Workshop to summarise GWRDC-funded research outcomes for wine and health, and to provide direction for further research



FINAL REPORT to

GRAPE AND WINE RESEARCH & DEVELOPMENT CORPORATION

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Table of contents

		Page
1. Abstract		**3**
2. Executive summary		**4**
3. Background		**7**
4. Project aims and performance targets		**10**
5. Method		**11**
6. Results/Discussion		**14**
6.1	**Introduction**	**14**
6.2	**Summary of presentations**	
6.2.1	Kevin Croft	16
6.2.2	Roland Stocker and Creina Stockley	19
6.2.3	Will Greenrod, Mavis Abbey and Michael Fenech	22
6.2.4	John Dixon	27
6.2.5	Trevor Mori and Ian Puddey	30
6.2.6	Sebeley Pal	32
6.2.7	Pierre-Louis Tiessedre and Jean-Claude Ruf	34
6.3	**Summary of post-presentation discussion on day 1**	**36**
6.4	**Summary of Affinity Diagram exercise**	**39**
6.5	**Summary of criteria for selection**	**40**
6.6	**Summary of areas requiring further research and potential new projects**	**42**
6.7	**Summary of potential research directions and considerations ensuing from the initial GWRDC-funded and other research projects presented on day 1**	**43**
6.8	**Summary of potential research directions from independent international researchers**	**45**
7. Outcomes/Conclusion		**47**
8. Recommendations		**54**
9. Appendix 1: Communication		**56**
10. Appendix 2: Intellectual property		**57**
11. Appendix 3: References		**58**
12. Appendix 4: Staff		**63**
13. Appendix 5: Other material		
13.1	**Grouping of issues (risks) and opportunities (benefits) associated with industry-funded research prepared by workshop participants**	**64**
13.2	**Recommended research directions from international and Australian researchers**	**66**
13.3	**Winemakers' Federation of Australia core policy**	**74**
14. Appendix 6: Budget reconciliation		**75**
15. Appendix 7: New GWRDC Project Applications for wine and health		**76**

1. Abstract

A workshop to summarise the Grape and Wine Research and Development Corporation (GWRDC)-funded research outcomes for wine and health (projects CSN 97/2, HRI 97/2 and UWA 97/2) was held in December 2002. An objective of the workshop was also to provide direction and recommendations for further research initiatives which impact on policy. The results of the collaborative research which was undertaken by three Australian research groups suggests that the wine-derived phenolic compounds are absorbed into the body and that the most efficacious beverage to reduce and prevent the oxidation of low density lipoprotein, associated with atherosclerosis and cardiovascular disease, is dealcoholised red wine. Ethanol-containing red wine is less efficacious but may counter the harmful pro-oxidative effects of the ethanol component in plasma, low density lipoproteins and on DNA. Dealcoholised red wine is also more efficacious at protecting DNA from oxidative damage. Background diet, disease and smoking status, however, may influence the antioxidant effects of the wine-derived phenolic compounds, which may act synergistically with the endogenous antioxidant, vitamin E. Further clinical research is recommended to confirm these results, as is clinical research to determine whether moderate wine consumption is cardioprotective in two population groups at higher risk of cardiovascular disease—the obese and those with type 2 diabetes, which are increasing in prevalence in the developed and developing world. To assist the GWRDC in assessing whether it should continue to fund wine and health research in future, a list of prioritised research projects was prepared as well as a list of criteria with which to evaluate and select future projects. Furthermore, an assessment of the risks and benefits in funding wine and health research highlighted that there were more benefits and opportunities for industry, and that any potential risks or be managed and hence minimised. A significant and tangible benefit that was highlighted is the ability of industry to use this research to demonstrate its duty of care to consumers.

2. Executive summary

Funded by the Grape and Wine Research and Development Corporation (GWRDC) funded a workshop was conducted in December 2002 to summarise GWRDC-funded research outcomes for wine and health, and to provide direction for further research initiatives, which impact on policy. The workshop was organised by Creina Stockley, Health and Regulatory Information Manager at The Australian Wine Research Institute for the past 12 years, and attended by Australian researchers, an international researcher and representatives from the Australian wine industry, including the GWRDC, South Australian Wine and Brandy Industry Association (SAWBIA) and the Winemakers' Federation of Australia (WFA). The workshop relates to Program 4 of the GRWDC 5-Year Plan 2002–2007, which refers to the impact of wine on the community in a social context, and the following specific strategies:

- Evaluate and quantify the costs and benefits of…social…effects on the Australian community by the wine industry;
- Monitor current scientific research findings on the health aspects of wine; and
- Increase Australian influence in the agendas and access to the information resources of global wine forums.

Following the Wolf Blass Foundation International Wine and Health Conference, *Medically is wine just another alcoholic beverage?* in June 1996, the GWRDC funded, for the first time, three collaborative wine and health-related research projects (CSN 97/2, HRI 97/2 and UWA 97/2). These projects were undertaken at The University of Western Australia, Heart Research Institute and CSIRO Health Sciences and Nutrition, in conjunction with The Australian Wine Research Institute, and strove to answer questions arising at the Conference on the potential cardio and cancer-protective effects of wine and the wine-derived phenolic compounds. The aims and objectives of the research projects were also influenced by specific objectives of Strategy 2025 of the Australian wine industry such as:

1. Progress and sustain the community acceptance positioning of wine (health, environment and lifestyle);
3. Extend the influence of Australia in world wine forums and institutions; and
26. Continue, in partnership with government, alcohol and health programs to reduce alcohol abuse.

Six years later, the Australian GWRDC-funded research has answered some of the Conference questions and has shown that some of the wine-derived phenolic compounds are absorbed in sufficient amount to be measurable in plasma after the regular short-to-medium term consumption of wine. Concerning effect and efficacy of the phenolic compounds in the human body (*in vivo*) it appears that the most 'efficacious' beverage to effect the blood lipid profile by reducing and preventing the oxidation of low density protein (LDL) associated with atherosclerosis and cardiovascular disease, may be dealcoholised red wine. This is because the positive anti-oxidant effects of the wine-derived phenolic compounds may mainly counteract the negative pro-oxidant effects of the ethanol component. It has, however, been shown that background diet and smoking-status of consumers may influence the antioxidant effects of the phenolic compounds, which may act in conjunction with the endogenous antioxidant, vitamin E. These results are consistent with those being published internationally and imply that the primary cardioprotective effects of wine may be more related to effects other than anti-oxidation such as on blood clotting.

