common to all alcoholic beverages) is associated with the initiation and progression of cancer. The wine-derived phenolic compounds (common only to wine), however, are associated with preventing the initiation and progression of cancer.

The primary wine-derived phenolic compounds of catechin, quercetin and resveratrol, for example, protect cells and DNA from damage leading to cancer. They also either reverse any cellular damage or destroy any damaged cells, which has been demonstrated in test tube, animal and limited human studies with both alcohol-containing and de-alcoholised wine.

Light to moderate wine consumption has thus been associated with a decreased risk of mortality from certain cancers compared to life-long abstainers and heavier consumers.

Therefore protecting against the initiation and progression of certain cancers such as bowel cancer by means such as 1 or 2 glass/day of wine consumed with food might represent an important therapeutic target

Food accompaniment reduces adverse impacts and prolongs health benefits of alcohol consumption

Wine consumed at mealtimes has benefits for CVD including coronary heart disease, heart failure and hypertension, while alcohol consumed apart from meals shows significantly less benefits.

The frequency of alcohol intake is as important for the benefits as is the amount. The most favourable pattern is frequent days with light-moderate amounts of alcohol and, in particular, wine. The least favourable pattern is binge drinking.

Wine in comparison to beer and spirits is generally consumed with food. Food slows the absorption of the alcohol and a phenolic component into the blood stream, which reduces the maximal blood alcohol concentration achieved and thereby harm to the body's cells, organs and tissues, but prolongs the beneficial effects of the alcohol and phenolic components on the body's cells.

6. Current Challenges Facing the Wine Sector

The 2009 vintage marks the start of what most in the Australian wine industry believe will be the toughest year for at least two decades.

A range of factors has contributed to the rapid deterioration of domestic and export markets, requiring widespread industry restructuring to facilitate a return to sustainable margins.

Over the past year sales have declined in nine out of our top 10 markets, with total exports down by 18% (volume). The domestic market, which accounts for 40% of sales, dropped for the first time in 15 years with imports now accounting for 13% of domestic sales and NZ Sauvignon Blanc has overtaken Australian Chardonnay as the top retail white wine category.

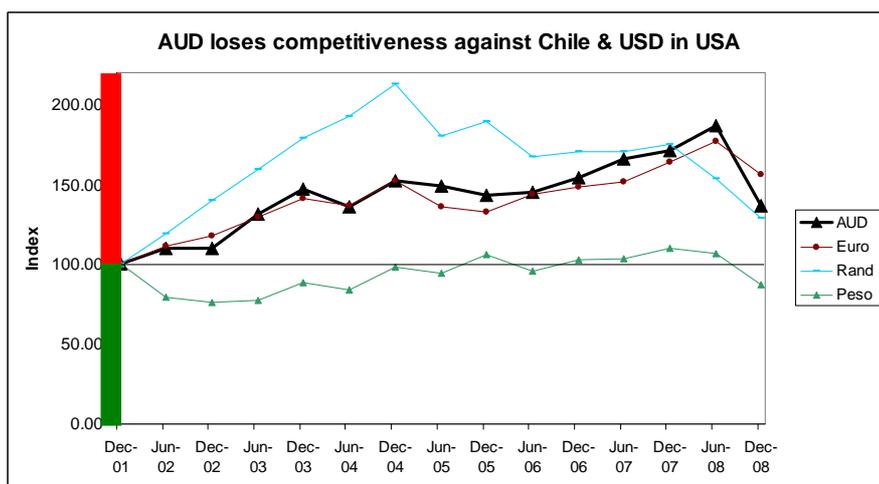
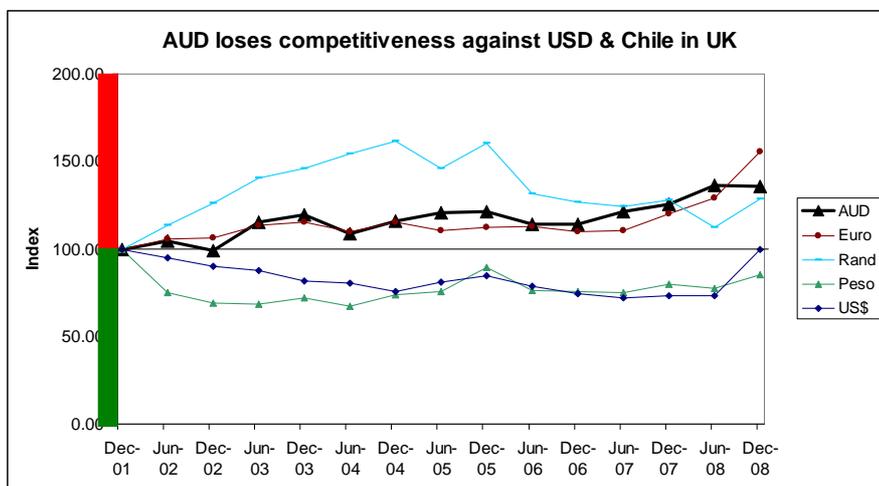
This reduced demand coincides with more than a decade of unprecedented change in wine trading conditions, greater environmental responsibilities (exacerbated by climate change), and several key factors that are putting pressure on wine businesses:

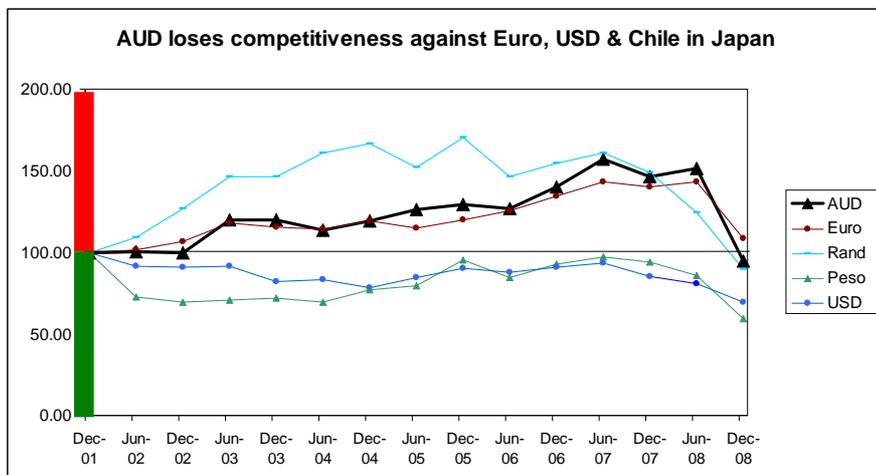
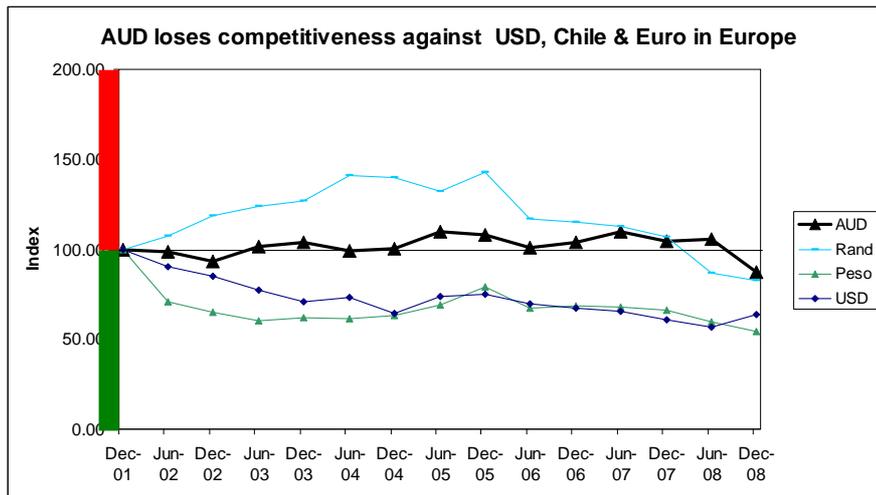
- **Drought**
 - Water availability and cost
- **Exchange rates**
 - Loss of competitiveness against competitors since 2002, refer to AUD exchange rate graphs that follow
- **Retail market power**
 - Our 2 largest markets are Australia and the UK
 - 2 major retailers in the Australian market control 70% off premise and they account for more brand ownership than any single Australian winery. Likewise the UK market exhibits a high degree of retail market power.
- **Global Financial Crisis impact on export sales**
 - Australian wine's largest markets UK and the USA are the worst affected
- **Global Financial Crisis impact on funding for high working capital requirements**
- **Oversupply**
 - Speculative vineyard plantings have created excess capacity
 - *Oversupply has dogged the Australian wine industry since the record harvests of 2004, 2005 and 2006. While the sustainability of the current status quo is being hotly debated by the industry, the underlying problem is becoming increasingly acute as Australian wine demand falters. We believe the industry needs to remove at least 25% of bearing vineyards to balance supply with existing demand." (Citigroup Industry Focus, 8 January 2009)*

By way of response, the wine sector is focussed on developing and implementing strategic initiatives to help manage through these uncertain times, ensuring a more sustainable local industry in terms of the economic, environmental and social aspects of the sector.

Exchange rate has impeded Australian wine competitiveness in major markets since 2002

Adverse movements in the Australian dollar against the key Australian wine industry competitors of USA, Europe and Chile have eroded profitability in the UK, USA, Japan and European markets.