In addition, the research suggests that individuals at higher risk of cardiovascular disease, such as obese individuals and type 2 diabetics, who regularly consume wine in moderation may also have a

relative reduction in risk for cardiovascular disease compared to abstainers and heavy consumers. In Australia, 50% of men and women are overweight and 20% are actually obese, and approximately 10% of Australians have become type 2 diabetics, the prevalence of which has trebled since 1981. This research could foster the adoption of regular and moderate consumption of wine as part of all healthy diets and lifestyles, as abstinence has been traditionally advised by medical practitioners for obese and type 2 diabetic individuals.

Also shown by the GWRDC-funded research is that the wine-derived phenolic compounds may protect DNA and cells from induced and spontaneous oxidative damage, such as from ionizing radiation, which has important implications for radiotherapy whereby cancerous cells are targeted but normal cells may be protected.

Recommendations were sought from the workshop participants and from independent Australian and international researchers for further wine and health research projects; the views of the researchers were generally consistent. Nine of these are recommended to be funded and undertaken during the next five years in Australia, and primarily extend or primarily build upon the initial GWRDC-funded wine and health research projects. The emphasis is on clinical rather than animal, test tube and population studies, and include:

- determination as to whether there is a dose dependent relationship between the phenolic component of wine (and anti-oxidation) and the ethanol component of wine (and per-oxidation) in plasma, lipids and cells/DNA; the significance of background diet and smoking status on plasma and lipid oxidation and hence interaction with wine consumption also need to be determined, as well as effects on other biological markers for cardiovascular disease. Such a study would confirm and strengthen the results of the initial research projects;

- confirmation of cardioprotection and determination of cardioprotective effects from moderate wine consumption in individuals with higher risk of cardiovascular disease such as obese individuals and type 2 diabetics. Two such projects are seeking co-funding from the GWRDC to include a wine component in their protocols; the co-funders are the National Heart Foundation and the Australian Health Management Group Medical Research Fund, respectively;

- determination as to whether the wine-derived phenolic compounds protect against other induced DNA damage, and whether protection is also afforded to individuals with increased genetic susceptibility to DNA and alcohol damage; A wine could then be developed for optimal prevention of oxidative and alcohol damage to DNA in individuals with susceptible genotypes by manipulating the phenolic and ethanol components;

- determination as to whether absorption and metabolism in the liver modifies the antioxidant and non-antioxidant cardioprotective effects of the wine-derived phenolic compounds, which would demonstrate differences between clinical and test tube results and thus the applicability or relevance of test tube data to clinical conditions, which is oft debated and discussed; and

- investigation of the potential protective effects of moderate wine consumption and the wine-derived phenolic compound on the development of other degenerative diseases, such as Alzheimer's disease, which has been observed from epidemiological studies.

Relatively few research groups have been identified as currently having the capabilities to undertake these or related research projects in Australia and internationally. Where there is potential duplication, the materials and methodologies of the projects have been assessed as different but

complementary to that of the Australian research groups; some duplication, however, provides credibility and credence to research results and conclusions drawn. Ten primary criteria were also developed by the workshop participants for the evaluation and selection of wine and health projects for future funding. Of the ten, the most important priority for industry was industry outcomes such as social responsibility, reduction of alcohol abuse and harm, and product differentiation, while the most important priority for researchers was scientific excellence and innovation; these two priorities are not mutually exclusive.

It was considered appropriate by the majority of workshop participants that the Australian wine industry via the GWRDC continue to fund or co-fund wine and health research to gain the following benefits:

- funding from the Australian wine industry will help demonstrate the industry's duty of care to its consumers regarding the appropriate amount and pattern of wine consumption, which minimizes the harmful effects of wine whilst maximizing the potential benefits to human health—this duty of care must be visible;

- community and consumer perception of the social benefits will be improved by a rigorous scientific approach to the evaluation of the health benefits associated with the regular and moderate consumption of wine, and will help position wine as a healthy diet and lifestyle choice; and

- there are few funding bodies available to provide all the funds required to undertake a research project, and universities and related research organizations are actively encouraged to seek supplementary funding from industry. Therefore, the funding or even co-funding with other funding bodies of wine and health research will ensure that the research undertaken will be relevant to government, allied government such as the World Health Organisation, and Australian wine industry policy on alcohol/wine and health. It will also provide information that can be used by the industry in discourse with government and consumers. The recommended research projects are relevant to current Australian and international health priorities on cardiovascular disease, cancer, diabetes and obesity, which are escalating health problems in the developed and developing world.

The primary risk of industry funding wine and health research identified by workshop participants was the allegation of bias and lack of credibility or integrity. This risk can be largely dispelled or minimised by choosing credible researchers that are established, and nationally or internationally recognised in their field of research, and by allowing the research to be driven by the researchers rather than by industry. This risk can also be minimised by publication of complete research results in credible peer-reviewed journals and forums, and by actively acknowledging the harmful health and societal impacts of excessive wine consumption. In addition, co-funding the research with independent funding bodies will minimise this risk and is cost-effective. Synergistic or complementary collaboration is also cost-effective where the outcomes of research projects are more powerful and can be more quickly achieved if the research project is multi-centre. The risk of negative rather than positive research results can always be managed by undertaking evidence-based research, and by balancing any negative results again positive results, as well as by placing all results in context with other health benefits, risks and observations. In conclusion, more benefits and opportunities for the Australian wine industry were identified by workshop participants as associated with industry-funded wine and health research than were risks and all the risks could be managed.

3. Background

In Australia, over the last decade, the domestic per capita consumption of wine has declined from approximately 21.5 L/year and plateaued at approximately 20 L/year. This change in consumption has been accompanied by a repositioning of wine in the diet and in the lifestyle of Australians, approximately 20% of whom consume wine in preference to the other alcoholic beverages. The regular and moderate consumption of wine is also allied to tourism. This is projected onto a background where the domestic consumption of alcohol per se in Australia has declined over the last decade by approximately 15% and is continuing to decline. Conversely, in contrast to volume, the value of the wine consumed has increased significantly.

In 1996, six years ago, the Wolf Blass Foundation hosted the Wolf Blass Foundation International Wine and Health Symposium entitled *Medically, is wine just another alcoholic beverage?* on 12-13 June in Sydney. Creina Stockley organised the Symposium as Medical Advisor, Dr Robert Ali, the Director of Clinical Policy and Research at the Drug and Alcohol Services Council of South Australia was the Symposium Moderator, and the Symposium was supported by the Australian Wine Foundation. The Symposium was attended by approximately 100 delegates from academia, government, and the beer, spirits and wine industries. The Symposium was developed immediately following the initial 1994/95 *Inquiry into the Winegrape and Wine Industry*, where the industry argued that wine be taxed at a lower rate to that of beer and spirits partly based on differences in the general amount and pattern of consumption and hence lower contribution of wine to alcohol abuse and misuse costs in Australia.

There were four considerations in developing and structuring the program of the Symposium. The first was to provide a background and understanding of the cardiovascular sites and systems where alcohol is purported to act. The second was to examine the international epidemiological research indicating that the moderate consumption of alcohol, and in particular wine, may have beneficial effects, which may outweigh the detrimental effects, and hence risks, for particular populations. The third was to review the research being undertaken in Australia and internationally to determine the mechanisms underlying these purported beneficial effects, and the fourth was to put this research in context with Australian and international policies on alcohol and health. Thus the objective of the Symposium was to facilitate discussion and debate between academia, government, health practitioners and industry, in order to give direction to future research, and future political and social policies.

Ensuing from this Symposium were three research project proposals that were submitted to, and funded by, The Grape and Wine Research and Development Corporation (GWRDC). These proposals addressed the concerns raised at the conclusion of the Symposium that although there is substantial epidemiological (population) and *in vitro* (in the test tube) data which suggest that the wine-derived phenolic components exhibit different effects on the blood lipid profile as compared to ethanol, it has not been conclusively confirmed whether these effects occur *in vivo* (in the body) and, indeed, whether these phenolic compounds are even absorbed into the body in sufficient amount to be effective.

The three research projects are**:**

- *Grape antioxidant phenolics: absorption and inhibition of lipid peroxidation in humans*, which was undertaken by the Department of Medicine at The University of Western Australia (UWA 97/2);

- *Reduction of damage to LDL and DNA from oxidative free radicals by the regular and moderate consumption of wine*, which was undertaken by CSIRO Health Sciences and Nutrition (CSN 97/2); and

- *Potential cardioprotective activities of wine components based on synergistic interaction with vitamin E*, which was undertaken by the Heart Research Institute (HRI 97/2).

From the Wine and Health Section of 26th World Congress of the Office International de la Vigne et du Vin (OIV) in Adelaide on 15 October 2001 (CSS was Section President), and from Vinsalud Chile 2002 International Wine and Health Conference in Santiago on 20–23 October 2002 (CSS was a member of the Scientific Advisory Board), it appears that the most significant cardioprotective mechanisms of the phenolic compounds may be related to blood clotting or thrombosis and haemostasis rather than to antioxidation.

Concerning the Australian wine industry, these research results add a valuable perspective to the views of the alcohol tax reform lobbyists that continue to state the position that wine is as detrimental to health as are beer and spirits. Indeed, irrespective of the substantial epidemiological data and increasing clinical data that the moderate consumption of wine reduces the risk of death from cardiovascular disease and certain cancers in many population groups, where CVD and cancer account for approx. 25 and 20%, respectively, of all deaths in Australia, wine consumption remains vilified by a proportion of health and medical professions, government officials and academics associated with alcohol reform per se; alcohol consumption per se, however, is associated with an increased risk of breast cancer. For example, the new NH&MRC *Australian Alcohol Guidelines: health risks and benefits* (2001) are more relaxed and realistic concerning the amount of alcohol that can be safely consumed by the community per se and for individual community groups. However, the literature review that accompanies the Guidelines does not differentiate the health and societal effects of wine consumption from that of beer or spirits despite substantial data to the contrary. Furthermore, the Alcohol and Other Drugs Council of Australia, a lobby group that is allied with the National Drug Research Institute and the Independent Wineries Association, has recently released its Alcohol Taxation Statement. This Statement only focuses on the harmful effects of alcohol consumption per se discounting any beneficial health effects from light to moderate wine consumption, and hence advocating significantly increased taxation on wine, broadly based on alcohol content; wine is deemed to be closely substitutable with beer and spirits.

The international environment faces increasing pressure in many European Union countries as well as developing countries to include health warnings on the labels of alcoholic beverages including wine, and to ban alcohol, again including wine, advertising. These international trends will eventually influence or at least question Australian policies where the Australian wine industry will again be required to demonstrate that wine, although an alcoholic beverage, is consumed in a different pattern to beer and spirits, by consumers with different lifestyle patterns to those of beer and spirits, such that consumers of wine generally have a greater life expectancy than consumers of beer and spirits.

A need for differentiating wine consumption from that of beer and spirits is also clear from the World Health Report 2002 *Preventing Risks, Promoting Healthy Life.* This report identifies principal global risks for disease, disability and death in the world today. The Report also highlights 10 top global risks including alcohol along with factors such as unsafe water, high blood pressure and obesity. Specific suggestions are outlined on how these risks could be reduced, such as by legislation and increased taxation. The World Health Organization (WHO), in consultation with many Ministers of Health from around the world, identified alcohol as "…another commonly cited and increasing risk to health…" The Report also states, however, that "alcohol has been consumed in human populations for millennia, but the considerable and varied adverse health effects, as well as some benefits, have only been characterized recently." While this Report emphasizes health and social consequences of alcohol abuse, it highlights that "there is increasing evidence that patterns of drinking are relevant to health as well as volume of alcohol consumed…" Furthermore, the WHO acknowledges that despite causal

relationships between volume of alcohol consumption and diseases and injury, "…there are beneficial relationships with coronary heart disease, stroke and diabetes mellitus, provided low-to-moderate average volume of consumption is combined with non-binge patterns of drinking."

4. Project aims and performance targets

The general aims of the workshop were three-fold as follows:

1. to present the research outcomes from the three GWRDC-funded research projects (CSN 97/2, HRI 97/2 and UWA 97/2) for peer-critique and examination of outcomes;

2. to present the research outcomes of relevant international research projects; and

3. to identify, plan and prepare research priorities for 'wine and health' in Australia, which complement that being undertaken internationally, and which may impact on industry and government policy.