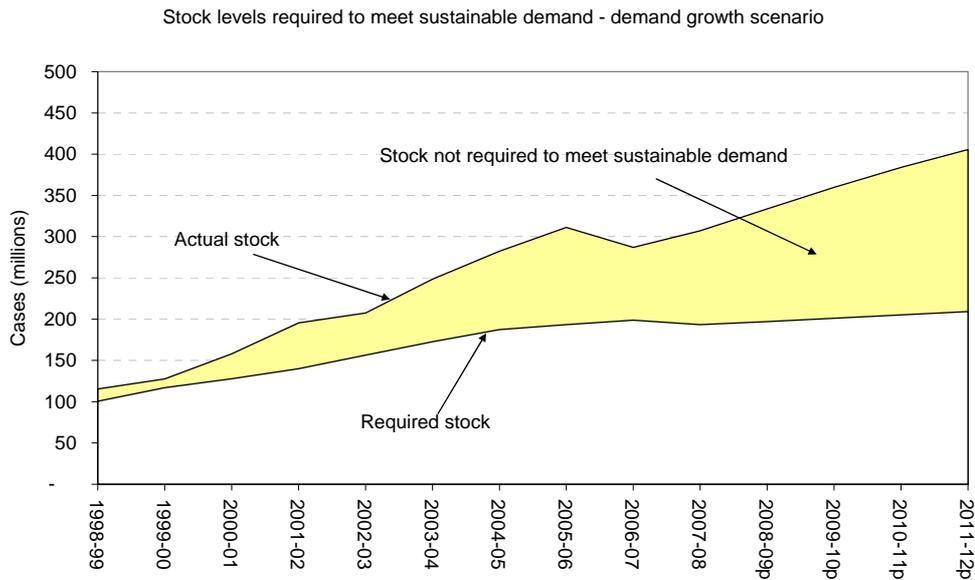




Wine industry – structural excess supply of grapes

Industry estimates that over the medium term the current Australian grape supply capacity will produce each year between 20 and 40 million cases more than sustainable demand.

The estimated below average yields 2009 vintage of approximately 1,600,000 tonnes will make only a minor contribution to alleviating projected grape over supply, making supply restructuring an imperative. Ongoing surplus annual production is adding to already excessive inventory.



Therefore at this critical time, taxation changes would greatly magnify the scope and scale of adjustment thereby jeopardising the wine industry’s capability to manage an orderly restructuring.

7. Conclusion

The preceding analysis strongly supports the WFA's submission that the current system and level of wine taxation is appropriate, effective and well understood and should not be changed.

The common theme is that alcohol is a complex product and wine is distinct from other forms of alcohol in terms of the way it is produced, purchased and consumed. In particular, its lifestyle connections, strong links with regional prosperity and health benefits when consumed in moderation cannot be ignored.

The key points in our submission are that:

- Australian wineries already pay among the highest taxes in the world and make a significant total contribution to taxation revenue through the WET, on top of that required of other industries. The net effect of changing to a beer rate volumetric system would be small financially but significant in terms of its impact on the industry. Economic modelling of the impact in just 6 of the key wine regions shows that the combined loss in GDP in those wine regions would be almost equivalent to the tax raised by such a volumetric tax scenario.
- The wine industry cannot afford further destabilisation – and a likely tax-induced reduction in sales – as it undergoes a major restructuring while dealing with the toughest economic conditions in two decades. The pace and finesse with which it navigates these pressures will have substantial bearing on the 63 regional communities and 60,000 jobs.
- The industry's strategic plan, *Directions to 2025*, identifies the pathway forward and clearly articulates the key issues that need to be tackled to restore the Australian wine industry to a position of ascendancy and leadership in the world wine industry. Most of these initiatives the wine industry can and will undertake itself, though it needs direct and indirect assistance.
- While the wine industry supports the Government's determination to address problems of alcohol abuse in Australia, there is no evidence to suggest increasing taxation, and thus prices, is the best way to discourage such behaviour. This is particularly the case for wine, which is not generally associated with binge drinking. Wine is most commonly drunk in moderation and with food by older adults, many of whom would be unfairly disadvantaged by unnecessary price rises.

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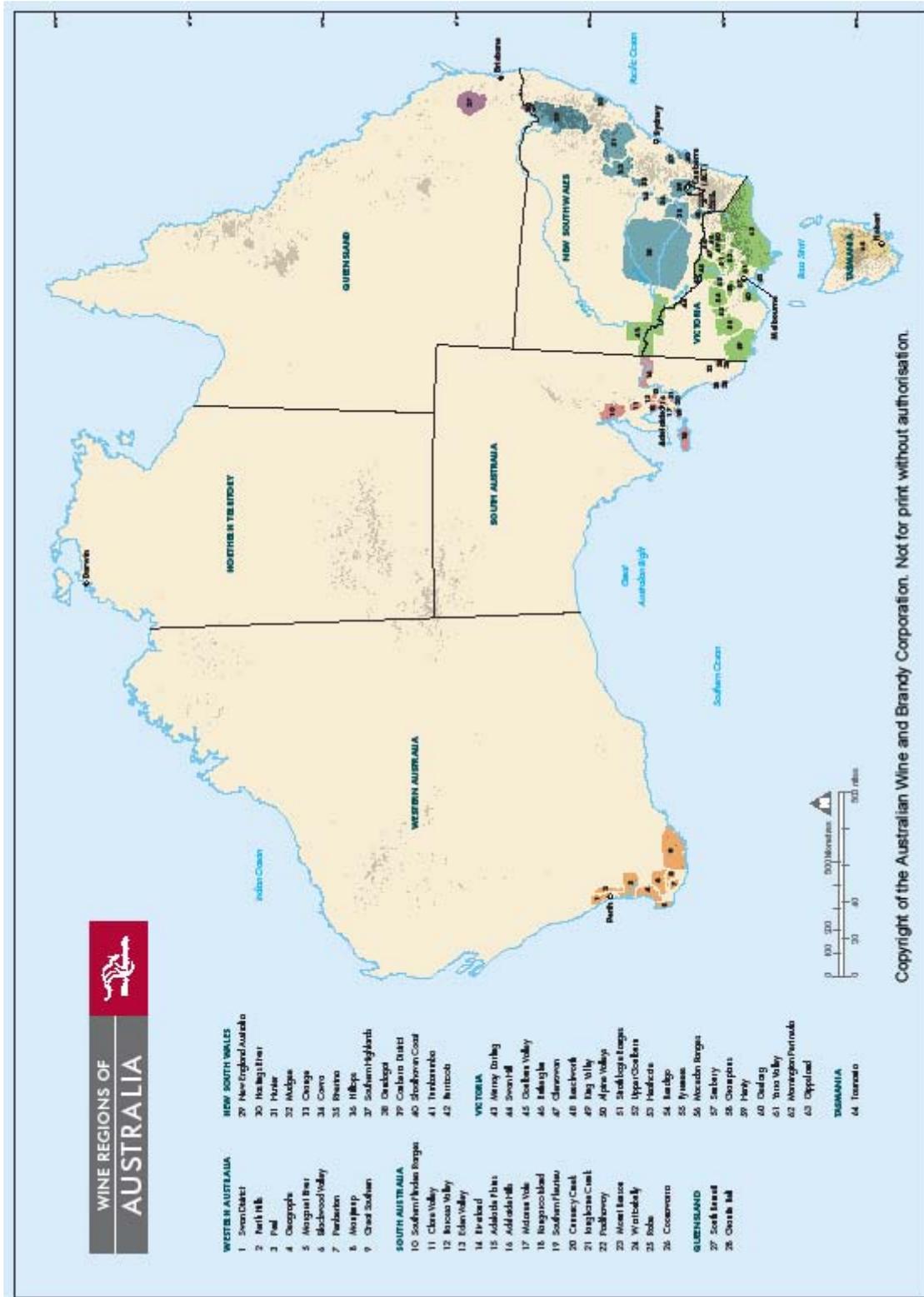
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Appendix 1



Appendix 2

Table 1: Short Term Risk - Alcohol consumption, risk of harm in the short term: proportion of the population aged 14 years or older, by age and sex, Australia, 2001, 2004 and 2007

Age Group	Abstainers ^(a)			Low Risk			Level of Risk ^(b)								
							At least yearly			At least Monthly			At least weekly		
(per cent)															
Males															
	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007
14-19	27.2	30.4	29.2	30.0	32.7	33.4	13.3	10.9	12.9	19.8	15.1	15.7	9.6	10.9	8.8
20-29	8.4	7.8	11.1	27.4	27.4	26.1	21.7	20.8	19.0	27.8	26.6	26.6	14.6	17.4	17.2
30-39	9.8	8.9	10.9	39.7	37.5	40.6	22.2	24.4	21.1	20.4	18.9	17.5	7.8	10.3	10.0
40-49	11.4	8.6	10.8	50.7	49.5	47.0	17.2	19.4	18.9	12.9	12.8	14.5	7.7	9.7	8.7
50-59	12.5	10.5	9.9	59.1	58.3	59.4	11.7	13.4	12.9	8.5	10.6	9.5	8.2	7.1	8.2
60+	20.1	17.3	17.3	66.5	68.1	67.8	5.8	6.5	6.4	3.6	3.8	4.5	4.0	4.3	4.0
Total	14.1	12.9	14.0	46.5	46.8	47.2	15.5	16.1	15.1	15.3	14.4	14.3	8.5	9.8	9.3
Females															
	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007
14-19	25.3	27.6	28.7	28.3	30.2	30.1	13.4	12.9	12.9	21.2	18.8	18.8	11.8	10.5	9.5
20-29	11.3	13.4	14.8	32.1	29.4	29.2	20.4	20.3	20.7	26.8	26.0	23.1	9.3	10.9	12.2
30-39	16.0	13.0	13.5	47.5	47.8	46.9	18.9	19.5	19.5	12.8	13.8	13.3	4.8	5.8	6.8
40-49	16.4	13.8	13.9	55.1	53.4	53.4	14.7	16.8	16.2	9.3	10.5	10.2	4.6	5.5	6.3
50-59	21.9	19.5	18.1	62.0	63.4	62.5	8.6	9.4	10.2	4.3	4.6	4.8	3.3	3.2	4.4
60+	33.0	31.6	31.1	62.3	61.3	61.3	2.0	4.0	3.9	1.3	1.5	2.1	1.3	1.6	1.5
Total	20.8	19.8	20.1	49.6	49.4	49.3	12.7	13.5	13.4	11.6	11.5	10.9	5.3	5.7	6.2
Persons															
	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007
14-19	26.2	29.0	29.0	29.2	31.5	31.8	13.4	11.9	12.9	20.5	16.9	17.2	10.7	10.7	9.1
20-29	9.9	10.6	12.9	29.8	28.4	27.6	21.1	20.5	19.8	27.3	26.3	24.9	12.0	14.2	14.7
30-39	13.0	11.0	12.2	43.7	42.7	43.8	20.5	21.9	20.3	16.5	16.4	15.3	6.3	8.0	8.4
40-49	13.9	11.2	12.4	52.8	51.4	50.2	16.0	18.1	17.6	11.1	11.6	12.3	6.2	7.6	7.5
50-59	17.1	15.0	14.0	60.5	60.8	61.0	10.2	11.4	11.6	6.4	7.6	7.1	5.8	5.1	6.3
60+	27.1	25.0	24.7	64.2	64.5	64.3	3.7	5.2	5.1	2.4	2.5	3.2	2.6	2.9	2.7
Total	17.5	16.4	17.1	48.1	48.2	48.3	14.1	14.8	14.2	13.4	12.9	12.6	6.9	7.7	7.8

(a) Not consumed alcohol in the previous 12 months.

(b) For males, the consumption of 7 or more standard drinks on any one day. For females, the consumption of 5 or more standard drinks on any one day.

Sources: 2001, 2004 and 2007 National Drug Strategy Household Survey: First results

Table 2: Long Term Harm - Alcohol consumption, risk of harm in the long term: proportion of the population aged 14 years or older, by age and sex, Australia 2001, 2004 and 2007

Age Group	Level of Risk ^(b)											
	Abstainers ^(a)			Low Risk			Risky			High Risk		
(per cent)												
Males												
	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007
14-19	27.2	30.4	29.2	64.0	62.0	63.7	6.1	4.9	4.4	2.7	2.8	2.6
20-29	8.4	7.8	11.1	77.1	77.7	73.4	9.5	8.7	9.3	5.0	5.7	6.2
30-39	9.8	8.9	10.9	81.4	80.8	79.2	5.8	7.5	6.2	3.1	2.8	3.7
40-49	11.4	8.6	10.8	79.0	82.1	79.6	6.4	5.7	6.0	3.2	3.6	3.5
50-59	12.5	10.5	9.9	75.8	78.8	78.9	7.3	6.9	6.1	4.3	3.8	5.1
60+	20.1	17.3	17.3	71.9	74.8	75.3	5.4	5.2	4.9	2.6	2.7	2.5
14+	14.1	12.9	14	75.6	77.0	75.8	6.7	6.5	6.2	3.5	3.6	3.9
Females												
	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007
14-19	25.3	27.6	28.7	60.1	60.1	60.7	9.9	8.3	6.7	4.7	4.0	3.9
20-29	11.3	13.4	14.8	73.7	71.6	68.8	10.9	12.2	11.0	4.0	2.9	5.4
30-39	16.0	13.0	13.5	75.4	77.1	75.8	6.8	7.7	7.7	1.9	2.1	3.0
40-49	16.4	13.8	13.9	73.9	75.9	74.1	7.8	8.0	9.3	1.9	2.3	2.6
50-59	21.9	19.5	18.1	70.7	73.1	72.3	5.9	6.0	6.9	1.5	1.4	2.7
60+	33.0	31.6	31.1	62.6	63.3	63.4	3.7	4.3	4.7	0.7	0.9	0.8
14+	20.8	19.8	20.1	69.8	70.6	69.4	7.2	7.5	7.6	2.2	2.1	2.8
Persons												
	2001	2004	2007	2001	2004	2007	2001	2004	2007	2001	2004	2007
14-19	26.2	29.0	29.0	62.1	61.1	62.2	8.0	6.6	5.6	3.7	3.4	3.2
20-29	9.9	10.6	12.9	75.4	74.7	71.1	10.2	10.4	10.2	4.5	4.3	5.8
30-39	13.0	11.0	12.2	78.3	78.9	77.5	6.3	7.6	7.0	2.5	2.4	3.3
40-49	13.9	11.2	12.4	76.5	79.0	76.8	7.1	6.9	7.7	2.6	3.0	3.1
50-59	17.1	15.0	14.0	73.3	76.0	75.6	6.6	6.4	6.5	2.9	2.6	3.9
60+	27.1	25.0	24.7	66.8	68.6	68.9	4.4	4.7	4.8	1.6	1.7	1.6
Total	17.5	16.4	17.1	72.7	73.7	72.6	7.0	7.0	6.9	2.9	2.8	3.4

(a) Not consumed alcohol in the previous 12 months

(b) For males, the consumption of up to 28 standard drinks per week is considered 'Low risk', 29 to 42 per week 'Risky', and 43 or more per week 'High Risk'. For females, the consumption of up to 14 standard drinks per week is considered 'Low risk', 15 to 28 per week 'Risky', and 29 or more per week 'High Risk'.

Sources: 2001, 2004, and 2007 National Drug Strategy Household Survey: First results

Appendix 3

Is there a role for wine in the degenerative diseases of ageing?

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Abstract

Population ageing is associated with the increased incidence of degenerative diseases. Population ageing is occurring on a global scale, with faster ageing projected for the coming decades than has occurred in the past. Globally, the population aged 60 years and over is projected to nearly triple by 2050, while the population aged 80 years and over is projected to experience a more than five-fold increase. Increased numbers of older individuals may have implications for associated expenditure on income support, housing and health services, although a healthy, independent older population can also form a valued social resource, for example in providing care for others, sharing skills and knowledge and engaging in volunteer activities.. Simple dietary measures such as moderate wine consumption to supplement a healthy exercise and nutrition routine, or as an adjunct to prescription medicines when appropriate, are thus needed to maintain an ageing population. The role of wine in the degenerative diseases of ageing is thus discussed.

1. Introduction

Damage to DNA, lipids and proteins by reactive oxygen species (oxidative free radicals) has been implicated in accelerated aging, degenerative diseases including cancer (Ames et al. 1995) and Alzheimer's disease (Smith et al. 1996, Commenges et al. 2000), as well as cardiovascular disease. These diseases of old age are expected to increase significantly over the next few decades as people increasingly survive beyond the age of 80 years (Kelner and Marx 1996). Consequently there is interest in identifying lifestyle factors and molecular mechanisms that can minimise the risk of these debilitating conditions.

There is a clear J-shaped relationship between alcohol consumption and the risk of cardiovascular disease which has been extended to a reduced risk of certain cancers (Boffetta and Garfinkel 1990, Marmot and Brunner 1991, Thun et al. 1997). Data is now accumulating which suggests that the regular and moderate consumption of alcohol may reduce the risk of: Alzheimer's disease; bone mineral density; chronic obstructive airways disease; diabetes; disorders of the immune system; gallstones; gastrointestinal diseases; kidney stones; osteoporosis; rheumatoid arthritis; and age-related visual impairment, or macular degeneration in addition to psychological or social benefits (Kono et al. 1992, Holbrook et al. 1993, Lipton 1994, Voigt et al. 1994, La Vecchia 1995, Rimm et al. 1995, Weisse et al. 1995, Brenner et al. 1997, Heath 1998, Obisesan et al. 1998, Renaud et al. 1998, Roche 1998). The literature defines consistently light to moderate consumption as 20–40 g ethanol per day (Jackson et al. 1992, Palomaki and Kaste 1993, Stockley 1998). The chemical components of wine purportedly primarily responsible for these therapeutic effects are ethanol and the monomeric phenolic compounds and their polymeric forms. The ethanol component is common to all alcoholic beverages.

2. Wine consumption and the risk of cancer

Alcohol consumption per se has been associated with an increased risk of developing cancer of the mouth, pharynx, oesophagus, stomach, liver, colon and rectum (IARC 1988, 1998, Longnecker 1990, Lewis et al. 2008). North America has the highest incidence or rate of cancer per 100,000 population followed by Australia, and then Europe (IARC GLOBOCAN 2002 database). In Australia, for example, cancer is now the major cause of premature death, and the major cause of death, in the 45 to 65 year old age group (Begg et al. 2007). The level of alcohol consumption that increases risk has not been determined and there are usually other risk factors for cancer, which confound determination (Longnecker 1995). The risk of cancer of the mouth, tongue and larynx, however, is associated with the number of drinks per day. While it is unlikely that ethanol itself causes cancer to develop, alcohol may act in conjunction with other cancer-inducing compounds or carcinogens. Indeed, both while alcohol consumption and smoking both independently increase the risk of these cancers, the risk is amplified if individuals both drink and smoke (Williams and Horn 1977, MacFarlane et al. 1996, Launoy et al. 1997).

In addition, alcohol consumption has been associated with an increased risk of breast cancer, particularly in women who have a family history of breast cancer (Gapstur et al. 1992, Rosenberg et al. 1993, Longnecker 1994, van den Brandt et al. 1995, Swanson et al. 1997, Vachon et al. 2001, Horn-Ross et al. 2004). From a pooled analysis of data, the relative risk increases by 1.09 for each 10 g alcohol (equivalent to one standard drink) consumed per day up to 60 g. Consumption above 60 g per day is not associated with a further increased risk (Smith-Warner et al. 1998, Singletary and Gapstur 2002). It has been suggested that consumption patterns may modify risk (Morch et al. 2007), such that the consumption of 40 to 50 g alcohol per session may increase the risk by 50% compared to the consumption of only one 10 g alcohol per session. Paradoxically, alcohol dependence does not increase the risk of breast cancer (Kuper 2000).

An adequate consumption of folate, however, may reduce the increased risk of breast cancer associated with alcohol consumption (Zhang et al. 1999, 2005, Rohan et al. 2000, Sellers et al. 2001, Baglietto et al. 2005, Stolzenberg-Solomon et al. 2006, Tjonneland et al. 2006). For example, while ethanol interferes with DNA synthesis and repair, folate is involved in DNA synthesis, repair and methylation. In animal models, folate supplementation reduces DNA strand breaks in the *p53* gene (Kim et al. 2000); the P53 protein regulates the cell cycle to prevent genome mutation, and hence functions to suppress tumours. It can activate DNA repair proteins when it recognises damaged DNA, hold the cell cycle at the G₁/S regulation point on DNA damage recognition to prevent uncontrolled cell division and can initiate apoptosis, the programmed cell death, if the DNA damage proves to be irreparable. Cancer occurs when the rate of proliferation of mutated cells greatly exceeds the rate of apoptosis. In breast cancer, the gene has been observed to be mutated in 15 to 50% of tumours (Olivier and Hainaut 2001).