Specifically, the aims and performance targets of the workshop as stated in the GWRDC project application were as follows:

Output (aim)	Performance Targets	Date
1. List of Australian research priorities for wine and health	Development of a prioritized list of potential wine and health projects which address gaps in current knowledge and understanding	December 2002
2. Clarified Australian wine industry policy on wine and health issues and research priorities	Development of policy paper on wine and health issues on which to base future political and research decisions for the Australian wine industry	January 2003
3. New GWRDC Project Applications for wine and health	Preparation of New GWRDC Project Applications based on the list of Australian research priorities for wine and health (see Output 1)	February 2003

5. Method

A closed workshop was held over two days on 25 and 26 October 2002 at The Australian Wine Research Institute. Invited participants, all active in wine and health-related research and/or alcohol policy, include the following—

Australian participants invited:

- Dr Mavis Abbey, CSIRO Health Sciences and Nutrition*
- Dr Peter Clifton, CSIRO Health Sciences and Nutrition*
- Associate Professor Kevin Croft, Department of Medicine, The University of Western Australia*
- Dr John Dixon, Monash University Department of Surgery, Alfred Hospital (Vic)*
- Dr Michael Fenech, CSIRO Health Sciences and Nutrition*
- Mr Will Greenrod, CSIRO Health Sciences and Nutrition*
- Dr Trevor Mori, Department of Medicine, The University of Western Australia*
- Dr Sebely Pal, Department of Nutrition, School Of Public Health, Curtin University (WA)*
- Professor Ian Puddey, Department of Medicine, The University of Western Australia*
- Dr Roland Stocker, Centre for Thrombosis and Vascular Research, The University of NSW
- Ms Creina Stockley, The Australian Wine Research Institute*

International participant:

- Dr Jean-Claude Ruf, Oenology—Wine, Nutrition & Health Subcomission, Office de la Vigne et du Vin, on behalf of Associate Professor Pierre-Louis Tiessedre, Department of Oneology, Faculty of Pharmacy, The University of Montpellier, France*

Invited industry participants:

- Dr DeAnne Glenn, Grape and Wine Research and Development Corporation*
- Mr Tim James, Deputy Chairman, Grape and Wine Research and Development Corporation*
- Mr Ian Sutton, Winemakers' Federation of Australia*
- Mr Stephen Strachan, Winemakers' Federation of Australia
- Ms Linda Bowes, South Australian Wine and Brandy Industry Association *
- Professor Peter Høj, The Australian Wine Research Institute

Invited government-allied participants:

- Dr Dick Wilson, Chairman, Drug and Alcohol Services Council of South Australia on behalf of Dr Robert Ali, Director, Clinical Policy and Research, Drug and Alcohol Services Council of South Australia
- Professor Ann Roche, National Centre for Education and Training on Addiction
- Mr Keith Evans, Director, Drug Strategy and Programs Branch, Department of Human Services (SA) and Chair, Intergovernmental Committee on Drugs

* attended all or part of the Workshop

On the first day eight of the invited participants gave a 30–45 minute presentation on their major research outcomes, which was followed by a round table discussion. The second day comprised identifying and elaborating research priories on wine and health, which address the gaps identified the

first day in general wine and health knowledge, including that ensuing from the three GWRDC-funded projects. This was undertaken with the aid of facilitators. The political and social significance of these research priorities was also be assessed. Unlike oenology and viticulture, there is no industry priorities reference group for wine and health issues.

Following the workshop, it was anticipated that research priorities identified would be converted into new GWRDC-project applications and submitted to the GWRDC by February 2003 for future funding.

Workshop program

Thursday, 12 December 2002

Time	Presentation
8.30–9.00 am	Creina Stockley (*introduction and overview*)
9.00–9.40 am	Kevin Croft *(summary of research results and questions outstanding or arising from the results)*
9.40–10.20 am	Roland Stocker and Creina Stockley (*summary of research results…*)
10.20- 10.50 am	**Morning tea**
10.50–11.30 am	Will Greenrod and Mavis Abbey (*summary of research results…*)
11.30 am –12.10 pm	John Dixon (*summary of research results…*)
12.10–12.50 pm	Will Greenrod and Michael Fenech (*summary of research results…*)
12.50–1.50 pm	**Lunch**
1.50–2.30 pm	Trevor Mori and Ian Puddey *(overview of planned research and previous results)*
2.30–3.10 pm	Sebely Pal *(overview of planned research and previous results)*
3.10 - 3.40 pm	**Afternoon tea**
3.40–4.40 pm	Jean-Claude Ruf and Pierre-Louis Teissedre *(overview of relevant research projects being undertaken in Europe)*
4.40–5.10 pm	General discussion
7.30 for 8.00 pm	Dinner

Friday, 13 December 2002

Time	Presentation
8.30–9.15 am	Review and summary of presentations (Facilitator)
9.15–10.00 am	Affinity diagram: What are the issues (risks) and opportunities (benefits) associated with industry funded research? (Facilitator) Participants asked to write the issues and opportunities on small pieces of paper, one per piece. This exercise performed in silence, without any discussion. The items are then grouped and summarised.
10.00- 10.30 am	**Morning tea**
10.30 –11.30 am	Criteria for research (Facilitator) Criteria, as presented by participants, listed on a whiteboard. Criteria then ranked asking each participant to rank their top three choices, 3,2,1. This exercise performed silently, with the ranking's listed against each criterion on the board. The group will be then agree the top criteria for selection.
11.30–12.30 am	Potential research projects (Facilitator)
12.30- 1.30 pm	**Lunch**
1.30–2.30 pm	Summary of outcomes and close

6. Results/Discussion

6.1 Introduction

All alcoholic beverages have the ability to reduce the risk of all-cause mortality by approximately 20 to 50 percent, when consumed in moderation. This ability has been demonstrated by the extensive epidemiological studies, which have been undertaken in men and women, for different age groups, and for different nationalities or populations.

Some of these studies have also considered the alcoholic beverage consumed and the reduction in risk of, for example, cardiovascular disease. From these studies it can be concluded that the alcohol component, which is common to all the beverage types, does confer a benefit. This benefit is considered to be, primarily, an increase in the plasma concentration of high density lipoprotein (HDL) cholesterol, where a low plasma concentration of HDL is correlated with a high risk of cardiovascular disease (Langer *et al.* 1992, Renaud *et al.* 1992, Suh *et al.* 1992, Gaziano *et al.* 1993, Folts *et al.* 1994, Hendriks *et al.* 1994, Ridker *et al.* 1994, Fielding and Fielding 1995, Renaud and Ruf 1996, Simons *et al.* 1996). HDL transports dietary -derived cholesterol from the arteries and body organs and tissues to the liver, where it is removed from the body. In addition, alcohol decreases blood clotting by reducing the ability of the blood cells to aggregate and clot together, and also by increasing their ability to de-aggregate or break down once blood clots have formed in arteries and veins.