For women consuming greater than 15 g alcohol/day, the concurrent consumption of 300 µg folate per day reduces the relative risk of breast cancer to 1.05, and to 0.74 when 600 µg folate per day is concurrently consumed (Zhang et al. 1999). The interaction between alcohol and folate has, however, been observed to be primarily limited to estrogen receptor negative (ER-) breast cancer tumours (Zhu and Williams 1998, Sellers et al. 2002, Zhang et al 2005).

Regular and moderate alcohol consumption has, however, been associated with a decreased risk of mortality from certain cancers (Boffetta and Garfinkel 1990, Gronbaek et al. 2000), although the risk increases progressively with immoderate consumption. Briggs et al. (2002), for example, calculated that the moderate consumption of wine decreased the risk of Non-Hodgkin's Lymphoma by approximately 20 to 40%, in particular in individuals who began consuming wine as young adults, and similar decreases in risk were observed for aero-digestive tract and lung cancers (Gronbaek et al. 1998, Prescott et al. 1999). In contrast to beer and spirits, the moderate consumption of wine also shows null associations with, or reduces the risk of colorectal cancer at three subsites [proximal colon, distal colon, and rectum] (Gronbaek et al. 2000, Pedersen et al. 2003). Renaud et al. (1998) suggested, however, that the risk of mortality from all cancers may be decreased by approximately 20% when 20 g alcohol in the form of wine are consumed daily.

Genetic damage is a risk factor for the formation and progression of cancer (Ames et al. 1995). Oxidative free radicals also cause mutation of DNA sequences and breakage of DNA strands (Ames et al. 1993). For example, when the genetic material or DNA of cells is damaged, the characteristics of the cell are altered causing it to malfunction or die. It is the excess occurrence of dead cells and mutant cells in the body that ultimately accelerates diseases of old age. A number of factors may contribute to this damage, including chemical genotoxins, lifestyle factors (diet, exercise and the environment), and medical therapies including radiotherapy and cytotoxic drugs. Oxidising agents such as hydrogen peroxide and ionising radiation cause chromosome breakage and loss, as well as cell death (Fenech et al. 1999a, Fenech et al. 1999b).

Role of wine-derived phenolic compounds on the risk of cancer

A diet high in fruit and vegetables has been associated with a reduced risk of cancer, and this has prompted researchers to investigate whether any of the wine-derived phenolic compounds might protect cells and DNA from damage leading to cancer by inhibiting the oxidizing agents (Ames et al. 1995, DeFlora et al. 1997, Andreassi et al. 2000, Izzotti et al. 2001). A link between cardiovascular disease and cancer is an elevated micronucleous frequency, which is a biomarker of DNA damage (Botto et al. 2002). The results from numerous *in vitro* and animal studies suggest that individual and collective wine-derived phenolic compounds may be protective against DNA damage. Fenech et al. (1997) showed that following the acute consumption of red or white wine there was a significant increase in the antioxidant capacity of plasma, which reduced the oxidative damage to DNA from hydrogen peroxide *in vitro* and *ex vivo*. This was the first evidence that moderate wine consumption could minimise the DNA-damaging effects of oxidizing agents. The observation that the duration of this protective effect was diminished by eight hours post-consumption, implied that the regular consumption of wine is important to maintain a protective effect. Leighton et al. (1999), using different biomarkers of DNA damage, has also recently shown that the short-term consumption of red or white wine, in particular in combination with a Mediterranean diet, could significantly reduce DNA damage in both elderly men and women. Interestingly, the women consumed half the amount of wine consumed by the men but showed a similar reduction in extent of DNA damage. No cellular mechanism of action has, however, been determined.

Greenrod and Fenech (2003) demonstrated that although ethanol exacerbated oxidative stress and hence DNA damage, the wine-derived phenolic compounds significantly countered the oxidative stress as well as the additive effects of ethanol; DNA damage was reduced by approximately 45% at approximately 2 hours post consumption when de-alcoholised wine was consumed in moderation. Whole red wine also reduced DNA damage but to a lesser extent. Two studies were undertaken and the first was an *in vitro* study which tested human plasma or whole blood from four healthy male subjects ages 20–25 years that was spiked with different wine components for protection against hydrogen peroxide and ionizing radiation induced DNA damage. The components examined were ethanol, glycerol, tartaric acid, and caffeic acid/ catechin mixture and compared to a Riesling wine stripped of phenolic compounds and a control salt solution, which was a diluent for the wine components. The components were added at 2.5% and 10% of the concentration observed in wine, where 2.5% corresponds to the concentration observed in the body fluids of a 60 kg volunteer after consuming 300 mL (approximately three glasses) of white wine. The cells were then analysed via the cytokinesis block micronucleus assay, which enables chromosome or DNA damage to be scored (Fenech 1993).

Greenrod and Fenech (2003) observed that the phenolic compounds, such as catechin and caffeic acid, and the mixture including these components, significantly decreased baseline DNA damage and DNA damage caused by ionising radiation *in vitro*. It was observed that the ethanol component significantly increased base-line DNA damage, but the mixture that included both ethanol and the phenolic compounds completely countered the DNA damaging effects of ethanol. These effects were observed for both the 2.5% and 10% concentration of the components, although the protective effect of the phenolic compounds was most significant for the 10% concentration. The component mixtures, also produced the strongest protective effects against DNA damage by hydrogen peroxide. The protective effects of the mixture did not account for the expected additive protective effects of the individual components, which suggests that the components may be exerting their effects through similar mechanisms, which are saturated at the concentration tested. These observations suggest that the primary phenolic components of wine can reduce the DNA damaging effects of two important oxidants, hydrogen peroxide and ionising radiation, in a physiologically relevant *in vitro* system.

The second study undertaken by Greenrod and Fenech (2001) was an *ex vivo* study in which blood from six healthy male subjects analysed for its resistance to DNA damage induced by hydrogen peroxide or ionising radiation, following the consumption of 300 mL red wine, dealcoholised red wine or a model wine (12% alcohol solution). The subjects were placed on a plant phenolic compound free diet for 48 hours prior to each study day. The results of this study showed a clear protective effect of the dealcoholised red wine, an aggravating or negative effect of ethanol and an intermediate but protective effect of whole red wine. The most significant protective effects were observed at two hours post consumption. These results were important in verifying that it is the phenolic component of wine that has DNA-protective properties in blood and body tissues.

A DNA-protective effect against the hepatic carcinogen or oxidising agent, 2-nitropropane, was also observed in a rat animal model administered with a mixture of wine of phenolic compounds (Casalini et al. 1999), but was not observed against 2-dimethylhydrazine, which is a colon carcinogen. These results imply that the phenolic component may not protect DNA against all oxidizing agents.

Other researchers have examined the effect of specific wine-derived phenolic compounds on cancer, in particular, resveratrol (stilbene), quercetin (flavonol), catechin (flavanols) and gallic acid (hydroxybenzoic acid). These wine-derived phenolic compounds appear capable of inhibiting cellular events at each of the three steps involved in the development of cancer—initiation, promotion and progression. Experimental approaches include cell lines, (whole) animal cancer models and human cancer patients. For example, quercetin has demonstrated chemopreventative activity in azoxymethane-induced colorectal cancer in mice and male F344 rats (Dihal et al. 2006), while catechin protected against the heterocyclic amine 2-amino-3-methyl-imidazo[4,5-f] quinoline (IQ)-induced aberrant crypt formation in male F344 rats (Franke et al. 2003).

Other plausible mechanisms for the potential cancer-protective effects of the wine-derived phenolic compounds include: inhibition of the cell growth or proliferation resulting from arrestation at one or more phases of the cell cycle, which then activates apoptosis of cells; inhibition of DNA synthesis by inhibiting ribonucleotide reductase or DNA polymerase; and apoptosis by modulation of signal transduction pathways that regulate the cell cycle, by altered expression of primary enzymes such as cyclooxygenases and protein kinases, including modulation of tumor suppressor genes (Tsan et al. 2000, Ahmad et al. 2001, Stivala et al. 2001). These are in addition to the removal of reactive oxygen species.

Resveratrol appears to have been the most widely examined phenolic compound over the past decade. In 1997, Jang et al. observed that 1–25 μM resveratrol inhibited the initiation and promotion of hydrocarbon-induced skin cancer in a mouse model as well as the progression of breast cancer in the same model. In human cancer cell lines, resveratrol has been observed to inhibit or suppress the growth and proliferation of, for example, breast, colon, prostate and oral squamous cancer cell lines (Elattar and Virji 1999a, Hsieh et al. 1999a,b,c, Damianaki et al. 2000, Kampa et al. 2000, Mutoh et al. 2000). These studies also suggest that the DNA-protective effect of resveratrol is dose-dependent. Latruffe et al. (2002) examined the effect of resveratrol on two different human tumor cell lines, and has shown that resveratrol is actually taken up by the cells, whereupon it is conjugated and released into the cell medium by the hepatic HepG2 cells and to a lesser extent by colorectal tumor SW480 cells²¹. Phenolic compounds may not be antiproliferative or active against all tumor cell lines, however, as no uptake and conjugation was observed with cells from the intestine. Elatter and Virji (1999a) examined the effect of quercetin alone and in combination with resveratrol on human oral squamous carcinoma cells (SCC-25), and showed that quercetin is an equipotent inhibitor of SCC-25 cell growth and DNA synthesis, but the combination of quercetin and resveratrol was most potent (Elatter and Virji 1999b).

Studies have shown that resveratrol also possesses chemopreventative activity against colorectal cancer (Schneider et al. 2001, Wolter et al. 2001). Schneider et al. (2001) showed that treatment of CaCo-2 human colon tumor cells with 25 μM (5.7 mg) resveratrol inhibited cell growth by 70%. The cells accumulated at the S/G2 phase transition of the cell cycle. Furthermore, resveratrol significantly decreased the activity of the polyamine biosynthesis enzyme, ornithine decarboxylase, which is enhanced in tumor cell growth. Wolter et al. (2001) showed that inhibition of cell CaCo-2 human colon tumor cells with resveratrol was dose dependent (12.5–200 μM) (Wolter et al. 2001). A lower concentration of resveratrol (50 μM) perturbed cell cycle progression from the S to G2 phase

whereas a higher concentration led to reversal of the S phase arrest. A similar activity was observed for HCT-116 human colon tumor cells, which indicates that cell cycle inhibition by resveratrol is independent of cyclooxygenase inhibition. Recent research, however, suggests that the chemopreventative activity of resveratrol at physiological doses is primarily linked to its ability to induce cell division cycle arrest and mitochondrial apoptosis, the latter through activation of pro-apoptotic proteins such as Bax, as well as independently of Bax (Pohland et al. 2006). This ability is also independent of the p53 tumor suppressor activation (Pohland et al. 2006).