Particular prospective epidemiological studies have indicated that consumers of wine have a greater reduction in the risk of cardiovascular disease than consumers of beer or spirits. The reduction in risk was similar to that for consumers of certain fruits, grains and vegetables, where the linkage between wine and these foodstuffs is their concentration of phenolic compounds (Grundy 1986, Block 1992, Block *et al.* 1992, Ames *et al.* 1993, Hertog *et al.* 1993, Kinsella *et al.* 1993, Willett *et al.* 1995, Halliwell *et al.* 1995, Hertog *et al.* 1995, Renaud 1996). Phenolic compounds, such as flavonols, phenolic acids and their esterified derivatives, are purported to act as antioxidants. Another risk factor for cardiovascular disease is a high plasma concentration of low density lipoprotein (LDL) cholesterol. In its oxidised form, LDL accumulates on arterial walls and if not removed, continues to accumulate forming atherosclerotic plaques. As the artery narrows, blood pressure increases to maintain blood flow. Eventually, blood flow may be completely blocked, which would result in a heart attack or stroke depending on the site of the blockage.

Antioxidants are molecules that destroy oxidants, and can prevent the oxidation of fats or lipids. Lipoprotein particles, such as LDL, transport fat-soluble antioxidants, including vitamin E within the blood and to the wall of arteries, and as such are believed to protect against atherosclerosis and cardiovascular disease by preventing lipids in the artery wall from oxidation. It is postulated that oxidation occurs when the protective antioxidant compounds present in the LDL particle are depleted.

In vitro studies have demonstrated that the phenolic compounds may also prevent and even reverse the oxidation of LDL, and hence prevent and reduce the accumulation of oxidised LDL in arteries (Witzum and Steinberg 1991, Halliwell and Chirco 1993, Whitehead *et al.* 1995, Abbey and Kerry 1996). *In vivo* and *ex vivo* studies, however, have not necessarily confirmed the conclusions of the initial *in vitro* studies, and are generally inconsistent in their observations. Instead subsequent *in vitro* and *in vivo* studies suggest that the primary effect of phenolic compounds related to cardioprotection may be in preventing platelet aggregation, complementary to that of the alcohol component of wine (Pendurthi *et al.* 1999, Agewall *et al.* 2000) and/or in repairing endothelial function. Endothelial dysfunction is related to, and hence a risk factor for, the initiation and development of atherosclerosis

and hypertension (Mano *et al.* 1996, Henderson *et al.* 1997, Vogel *et al.* 1998); it is often observed before any anatomical signs of atherosclerosis appear.

Oxidative free radicals also cause mutation of DNA sequences and breakage of DNA strands, which are the underlying causes of the initiation and progression of cancer. A diet high in fruit and vegetables has also 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. The results from numerous *in vitro* and animal studies suggest that individual wine-derived phenolic compounds may be protective against DNA damage. For example, in 1996, an initial *in vivo* study was undertaken by the CSIRO Division of Human Nutrition in conjunction with The Australian Wine Research Institute (Fenech et al. 1997) to determine if the acute consumption of wine produces a measurable change in the antioxidant capacity of blood plasma, and whether this in turn, reduces oxidative damage to DNA. The results indicated that the consumption of wine, both red and white, produced significant, but not necessarily antioxidative, changes in the plasma which protected DNA from damage induced by hydrogen peroxide, but only red wine consumption, however, reduced spontaneous chromosome damage. The observation that the duration of this protective effect was diminished by eight hours post-dose, implied that the regular consumption of wine is important to maintain a protective effect. Leighton et al. (1999) 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.

6.2 Summary of presentations ¾ research results and questions outstanding or arising from the results

6.2.1 Kevin Croft, Department of Medicine, The University of Western Australia

Grape antioxidant phenolics: absorption and inhibition of lipid peroxidation in humans

The aims of Project UWA 97/2 were:

1. to determine if specific phenolic antioxidant compounds can be absorbed and detected in plasma following the ingestion of wine; and

2. to utilize a highly sensitive biological marker for *in vivo* lipid peroxidation (F_2-isoprostanes) to determine if the ingestion of wine influences oxidative stress.

An acute and a short-term study of wine-derived phenolic acids were undertaken in 12 and 18 human male subjects, respectively. In the initial acute study, 350 mL (approximately 3 and half standard drinks) of red wine, dealcoholised red wine, phenolic stripped red wine or water was consumed with food on four consecutive occasions. Each occasion was separated by one week, and two days prior to each occasion subjects abstained from food and beverages containing a high concentration of phenolic compounds. Phenolic acids were absorbed and detected in plasma (at a concentration of less than 250 nmol/L) following the consumption of the red wine and the dealcoholised red wine. No change in the total antioxidant capacity of the plasma, however, was detected, but the plasma concentration of the phenolic acids may have been inadequate to affect LDL and plasma oxidation.

In the subsequent short-term study, 375 mL (approximately 3 and half standard drinks) of red wine, dealcoholised red wine or white wine was consumed daily for two weeks. The subjects were all cigarette smokers that were selected on the assumption that they would have increased oxidative damage and stress, that is, a decreased plasma total antioxidant capacity and increased plasma concentration of oxidation products as a consequence of their smoking habit. Similar to the acute study, phenolic acids were detected in plasma and urine post the consumption of red and dealcoholised red wine, confirming that the phenolic compounds are absorbed. Following the consumption of dealcoholised red wine, but not red or white wine containing ethanol, the plasma and urine concentration of oxidation products, such as the F_2-isoprostanes, decreased which suggests that the phenolic compounds were acting as antioxidants in the plasma. However, a similar decrease was not observed with the red or white wine containing ethanol. Ethanol is known to promote plasma oxidation. This suggests that the antioxidative phenolic acids absorbed from the whole red and white wine may have merely countered the pro-oxidative ethanol concomitantly absorbed, as there was also no increase in the concentration of plasma oxidation products.