3. Effect of wine on diabetes mellitus

The prevalence of diabetes mellitus is escalating worldwide and its incidence is projected to increase from about 135 million in 1995 to 300 million in 2025 (AusDiab Steering Committee 2001). Type 2 diabetes mellitus, which accounts for more than 85% of all incidences of diabetes mellitus, is a disorder characterised by resistance to the effects of circulating insulin. This disorder leads to a substantial increase in risk of cardiovascular disease, which is the major cause of mortality, accounting for up to 80% of all deaths in individuals with type 2 diabetes mellitus (Feener and King 2001, Gu et al. 2003, Mooradian 2003); the age-adjusted relative risk of death due to cardiovascular disease is approximately three-fold higher than in the general population. Approximately 30 to 60% of diabetic patients have hypertension (Nilsson et al. 2003, Vijan and Hayward 2003). In addition, patients with type 2 diabetes mellitus have coexistent lipid disorders characterised by increased blood triglycerides and reduced HDL-cholesterol, as well as haemostatic and fibrinolytic abnormalities (Mooradian 2003).

Apart from obesity and physical inactivity there are few well-established modifiable risk factors for type 2 diabetes mellitus. Recent evidence suggests, however, that alcohol consumption may be a potentially modifiable risk factor for type 2 diabetes mellitus and a J-shaped relationship has been observed between level of alcohol consumption and risk of developing diabetics in both men and women (de Vegt et al. 2002, Wannamethee et al. 2002, Wannamethee et al. 2003). The risk of developing type 2 diabetes mellitus was observed to be most reduced for women when their daily consumption was between 15.0 to 29.9 g of alcohol (Wannamethee et al. 2003). Indeed, as in the general population, there is also a decrease in cardiovascular risk with mild-to-moderate alcohol consumption in type 2 diabetics (Ajani et al. 2000b, Hu et al. 2001). For example, in males, the risk only increases when more than 21 standard drinks are consumed per week, however, a similar increased risk has not necessarily been observed for wine consumers (Carlsson et al. 2000, Kao et al. 2001). A J-shaped relationship has also been observed between insulin sensitivity and level of alcohol consumption, where the moderate consumption of alcohol has been observed to improve insulin sensitivity, possibly by reducing the concentration of free fatty acids in blood (Avogaro et al. 2002, Koppes et al. 2005). In turn, the improved insulin sensitivity lowers the concentration of insulin, glucose and triglycerides in the blood, and increases that of HDL, while LDL particles become less dense, less adherent and less easily oxidized. Altogether, this reduces the risk of developing type 2 diabetes mellitus, as well as improving control of blood glucose and reducing the risk of cardiovascular disease in type 2 diabetic (Ajani et al. 2000a, Solomon et al. 2000). Following the consumption of 120 to 240 mL wine daily for 30 days fasting serum insulin concentration was also lowered (Bantle et al. 2008).

Patients with diabetes mellitus have other risk factors for cardiovascular disease such as a decreased total antioxidant capacity of plasma and concomitant increased LDL oxidation post-prandially (Ceriello et al. 1999a, Diwadkar et al. 1999). Ceriello et al. (2001) observed, however, that the consumption of red wine with food in type 2 diabetic patients decreased LDL oxidation post-prandially (Ceriello et al. 1999b). Furthermore, the post-prandial hypoglycaemia experienced in diabetes mellitus, which activates coagulation (Ceriello et al. 1996), was decreased by the consumption of red wine. The consumption of red wine by fasting type 2 diabetic patients, however, did not decrease either LDL oxidation or coagulation. Landrault et al. (2001) also investigated whether wine-derived phenolic compounds increased the total plasma antioxidant capacity in an insulin-deficient diabetic rat model, as well as affecting glycaemia or blood sugar concentration, the biomarker of diabetes. Following the medium-term administration of both phenolic-enriched white wine and de-alcoholised phenolic-enriched white wine, the total plasma antioxidant capacity of the diabetic rats was increased to the level of non-diabetic rats and the level of glycemia reduced by 15 to 20%. This suggests that moderate wine consumption may also attenuate the debilitating hyper- and hypo-glycaemic symptoms of diabetes.

Furthermore, increased inflammation via an increase in circulating pro-inflammatory cytokines has been observed in both diabetic and non-diabetic patients and to be involved in the pathogenesis of cardiovascular complications such as endothelial dysfunction after a myocardial infarction (MI) (Nystrom et al. 2006). Wine-derived phenolic compounds have anti-inflammatory actions including inhibition of reaction oxygen species in neutrophils, monocytes and macrophages (Martinez et al. 2000, Feng et al. 2002). In subjects with diabetes, red wine consumption, taken with meals, significantly reduces oxidative stress and the circulating concentration of pro-inflammatory cytokines from lymphocytes and macrophages such as C-reactive protein, tissue necrosis factor-alpha and interleukin-6, as well as improving cardiac function after a MI (Marfella et al. 2006).

4. Effect of wine on metabolic syndrome

Blood fat disturbance in combination with high blood pressure and type 2 diabetes often occur together in susceptible individuals, and is referred to as the 'metabolic syndrome' (Reaven 1993). The blood fat disturbance relates to being overweight or obese (BMI greater than 30 kg/m²), especially in individuals who store their fat in the abdominal area. An excess of toxic free fatty acids in the blood stream may cause or contribute to the insulin sensitivity and impaired insulin function observed with this syndrome, which generally eventually develops into type 2 diabetes mellitus.

The severely obese (BMI greater than 35 kg/m²) are at increased risk of type 2 diabetes, cardiovascular morbidity and mortality. In a study of 486 severely obese subjects, consumers of alcohol showed a marked reduction in the prevalence of type 2 diabetes compared with non-consumers (Dixon et al. 2002). A U-shaped relationship was observed between both the amount and frequency of alcohol consumption and the plasma concentration of fasting triglyceride, fasting glucose, glycosylated haemoglobin A1c and insulin measurements. Consumers of less than 100 g of alcohol/week had more favorable insulin measures, with insulin sensitivity best in those consuming 20 to 100 g of alcohol/week. Of the 276 alcohol consumers, 165 nominated wine as the alcoholic beverage most frequently consumed, and they were observed to have a significantly lower fasting insulin level and improved insulin sensitivity.

The severely obese subjects went on to have a laparoscopic adjustable gastric band placed to help them lose weight. Those subjects consuming more than 100 g of alcohol/week, especially wine, had significantly better weight loss (50.4% of excess weight lost (EWL) at the end of the first year) than those with nil or negligible consumption (40.1% EWL). Those consuming 20 to 100 g/week had an intermediate outcome (45.4% EWL).

These results and those of other studies indicate that light to moderate alcohol consumption, and especially wine consumption, is associated with a lower prevalence of type 2 diabetes, improved insulin sensitivity and more favorable cardiovascular risk profile in the severely obese as well as non-obese (Dixon et al. 2002, Athyros et al. 2008).

Potential mechanism of action

An alteration in the relationship between the concentration of the amino acid homocysteine, and that of folate and vitamin B12 has been observed as people lose weight (Dixon et al. 2001). A higher plasma concentration of folate and vitamin B12 is needed to maintain the concentration of homocysteine as weight is lost. It may be postulated that the phenolic compounds alter or shift the dose-response curve (in the opposite direction) such that a lower plasma concentration of homocysteine is achieved with an equivalent micronutrient concentration (Dixon et al. 2002).

Four hundred and sixteen severely obese patients were recently studied for any relationship between both the amount and type of alcohol consumption and concentration of plasma homocysteine during fasting (Dixon et al. 2002). A U-shaped relationship was observed whereby light to moderate alcohol consumption was associated with a lower and more favorable plasma concentration of homocysteine. Above moderate alcohol consumption is conversely associated with an increased plasma concentration of homocysteine (Cravo et al. 1996, Bleich et al. 2001). Those patients consuming up to 100 g/week of alcohol had a significantly lower homocysteine concentration compared with non-consumers ($p=0.001$). The lower concentration of homocysteine in regular alcohol consumers was associated with a higher concentration of the micronutrient folate. Red wine consumers had a significantly lower mean fasting concentration of homocysteine compared with non-consumers, beer and spirit consumers and white wine consumers. Red wine consumption was an independent predictor for a lower plasma concentration of homocysteine after controlling for sex, age, and body weight, and plasma concentration of folate and vitamin B12.

Three micronutrients are important cofactors in homocysteine metabolism. Folate and vitamins B12 are cofactors for the methylation of homocysteine to methionine, and vitamin B6 is a cofactor for the trans-sulphuration of homocysteine to cysteine. Deficiency of any of these micronutrients leads to a higher concentration of homocysteine and increased risk of atherosclerosis and endothelial dysfunction. The mechanisms for the beneficial effect of red wine consumption on the plasma concentration of homocysteine remain unclear. The concentration of micronutrients are unlikely to provide the answer as it has been observed that the effect of red wine is independent of the plasma concentration of folate and vitamin B12, and red wine contains negligible quantities of vitamin B6 (van der Gaag et al 2000).

A high plasma concentration of homocysteine is, however, another risk factor for atherosclerosis, endothelial dysfunction and cardiovascular disease (Nygard et al. 1997, Welsh et al. 1998). The American Heart Association recommends that the concentration of homocysteine in plasma should be maintained below 10 $\mu\text{mol/L}$. Homocysteine is closely linked to the metabolism of the essential amino acid, methionine. It has a direct toxic effect on the endothelium of blood vessels that alters their function (Bellamy et al. 1998) and leads to key early steps in the atherogenic process. For example, in human umbilical vein endothelial cells, the addition of homocysteine resulted in a dose-dependent increase in the generation of reactive oxygen species and a correlated decrease in intracellular NO. Homocysteine also increased tyrosine kinase activity and phosphokinase stimulation of ERK5, Scr and p38, activated NF κ B, increased the concentration of nitrotyrosine and induced VCAM-1, which are markers of oxidative stress or endothelial dysfunction. All these effects were inhibited *in vitro* by the wine-derived phenolic compounds (Foncea et al. 2002).