These studies suggest that the wine derived phenolic acids are absorbed following the light to moderate consumption of wine. These studies also suggest that the LDL and plasma antioxidant effects of the wine-derived phenolic compounds are only observed in the absence of ethanol. The wine-derived phenolic compounds may independently protect against LDL and plasma oxidation, when consumed with ethanol they may merely act to counter the known pro-oxidant effects of ethanol. Such as countering effect has also been concluded by van der Gaag et al. 2000.

Stable compounds resulting from the oxidation of LDL and F_2-isoprostanes have also been identified in the advanced development of atherosclerosis, and an increased level is found in human atherosclerotic plaques. An animal study has consequently been undertaken with 50 C57BL/6J (control) and 100 apoE –/– mice placed on a high fat diet at age 6 weeks. Fifty of the apoE–/– mice

were also given dealcoholised red wine ad libitum as their sole fluid intake for 20 weeks. Apolipoprotein E gene knockout mice, abbreviated to apoE –/– mice, are an animal model for atherosclerosis as they have been genetically manipulated to spontaneously develop atherosclerosis as they grow older similar to humans. At 26 weeks, plasma and aortas were collected for measurement of atherosclerosis development, that is, the deposition of lipids and occurrence of lesions in the aorta, and for measurement of the concentration of total plasma antioxidant status and plasma oxidation products, such as the F_2-isoprostanes. No change in the concentration of plasma oxidation products was observed for any group of mice, which suggests that the wine-derived phenolic compounds did not act as antioxidants. Lipid deposition, however, was significantly increased only in the apoE–/– mice, which suggests that deposition or uptake of lipids in the aorta was independent of lipid oxidation. Furthermore, the consumption of dealcoholised red wine by the aopE–/– mice attenuated this deposition, which suggests that the wine-derived phenolic compounds may protect against the aortic deposition of lipids independent of any antioxidation activity.

In conclusion:

- *Dealcoholised red wine, red wine and white wine contain specific wine-derived phenolic compounds, such as phenolic acids, that are absorbed into, and detectable in, plasma following the ingestion of wine.*

- *In addition, the ingestion of dealcoholised red wine reduces oxidative stress in a cigarette smoking human population group, although the ingestion of alcohol-containing red or white wine has no effect on oxidative stress, positive or negative, which implies that the antioxidative wine-derived phenolic compounds may merely counter the peroxidative effects of the ethanol component.*

- *In addition, the ingestion of dealcoholised red wine by genetically manipulated mice reduces the deposition of lipids such as LDL in the blood vessel wall, apparently independently of any antioxidative effects.*

Questions arising from these studies include:

- What influences the absorption and metabolism of the wine-derived phenolic compounds?
- Does the metabolism of the wine-derived phenolic compounds affect or alter their antioxidation efficacy as compared to *in vitro*?

- Are cigarette smoking populations groups different to non-cigarette smoking populations regarding oxidative damage and stress, as well as efficacy of antioxidants?

- Is there a dose-dependent relationship between ethanol and pro-oxidation and phenolic compounds and antioxidation?

- At what plasma, tissue or cellular concentration may the wine-derived phenolic compound anti-oxidation effects completely counter the pro-oxidant effects of ethanol?

- Do acute and short-term studies accurately reflect longer and regular consumption oxidation/antioxidation effects?
- What is the mechanism of the non-antioxidative anti-atherosclerotic effect of wine-derived phenolic compounds?/How do the wine-derived phenolic compounds reduce or prevent the deposition of lipids in the aorta?

- Would the ethanol and wine-derived phenolic compound components of wine have a different effect in animals/humans with an increased risk of cardiovascular disease?

Limitations of these studies include:

- Did not use a water control group;
- Did not compare with a non-cigarette smoking population group; and
- Relatively short-term wine consumption.

Suggestions for further studies include:

- The results of these studies need to be confirmed in other animal models and humans, with particular emphasis on any non-antioxidative anti-atherosclerotic effects of the wine-derived phenolic compounds.

6.2.2 Roland Stocker, Centre for Thrombosis and Vascular Research, The University of NSW (formerly of the Heart Research Institute) and Creina Stockley, The Australian Wine Research Institute

Potential cardioprotective activities of wine components based on synergistic interaction with vitamin E

The aims of Project HRI 97/2 were:

1. To screen selected red and white wines, before and after removal of specific groups of redox active compounds, for vitamin E (α-tocopherol) synergising activity, using a recently developed *in vitro* screening test;

2. To test samples which give positive results in [1] for their ability to inhibit *in vitro* lipid oxidation in low density lipoprotein (LDL) and high density lipoprotein (HDL) under conditions where synergism with vitamin E is important for antioxidant protection;

3. To examine whether short-term administration of selected samples which give positive results in [2] to apolipoprotein E gene knockout mice (apoE −/−; an animal model of atherosclerosis) changes lipoprotein lipid parameters in these animals relevant to atherosclerosis and/or lipoprotein lipid oxidation and antioxidation;

4. To test whether short-term administration of selected samples, which give positive results in [2] to apoE −/− mice decreases the oxidizability of their plasma lipoproteins to *ex vivo* oxidation under conditions where synergism with vitamin E is important; and

5. To evaluate whether long-term administration of selected samples, which give positive results in [2] and [4] reduces atherosclerosis in apoE−/− mice.

The oxidation of LDL is by destructive oxidants and free radicals in the plasma that are formed when we metabolise food for energy. Vitamin E is biologically the most active and important fat-soluble antioxidant in humans. LDL transport lipid-soluble antioxidants, including vitamin E within the blood and to the wall of blood vessels, and as such are believed to protect against atherosclerosis and cardiovascular disease by preventing lipids in the artery wall from oxidation. There is a large body of literature that indicates that the principal role of vitamin E is to protect tissues against destructive oxidants. It has been postulated that LDL oxidation occurs when the endogenous protective antioxidant compounds present in the LDL particle are depleted. It has also been observed that vitamin E within the LDL particles requires co-antioxidants to provide antioxidant protection under all conditions. Several endogenous compounds have co-oxidant activity, such as ubiquinol-10, but are depleted in LDL particles in atherosclerotic plaque, which suggests that LDL oxidation associated with atherosclerosis may result from a lack of co-oxidants rather than vitamin E itself as vitamin E is not depleted in atherosclerotic plaques.

Therefore, underlying hypothesis of the project was that, in addition or separate to free radical scavenging, antioxidant compounds present in wines may act by interacting synergistically with vitamin E, and may provide significant antioxidant protection to lipoprotein lipids, such as LDL, even when absorbed ineffectively and present at a low micromolar level in the circulation and sub-endothelial space.

There was an *in vitro* and an animal intervention component to the study. Selected red and white wine were screened, before and after certain classes of compounds had been removed by fractionation, for their ability to interact synergistically with vitamin E. It was observed that red wine had a greater ability than white wine to reverse the oxidation of vitamin E. Of the classes of compounds fractionated from the red and white wines, the phenolic acids were most responsible for this reversal in alcohol-containing and dealcoholised red and white wine. When the wines and fractions were examined for their ability to prevent the oxidation of LDL, the phenolic acids were again the efficacious antioxidants compared to the other classes in alcohol-containing and dealcoholised red and white wine. Therefore, this study demonstrates that both red and white wine contain compounds that can interact with LDL-associated vitamin E and can increase the resistance of LDL to oxidation.

A short-term intervention study was initially undertaken in female apoE –/– mice (n=7 or 8 per group), whereby the mice were fed a high fat diet and given daily for one month water, dealcoholised red, red or white wine or the phenolic acid fraction of the red and white wine at a dose equivalent to 200 mL of wine by a 70 kg person. The results indicate that, in apoE –/– mice, dealcoholised red wine increased the resistance of LDL and other plasma lipids to oxidation when compared to the control and other wines and phenolic acid fractions.

A longer-term intervention study was then undertaken in female apoE –/– mice (n = 38 or 40 per group), whereby the mice were fed a normal diet and given daily for six months dealcoholised red wine at a dose approximately equivalent to 100 mL of wine by a 70 kg person. The regular consumption of dealcoholised red wine for six months, resulted in a small (5%) but significant decrease in the plasma concentration of triglyercides.

The concentration of LDL and the other plasma lipids was unchanged, as was the concentration of vitamin E, and there were no detectable primary products of lipid oxidation. The antioxidant status of the plasma was increased with the regular consumption of dealcoholised wine, however, which implies that the wine-derived phenolic compounds were supplementing the endogenous plasma antioxidants, such as vitamin E.

There was also an increase in the antioxidant capacity of the aorta wall of mice given dealcoholised wine and an non-significant increase in the tissue concentration of vitamin E, but again there was no concomitant decrease in the aortic tissue concentration of oxidized LDL and other lipid oxidation products; this is consistent with the results of Waddington, Puddey, Mori and Croft (2002). However, there was a 20% decrease in the progression of atherosclerosis in the aortic arch of mice given dealcoholised red wine.

Overall, this study demonstrates that there is a moderate beneficial effect of regular consumption of dealcoholised red wine on atherosclerosis in apoE-/- mice. The observed moderate decrease in atherosclerosis yet lack of effect on the arterial concentration of the primary products of lipid oxidation indicates that the protective activity of dealcoholised red wine may be independent of inhibition of lipoprotein oxidation in the blood vessel wall. While lipoprotein oxidation in the vessel wall rather than circulation is likely more relevant to atherogenesis, and a large body of literature supports the 'oxidation theory' of atherosclerosis, there is also recent evidence that the two processes are not causally related. The present study adds to the evidence dissociating blood vessel wall lipoprotein oxidation from atherogenesis. Thus, potential beneficial activities of dealcoholised red wine other than inhibition of the oxidation of LDL and other lipoproteins need to be considered.

This study also indicates the effective absorption of wine-derived phenolic compounds, although they were directly determined. Absorption of catechin and quercetin, the major phenolic compounds of red

wine, has been demonstrated in apoE-/- mice. The absence of direct evidence for an antioxidant protection on vessel wall parameters related to lipoprotein lipid oxidation in this study suggests that the bioavailability of wine-derived antioxidants is overall limited. This may be particularly relevant for sites other than blood, such as the blood vessel wall, and when considering the relatively minor contribution these antioxidants may make to the existing endogenous antioxidant defense.

In conclusion:

- *Dealcoholised red wine contains compounds that can act synergistically with vitamin E in vitro and that enhance the body's own antioxidant defenses when given for prolonged periods of time and in amounts corresponding to one glass of wine per day by humans.*

- *Although such consumption of dealcoholised red wine does not appear to decrease the concentration of oxidised LDL implicated in the initiation and development of atherosclerosis, it does significantly decrease atherosclerosis in genetically manipulated mice.*

- *This implies that the protective effect of the wine-derived phenolic compounds on atherosclerosis may be independent of any antioxidant effects, and hence adds to the growing evidence dissociating the oxidation of lipoproteins such as LDL in the arterial wall from atherogenesis.*

Questions arising from these studies include:

- Why was the *in vitro* observation of a greater effect with the Fraction 1 phenolic acid class of compounds not observed in the initial short-term intervention?

- Why was the effect of Fraction I *in vitro* different to that *in vivo*? Does this relate to the metabolism of the phenolic acids and changes in the structure:activity relationship?

- Why was the effect of Fraction 1 different to that of the dealcoholised red wine or alcohol-containing red wine? Does the presence of other phenolic compound dasses or the ethanol component influence activity?

- How similar is the mice atherosclerotic model, where atherosclerosis is accelerated, to the human atherosclerotic model?

Limitations of these studies include:

- Use of dealcoholised red wine only in the longer-term intervention study (which was based on the results from the *in vitro* and short-term intervention studies); hence the results of this study cannot be directly extrapolated to the effect of red wine.

Suggestions for further studies include:

- The non-antioxidative anti-atherosclerotic effect of wine-derived phenolic compounds needs to be confirmed in other animal models and humans, for example, a vitamin C sparing effect by red wine, but a decrease by beer and spirits has been observed in humans, but there was no effect on vitamin E by any of the beverages consumed.

6.2.3 Will Greenrod, Mavis Abbey, Michael Fenech, CSIRO Health Sciences and Nutrition, and Creina Stockley, The Australian Wine Research Institute

Reduction of damage to LDL and DNA from oxidative free radicals by the regular and moderate consumption of wine

The aims of Project CSN 97/2 were:

1. To test the hypothesis that the regular and moderate consumption of red wine elevates the plasma concentration of polyphenolic compounds, such as catechin, in humans.