5. Effect of wine on cognitive function

Over the last five years, evidence has accumulated which suggests that the J-shaped relationship could also be extended to a reduced risk of cognitive dysfunction. Cognitive function is defined as the intellectual or mental processes by which knowledge is acquired, including perception, reasoning, acts of creativity, problem-solving and possible intuition.

Cognitive dysfunction or impairment is associated with increased disability and an increased need for institutionalised care, especially in an ageing population over 65 years of age. Dementia is a form of cognitive dysfunction whereby an individual loses the ability to think, remember and reason due to physical changes in the brain.

Prior to a study by Zuccala et al. (2001), there was conflicting evidence on the relationship between alcohol consumption and cognitive function (Cervilla et al., 2000; Dent et al., 1997; Dufouil et al., 1997; Elias et al., 1999; Harwood et al., 1999; Hendrie et al., 1996; Leibovici et al., 1999; Teri et al., 1990). Zuccala et al. (2001) analyzed the association between alcohol consumption and cognitive impairment in 15,807 hospitalized older patients who were enrolled in an Italian multicentre pharmacoepidemiology survey. The probability of cognitive impairment was reduced among male patients who reported an average daily alcohol consumption of 1 L or less of wine, as compared with abstainers, but the probability increased among heavier drinkers. Among women, only the lightest-drinking category (<0.5 L) showed a decreased probability of cognitive dysfunction when compared with abstainers, whereas heavier drinking was associated with an increased probability of cognitive impairment. The prevalence of alcohol abuse was similar among participants with cognitive impairment (0.9%) and those with normal cognitive functioning (1%). The results of this study indicated that moderate alcohol consumption, that is, <40 g per day for women and <80 g for men, is associated with reduced probability of cognitive impairment as compared with abstinence, after adjusting for potential confounders. This nonlinear association persisted when cerebrovascular and Alzheimer's disease were considered separately. Such a nonlinear association might explain the conflicting results of previous studies regarding the relationship between alcohol consumption and cognitive functioning.

The observed gender difference in amount of alcohol consumption necessary for improved cognitive function, confirms that observed by Elias et al. (1999), who showed that 'superior' cognitive performance was found with in the range of four to eight drinks per day for men but only two to four drinks per day for women, compared to abstainers.

Subsequent studies have also independently assessed the association between alcohol consumption and cognitive function and have affirmed the observations of Zuccala et al. (2001) but have also provided more detailed data (Ganguli, et al. 2005, Stampfer et al. 2005, McDougall et al. 2006, Reid et al. 2006, Wright et al. 2006). For example, Reid et al. (2006) in a study of 760 US men aged 65 years or older showed that current light to moderate alcohol consumption considered as up to seven drinks per week, compared to abstinence, had better cognitive function. In particular, processing speed, which is the ability to perform tasks requiring rapid visual scanning and mental processing of information, was better even after adjusting for potential confounders such as education and occupation. In addition, the study assessed the effects of cumulative lifetime alcohol consumption on cognitive function and showed that the number of years of light to moderate alcohol consumption was strongly associated with better cognitive function. Results from a small survey study by McDougall et al. (2006) also suggested that men aged 65 years or older who drank moderately had significantly less depression, higher self-reported general health and higher cognitive function, flexibility and verbal memory.

Several studies had shown that the association between alcohol consumption and cognitive function is stronger for women than for men, which may simply reflect a gender difference in cognitive function or perhaps a misclassification of moderate alcohol consumers. Such a gender difference was not, however, observed by in a longitudinal study of 1624 Japanese American men and women aged over 65 years (Bond et al. 2005). Other studies which assessed women specifically, such as the US Nurses' Health Study, suggested that for women aged 71 to 80 years, up to 15 g alcohol per day did not impair cognitive function and actually improved it compared to abstinence (Stampfer et al. 2005); the women also had a decreased risk of cognitive impairment of approximately 20%. No significant differences were observed in cognitive performance or risk between beer and wine consumers. Furthermore, a study of women aged 65–80 years, showed that women consuming any alcohol performed better on tests of verbal knowledge, fluency and memory, and figural memory, attention and working memory and motor speed compared to abstainers ($P < 0.05$) (Espeland et al. 2006). After covariate adjustment, mean scores were higher among women reporting ≥ 1 drink/day by 5.7% for verbal knowledge ($p < 0.001$) and by 5.7% for phonemic fluency ($p = 0.004$), compared to abstainers.

Potential mechanisms of action

The beneficial effects of alcohol on the risk of cardiovascular and cerebrovascular diseases, such as heart attacks and strokes, have been partly attributed to changes in lipid and haemostatic or blood flow factors (Rimm et al., 1999). These changes include alcohol-induced increases in the concentration of high density lipoprotein-cholesterol and the thrombolytic proteins tissue type plasminogen activator activity and tissue type plasminogen activator antigen, and alcohol-induced reductions in fibrinogen, and clotting cofactors factor VII and von Willebrand factor. These changes

are also associated with atherosclerosis which is the accumulation of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries. As atherosclerosis has been associated with both Alzheimer's disease and vascular dementia, it had been suggested that any beneficial effect of alcohol on atherosclerosis could be expected to benefit these major subtypes of dementia by preserving brain vasculature, consequently resulting in better cognitive function. Wright et al. (2006), however, showed that the appearance of plaque on the carotid artery which carries blood to the brain was not associated with alcohol consumption and alcohol-associated improvements in cognitive function. This suggests then that alcohol may impact cognition through a separate vascular or degenerative pathway. Among older persons without cerebrovascular disease, those who moderately consume alcohol have been shown to have fewer white-matter abnormalities and infarcts on magnetic resonance imaging than abstainers (Mukamal et al. 2001), where pronounced reductions in the risk of both vascular dementia and Alzheimer's disease have been shown among persons consuming one to six standard drinks per week (Mukamal et al. 2003).

Indeed, there is also evidence which suggests that a light to moderate amount of alcohol may stimulate the release of acetylcholine in the hippocampus leading to improved cognitive function such that a light amount of alcohol in normal subjects appears to improve memory for events experienced before consumption where the impairment of memory performance by chronic and heavy alcohol consumption parallels the reduction of acetylcholine neurotransmission (Fadda and Rossetti 1998).

6. Effect of wine on Alzheimer's disease and dementia

The immoderate or excessive consumption of alcoholic beverages is associated with an increased risk of dementia probably directly resulting from the neurotoxic effect of ethanol or indirectly from concomitant malnutrition/nutritional deficiencies or trauma (French et al. 1985). The moderate consumption of alcoholic beverages, however, has been associated with comparatively better cognitive function in two studies—The Zutphen Elderly Study (Launer et al. 1996) and the Honolulu Asia Aging Study (Galanis et al. 2000). A third study, The Rotterdam Study, demonstrated that moderate alcohol consumption reduced the risk of vascular dementia in particular, and also that of Alzheimer's Disease in individuals aged 55 years or older (Ruitenberg et al. 2002), which is supported by the results of other recent studies by Huang et al. 2002 and Mukamal et al. 2003. In these prospective population-based studies, moderate consumption was defined as one to three drinks per day. It has been suggested that ethanol may directly stimulate the release of acetylcholine in the hippocampus, which is associated with learning and memory (Perry et al. 1999). In a rat model, a moderate concentration of alcohol (0.8 g/kg) stimulated the release of acetylcholine while a higher concentration (2.4 g/kg) inhibited its release (Henn et al. 1998).

Three studies have further suggested that moderate wine consumption is associated with a lower risk of dementia and specifically Alzheimer's Disease (Orgogozo et al. 1997, Lemeshow et al. 1998, Truelsen et al. 2002). In the latter Copenhagen City Heart Study (1991–1994) only wine was associated with a lower risk or incidence (Truelsen et al. 2002). In the prospective population-based

study by Orgogozo et al. (1997) the sole source of alcohol was wine for 95% of consumers, which did not allow for beverage differentiation. Supplementation of diet with antioxidants such as α -tocopherol may improve cognitive function and slow functional deterioration (Grundman 2000).

7. Conclusions

The protective effect of moderate alcohol consumption against cancer, diabetes, metabolic syndrome and cognitive dysfunction, including dementia has been consistently observed over the past five years. Indeed, there is sufficient epidemiological evidence and plausible biological mechanisms to support the J-shaped relationship between moderate alcohol consumption and risk of cardiovascular disease that can be extended to other degenerative diseases that are often inter-related (Simons et al. 1996, 2000, 2006). Thus, while excessive alcohol consumption should be avoided, it would appear safe and reasonable to recommend the continuation of light to moderate alcohol consumption in those already imbibing. A high level of risk factors for any degenerative disease, however, can mitigate any protective effects of moderate alcohol and wine consumption. In addition, the effects of the excessive consumption of alcohol may be additive to any other risk factors for disease, increasing the risk by two to three-times.

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Appendix 4

How do we demonstrate that there is a potential therapeutic role for moderate wine consumption?

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ABSTRACT

The light to moderate consumption of alcoholic beverages has been observed to reduce the risk of, and death from, cardiovascular disease (CVD) by potentially 20-50% compared to abstinence and excessive consumption. The main component considered responsible for the reduced risk is ethanol. One of the alcoholic beverages, wine, additionally contains phenolic compounds, that are also observed in fruits and vegetables, the consumption of which is associated with a similar reduced risk of CVD. It has thus been proposed that consumers of wine have a greater reduction in the risk of CVD than do consumers of beer and spirits, but potential confounders include the drinking pattern and associated diet and lifestyle of consumers.

What is perplexing scientists, however, is the amount of phenolic compound that is necessary to elicit a cardioprotective effect e.g. on platelet aggregation or coagulation. In *in vitro* studies effects are generally elicited with a 10- or 100-fold greater concentration of phenolic compounds than is present in blood and at cellular sites of action following moderate consumption. This suggests that the metabolites of phenolic compounds may also be bioactive.

This paper reviews the data generated to date on the amount of phenolic compounds necessary to elicit certain cardioprotective effects, and whether isolated individual phenolic compounds are as effective as those administered in a wine medium. The data suggests that although the phenolic compounds are absorbed into the blood stream in measurable amounts, the metabolite is more likely to be the biologically active compound *in vitro*. Furthermore, when seed-derived phenolic compounds are together with the skin and flesh-derived phenolic compounds in wine, they exhibit greater cardioprotective effects than when present individually in a non-wine medium and are potentially equi-potent to certain conventional pharmaceutical products at reducing the risk of CVD.

This data may have implications for national alcohol and dietary guidelines, for medical practitioners who 'prescribe' daily moderate wine consumption, as well as for the wine industry per se redeveloping healthier wine styles and types.

INTRODUCTION

From earliest times wine has been used as a therapeutic agent. For example, the physician Hippocrates of Cos (c 460–370 BC) prescribed it as a wound dressing, as a nourishing dietary beverage, as a cooling agent for fevers, as a purgative and as a diuretic (Lucia 1963: 63). Similarly, Claudius Galenus (Galen) (c AD 130–201) recommended that wine be used for the dressing of wounds, for fevers and for debility, therapies that became widely adopted throughout medieval Europe. Wine remained a therapeutic agent into the middle-ages through the *Liber de Vinis*, which was written by Arnaldus de Villanova (c AD 1235–1311), who again recommended wine as an antiseptic, a restorative, and for the preparation of poultices. Wines then fell from favour as a therapeutic agent, which is attributed to the Puritan religious movement led by Oliver Cromwell (c AD 1599–1658) that spread to the New World when the Pilgrim Fathers settled the east coast of North America in 1620. Wine only found favour again as a therapeutic agent in the last decades of the twentieth century, although, in the first decades, the first population-based study observed that there was a linear relationship between the prevalence of hypertension and cardiovascular disease (CVD) and the amount of wine consumed by French Troops on the western front during World War I (Lian 1915).

A J-shaped relationship between amount of wine consumed and risk of cardiovascular diseases such as hypertension was, however, first observed in 1974 by Klatsky et al. and independently by St Leger et al. in 1979. It only came to public prominence in 1992 (Renaud and de Lorgeril 1992) when French wine drinkers were observed to have a reduced risk of cardiovascular disease (CVD) compared to other population groups which had similar high risk factors for CVD, such as in the USA. Interestingly, in contrast to beer and spirits drinkers in the USA, US wine drinkers are observed to have a similar reduced rate to that of French wine drinkers (Klatsky and Armstrong 1993).

Why is this observation important?

CVD accounts for 25 to 50% of all deaths in developed countries and its incidence is increasing in developing countries (Tunstall-Pedoe et al. 1994). According to World Health Organization (WHO) estimates, in 2005, 17.5 million people died of CVD. This is 30% of all deaths globally, while at least 20 million people survived heart attacks and strokes, many require continuing costly clinical care (WHO 2006). The main factors responsible for these alarming figures are represented by the unacceptably high rates of patients with uncontrolled hypertension and dyslipidaemia, and the epidemic of obesity and type 2 diabetes, which tend to appear together as the metabolic syndrome (MS) (Dunstan et al. 2002, Zimmet et al. 2005).

The WHO estimates that there are currently 1.1 billion people who are overweight and expect this total to rise to over 1.5 billion by 2015 (WHO 2006); overweight is defined as a BMI ≥ 25 kg/m² (WHO 2002). It is estimated globally that the prevalence of diabetes mellitus is 5.1% of the adult population where type 2 diabetes mellitus is now found in almost every population (International Diabetes Federation 2006). Approximately 75–80% of diabetics die of CVD. In the Hoorn Study, a 10-year population-based cohort study, the metabolic syndrome, however defined, was associated with an approximate two-fold increased risk of incident CVD morbidity and mortality in a European population (Dekker et al. 2005).

Factors modifying the risk of CVD

Notably, CVD incidence varies 10-fold across different countries. Sources of the variation include impact of different risk factors for CVD such as body mass index (BMI), diet and exercise, diabetes, genetic predisposition, blood pressure, serum cholesterol concentration, cigarette smoking and socioeconomic status, as well as differences in the amount, pattern and even type of alcoholic beverage consumed, such as beer, wine or spirits (Wietlisbach et al. 1997).

Dietary factors modifying the risk of CVD

Diet is also a significant source of variation in CVD risk. For example, in a 30-year follow-up study in seven countries, the risk of CVD was at least two- to three-fold lower in countries consuming a Mediterranean-style diet compared to that in northern Europe and USA where the diet was generally higher in fat (de Lorgeril et al. 1999). The core components of a Mediterranean-style diet include the high consumption of cereals, fruits, legumes and vegetables, which typically contain a high concentration of phenolic compounds, and have previously been associated with a reduced risk of CVD (Trichopoulou and Lagiou 1997). Diet is a risk factor that can be readily modified to reduce the risk of CVD and the impact of other important cardiovascular risk factors. For example, subjects placed on a Mediterranean-style diet for 46 months had a 50–70% lower risk of recurrent CVD, compared to control subjects on a higher fat diet, (Kris-Etherton et al. 2001). Furthermore, 55% of patients with MS who followed a Mediterranean diet for two years were symptom-less and had a reduced risk of CVD at follow-up compared with only 14% of patients in the control group (Esposito et al. 2004).

Influence of wine on the risk of CVD

Wine is a major component of a Mediterranean-style diet (Kris-Etherton et al. 2001). Epidemiological studies have indicated that consumers of wine have a reduced risk of CVD, similar but additive to that for consumers of a traditional Mediterranean diet. This is exemplified in an epidemiological study assessing the geographical distribution of CVD in Spain, one of the 18 Mediterranean countries. A higher rate of CVD was observed in those Spanish regions with the lowest per capita wine consumption, despite having, overall, a Mediterranean-style diet. The rate of CVD was, however, still less than that of countries consuming a higher fat and lower phenolic compound diet (Rodriguez et al. 1996). The amount of wine associated with a reduced risk of CVD is generally considered as two to four glasses of wine per day consumed with food, which would attenuate a high blood alcohol concentration associated with cellular and tissue damage, prolong any acute and short-term anti-atherosclerotic, blood pressure and haemostatic effects, and prevent any rebound effects of the ethanol components of the beverage (Rodriguez et al. 1996, Klatsky 2003).

CVD involves a complex interplay between multiple altered cellular and molecular functions in heart muscle (such as cardiomyocytes), blood vessels (such as endothelial cells), vascular smooth muscle cells, blood cells (such as platelets and monocytes) and plasma components (such as lipoproteins, and blood clotting and blood flow factors) as well as gene function (Booyse et al. 2007).

The mechanisms involved in the CVD risk reduction provided by a Mediterranean-style diet are equally multifactorial, and include anti-inflammatory effects and enhanced endothelial function, thus providing a protective effect during the early phases of atherosclerosis (Esposito et al. 2004, Lopez-

Garcia et al. 2004, Ross 1999). The endothelium plays a crucial role in regulating peripheral blood flow and oxygen supply to organs and tissues through the production of nitric oxide (NO) (Ignarro et al. 2002). NO tonically regulates arterial and arteriolar tone and exerts significant anti-inflammatory and anti-atherosclerotic effects (Ignarro et al. 2002). Endothelial dysfunction has been shown to be an independent predictor of CVD even after adjusting for traditional risk factors (Lerman and Zeiher 2005), such as hypertension and hypercholesterolaemia, which are characterized by an impairment of endothelium-dependent vasodilatation. Therefore, improving endothelial function by means of pharmacological and non-pharmacological strategies such as moderate wine consumption with food might represent an important therapeutic target (Lerman and Zeiher 2005, Kawashima et al. 2001)).

Wine-derived phenolic compounds

The components of wine that might confer a reduced risk of CVD, by enhancing endothelial function and exerting anti-inflammatory and anti-atherosclerotic effects, are represented by the phenolic compounds. These compounds, also present in the fruit and vegetable components of a Mediterranean-style diet, have been associated with a reduced risk of CVD (Kris-Etherton et al. 2001; Genkinger et al. 2004).

Catechin, quercetin and resveratrol represent some of the primary phenolic compounds in wine (Carando et al. 1999). For example, *in vitro* and animal studies have demonstrated that catechin, quercetin, and resveratrol, administered either acutely or chronically, exert significant beneficial or positive effects on established markers of CVD risk such as endothelial function (Benito et al. 2002, Chen and Pace-Asciak 1996, Cishek et al. 1997, Wallerath et al. 2002; Wallerath et al. 2005; Sanchez et al. 2006) and blood pressure (Negishi et al. 2004, Garcia-Saura et al. 2005, Duarte et al. 2002, Liu et al. 2005). In both red and white wines, catechin is the most abundant and resveratrol is the least (Cabanis et al. 1999).

Catechin

The flavanol catechin, a simple monomeric compound, is found in both the seed and the skin of the grape berry as well as in the leaves and stems. The average concentration of catechin in red wine is 191.3 mg/L and is 34.9 mg/L in white wine (Soleas et al. 1997). A dose of 35 mg catechin in red wine yields a plasma total catechin concentration of *ca.* 91 nmol/L (Donovan et al. 1999). Free catechin and its free primary metabolite 3'-O-methylcatechin, was detected in plasma at 1 h post consumption but was not detected at 3-4 h. This implies that, immediately after absorption, catechin is metabolised to polar conjugates (glucuronate or sulfate) either in the epithelial cells or in the liver, before systemic circulation (Donovan et al. 1999). The presence or absence of alcohol does not influence the absorption or metabolism of catechin (Bell et al. 2000).

It has been shown that as atherosclerosis develops, vascular smooth muscle cells are released by platelets and endothelial cells, which proliferate and accumulate within the intima of the blood vessel wall, to further develop the atherosclerotic lesion or plaque. The primary mitogenic and chemotactic compound for the release of the vascular smooth muscle cells is platelet-derived growth factor, which exerts its effects via activation of two subtypes of trans-membrane receptor tyrosine kinases, α and β platelet-derived growth factor receptors (Tanizawa et al. 1996, Schwartz 1997, Heldin and

Westermmark 1999, Rosenkranz and Kazlauskas 1999). Recent *in vitro* research suggests that catechin, for example, may inhibit the activation of the β platelet-derived growth factor receptors, and hence platelet-derived growth factor and the subsequent proliferation and migration of vascular smooth muscle cells (Kerry and Abbey 1997).

Endothelial cells synthesise proteins such as tissue-type plasminogen activator (t-PA) and urokinase-type PA (u-PA) which activate fibrinolysis and plasminogen activator inhibitor type-1 (PAI-1) which activates thrombosis. Catechin has been observed to promote fibrinolysis by up-regulating both t-PA and u-PA gene transcription (Abou-Agag et al. 2001, Booyse et al. 2007) as well as by suppressing that of PAI-1 gene transcription (Pasten et al. 2007) in the human coronary artery, by activating the mitogen-activated protein kinases ERK and JNK signalling pathways at the transcription level.

Normal endothelial function depends on a controlled balance between the production of endothelium-derived relaxing factors such as nitric oxide and prostacyclin, and the release of constricting factors such as prostaglandins and thromboxane A₂. An imbalance towards an increased release of constricting factors is associated with endothelial dysfunction. Catechin has also been observed to induce endothelium dependent vasorelaxation in the rat aorta (Benito et al. 2002) and mouse renal artery (Gendron and Thorin 2007) by promoting NO production by promoting endothelial nitric oxide synthase (eNOS) mRNA expression and by preventing the release of the vasoconstrictor, thromboxane A₂; NO also inhibits lipid peroxidation in LDL and is hence anti-atherogenic (Hogg et al. 1993, 1998).

Quercetin

The simple flavonol quercetin is produced and found in the skin of the grape berry and in grape rachis and leaves. The average concentration of quercetin in red wine is 7.7 mg/L but can range from 2.0–29 mg/L (Soleas et al. 1997, McDonald et al. 1998), and is generally not found in white wine. There have been no human pharmacokinetic studies on quercetin following red wine consumption. Generally, however, quercetin is not found in plasma as the free form or as the parent glycoside but exclusively as methyl, sulfate or glucuronic acid conjugates (Day et al. 2001). Lower doses of quercetin are more methylated than higher doses, potentially yielding compounds such as tamarixetin and isorhamnetin, which may exert certain cardioprotective effects (Dragoni et al. 2006). As quercetin has a relatively long half-life compared with catechin, a 50 mg dose of quercetin would yield a plasma concentration of *ca.* 0.75–1.5 $\mu\text{mol/L}$ (Scalbert and Williamson 2000, Manach et al. 2005), and its metabolites may accumulate in plasma if it is consumed regularly.

Platelet function is pivotal in the formation and progression of atherosclerotic plaques and a diet high in fruits and vegetables has been observed to reduce the risk of thrombus formation. Quercetin has been observed to influence platelet function by inhibiting, for example, collagen-induced platelet aggregation through inhibition of GPVI-mediated signalling, as well as both thrombin-induced and ADP-induced platelet aggregation (Pace-Asciak et al. 1995, Hubbard et al. 2003). Quercetin has also been observed to inhibit the tyrosine phosphorylation and/or kinase activity of a number of critical components of the GPVI signalling pathway, such as the non-receptor tyrosine kinase Syk, phospholipase C γ 2 and P13-K (Hubbard et al. 2003, 2004). All inhibitions were dose-dependent.

Endothelial cells also release metabolites of arachidonic acid, most notably prostacyclin but also hydroxyeicosatetraenoic acids (HETEs), which influence platelet aggregation and quercetin has also been observed to inhibit 12-HETE synthesis from arachidonate by platelets (Pace-Asciak et al. 2005); in particular, 12-HETE impairs endothelial function. In addition, quercetin has been observed to promote fibrinolysis by up-regulating both tissue- and urokinase-type plasminogen activator gene transcription (Abou-Agag et al. 2001, Booyse et al. 2007, Pan et al. 2008). Furthermore quercetin, as well as catechin, increases the expression and activity of eNOS (Wallerath et al. 2005), while decreasing NADPH oxidase-mediated superoxide anion (O_2^-) generation (Pignatelli et al. 2006); the excessive generation of O_2^- is involved in the degradation of NO associated with endothelial dysfunction in clinical and experimental hypertension.

Resveratrol

The non-flavonoid stilbene phenolic compound, resveratrol, exists in both *cis* and *trans* forms in wine, but *trans*-resveratrol predominates in grapes. The average concentration of resveratrol in red wine is 7 mg/L, 2 mg/L in rosé and 0.5 mg/L in white wine (Waterhouse 2002). Recent research has demonstrated that while approximately 70% of resveratrol was relatively rapidly absorbed following oral administration to healthy humans, only trace amounts (<5 ng/mL) of un-metabolized resveratrol could be detected in the systemic circulation following a 25 mg dose (Walle et al. 2004). Sulfate and glucuronic acid conjugates were, however, measured in plasma and urine. The latter study utilized ^{14}C -labelled resveratrol administered both orally and intravenously. The maximum plasma concentration of both the parent compound and metabolites was, however, *ca.* 490 ng/mL or 2.146 μ mol/L. Boocock et al (2007) recently observed that a 5 g single oral dose of resveratrol provided a plasma resveratrol concentration of 2.4 μ mol/L, while the concentration of the sulfate and glucuronide metabolites was observed to be 3- and 8-fold higher. No adverse effects were observed at such an inflated dose. These human data appear to be consistent with those observed in animals, although the doses of resveratrol were significantly higher in animal studies (Meng et al. 2004). Both animal and human studies suggest that resveratrol has sufficient bioavailability to reach cellular target sites (Jannin et al. 2004). The chemopreventative effects of resveratrol *in vitro* require a concentration of at least 5 μ mol/L.

Purified or synthetic resveratrol enhances endothelial function, and inhibits inflammation. The endothelial effects of resveratrol, in addition to the potentiating effects on NO synthesis and release (Wallerath et al. 2002, Wallerath et al. 2005, Ekshyyan et al. 2007), can also be ascribed to its inhibitory effects on the most potent vasoconstrictor hormone in humans, that is, endothelin-1 (ET-1). ET-1 overproduction is another risk factor for the development and progression of atherosclerosis and is observed to increase in rabbits fed a high fat diet. Indeed, resveratrol has been observed *in vitro* to inhibit the synthesis of ET-1 by suppressing transcription of the prepro-ET-1 gene and by changing the morphology of the endothelial cell to modify tyrosine-kinase signalling and hence tyrosine phosphorylation (Zou et al. 2003). This inhibitory effect is dose-dependent, emphasizing the need for controlled studies aimed at assessing different concentrations of resveratrol on vascular and platelet function. Concerning the upregulation of NO, of the phenolic compounds, resveratrol has been observed to be the most efficacious stimulator of human eNOS expression and transcription, but this compound alone does not explain the total stimulatory effect of red wine on eNOS (Wallerath et al. 2005), such that the effects of the individual phenolic compounds appear to be additive and complementary.

The anti-inflammatory properties of resveratrol are secondary to the inhibition of the expression of the monocyte and endothelial adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), and the attachment of monocytes to endothelial cells, as well as inhibiting the lipopolysaccharide (LPS)-induced synthesis of the pro-inflammatory cytokine, tumor necrosis factor- α (TNF- α), and interleukin-1- β , and the release of interleukin 6 from monocytes, partly via a modulatory effect on the nuclear factor kappa B (NF-kappaB) and other signaling pathways (Carluccio et al. 2003).

Furthermore, resveratrol has independently been observed to interfere with the multiple protein kinase pathways and vascular smooth muscle cell protein synthesis activated by angiotensin II, the angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, and thus may also decrease the plasma concentration of angiotensin II and thereby inhibit the vascular smooth muscle cell hypertrophy (Hernandez-Ledesma et al. 2003).

Bioavailability of wine-derived phenolic compounds

At the same time as the phenolic compounds are observed to enhance endothelial function and reduce blood pressure, they appear, however, to undergo extensive first-pass phase II metabolism in the small intestine and in the liver (Manach and Donovan 2004). Metabolites conjugated with methyl, glucuronate, and sulfate groups are the predominant forms present in plasma, but these are usually not measured in human intervention studies (Kroon et al. 2004). Accordingly, it is thus suggested that these metabolites may actually exert the biological effects *in vivo*, although has yet to be confirmed. For example, metabolites of catechin, quercetin and resveratrol have been shown to exert endothelial, anti-inflammatory and anti-thrombotic effects *in vitro* (Day et al. 2000, Koga and Meydani 2001, Williamson et al. 2005).

CONCLUSION

Phenolic compounds are absorbed into the blood stream in measurable amounts following moderate wine consumption but are relatively rapidly and extensively metabolised such that their metabolites may actually exert the beneficial or positive biological effects on CVD in addition to or instead of the parent compound.

When the seed-derived phenolic compounds such as catechin are together in wine with the skin and flesh-derived phenolic compounds such as quercetin and resveratrol, they exhibit greater endothelial, anti-inflammatory, and anti-thrombotic cardioprotective effects than when present individually in a non-wine medium. The vast majority of the available data, however, have been obtained from *in vitro* studies using concentrations of the phenolic compounds that are not necessarily consistent with those observed in wine. Indeed, attempts to extend *in vitro* and animal findings to human studies have resulted in few studies in which effectiveness was shown at moderate oral 'doses' of wine and correspondingly, wine-derived catechin, quercetin and resveratrol. It is unknown as to whether these phenolic compounds *in vivo* reach the multiple proposed sites of action beyond the gastrointestinal tract, and although recent studies have been undertaken to determine their bioavailability, there is still limited information on their pharmacokinetics in humans. Therefore, the paucity of human data on the pharmacokinetics and pharmacodynamics of catechin, quercetin and resveratrol and their metabolites warrants more research, using escalating doses in accurately controlled human *in vivo* studies in conjunction with reliable and established markers of endothelial function, thrombogenic activity and inflammation.

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