2. To test the hypothesis that the regular and moderate consumption of red wine enhances in humans the antioxidant potential of plasma and thus:

2.1 Provides protection for DNA sequences against oxidative free radical damage, such as *ex vivo* exposure to ionizing radiation and to hydrogen peroxide (cancer-protective); and

2.2 Provides protection for LDL against oxidative free radical damage *ex viva* (cardioprotective).

Damage to fundamental molecules such as DNA, lipids and proteins by reactive oxygen species (oxidative free radicals) has been implicated in accelerated aging, as well as degenerative diseases including cancer (Ames et al. 1995), cardiovascular disease (Steinbrecher et al. 1990) and Alzheimer's disease (Smith et al. 1996). These diseases of old age are expected to increase significantly over the next few decades 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. Accordingly, Project CSN 97 was undertaken in two phases:

Phase I *¾ Potential benefits of wine in prevention of genetic damage induced by hydrogen peroxide and ionising radiation*

Genetic damage is a risk factor for the formation and progression of cancer. 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). It has been previously observed that wine-derived phenolic compounds may potentially reduce the damage associated with cancer initiation or progression by inhibiting the oxidising agents (Ames et al. 1995). In addition, between 1995 and 1997, in collaboration with The Australian Wine Research Institute, Fenech et al. (1997) showed that following consumption of two 100 mL glasses of red or white wine there was an important and significant improvement in the capacity of blood to resist the DNA-damaging effect of 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.

Two studies were undertaken in Phase I. The first study 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 (a hydroxycinnamic acid phenolic compound)/catechin (a flavanol phenolic compound) 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 micronulcleus assay, which enables chromosome or DNA damage to be scored (Fenech 1993).

It was 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. 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. Ethanol, as well as the component mixtures, produced the strongest protective effects against DNA damage by hydrogen peroxide. The protective effect 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.

In conclusion*:*

- *these observations suggest that the primary phenolic and ethanol 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.*

- *This has important clinical indications, such as in radiotherapy for the treatment of cancerous cells and the protection of normal tissue.*

The second study was an *ex vivo* study in which blood from six healthy male subjects was tested 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 wine, an aggravating or negative effect of alcohol and an intermediate but protective effect of whole wine. The most significant protective effects were observed at two hours post consumption. These results were important in verifying that it is the non-alcoholic fraction of wine that has DNA-protective properties in blood and body tissues.

Questions arising from these studies include:

- Why were results of ionising radiation challenge different to that from hydrogen peroxide for ethanol?

Limitations of these studies include:

- As only two concentrations of supplementary wine components were used in the initial in vitro study, further research is necessary to determine more accurately the dose response relationship between the wine components and protection against DNA damage;

- Further research is necessary to more accurately determine the time response relationship between the consumption of wine and protection against DNA damage; and

- Did not consider the effects of caffeic acid and catechin individually on DNA damage

Suggestions for further studies include:

- Investigation of the effects of wine consumption on other forms of cellular/DNA damage other than radiation or hydrogen peroxide.

Phase II ¾ Potential for wine consumption to reduce markers of cardiovascular disease risk

Phase II consisted of a relatively short-term *in vivo* study in 57 healthy male subjects aged approximately 50 years over 12 weeks to compare the consumption of red wine to (a) white wine; (b) de-alcoholised red wine; and (c) a model wine (12% alcohol solution). Throughout the duration of the study, the subjects were asked to maintain a low plant phenolic compound diet in order to reduce the background level of phenolic compounds in plasma and tissues, such that the wine provided became the main source of phenolic compounds in the diet and any vascular and lipid change observed would primary occur from the red wine provision. The first four weeks of the study required subjects to remain alcohol free, and acted as a clearance/washout period. For the next two four-week periods, subjects consumed a 200 mL red wine per day or an alternate control drink of either white wine, dealcoholised red wine or a 12% alcohol solution. At the beginning of the study, and after each intervention period, subjects were assessed for plasma biochemical markers of cardiovascular disease, such as the concentration of LDL and HDL. They were also assessed for physiological markers of cardiovascular disease such as blood pressure and arterial elasticity. For example, in addition to preventing the oxidation of LDL, it has been proposed that another cardioprotective mechanism of the wine-derived phenolic compounds could be the restoration of vascular function. Indeed, in addition to blood pressure, other physiological measures can serve as markers for cardiovascular disease. Vascular endothelium that is unable to respond to changes in blood pressure or other environmental stimuli is referred to as dysfunctional, and often hypertension is the result (Henderson 1997). It may be due to an increased break down of nitric oxide mediated by free radical damage, or due to a decreased production of endothelial nitric oxide (Vogel et al 1998). It has also been proposed that cardioprotective mechanism of action of the wine-derived phenolic compounds is the stimulation of nitric oxide production by the endothelium.

No changes in blood pressure or arterial elasticity from baseline were observed following the consumption of red wine for four weeks compared to that following white wine, dealcoholised red wine or the 12% alcohol solution. In addition, there was no change in nitric oxide activity with any of the subject groups. This implies that structural changes may take longer than the four-week red wine consumption period to occur.

There was, however, an increase in the plasma concentration of HDL from baseline in 74% of subjects following the consumption of red wine for four weeks compared to that following white wine, dealcoholised red wine or the 12% alcohol solution, and a concomitant improvement in the ratio of HDL to LDL. This observation confirms those of published studies, and support The Heart Foundation guidelines, which recommend that the plasma concentration of HDL should be increased to greater than 1.0 mM.

There was not, however, a change in the plasma concentration of LDL or that of triglycerides, or a change in the antioxidant capacity of the plasma. Again, this may reflect the short-term duration of the study and support the observations of van der Gaag et al. (2000) who observed no change in the antioxidant capacity of the plasma after a three-week period of red wine consumption on a controlled

diet although small changes in specific plasma antioxidant compounds was observed, and those of Kerry and Abbey (1997), who concluded that phenolic compounds may need more than four weeks to accumulate in LDL particles.

Furthermore, there was no increase in the plasma concentration of the phenolic compound, catechin, but instead a continuous decrease over the 12-week study period from baseline, with a concomitant increase in the plasma concentration of F_2-isoprostanes, primary plasma oxidation products. This implies that when on the low plant phenolic compound diet, the regular consumption of red wine in the short-term is unable to improve vascular function or increase the antioxidant capacity of the plasma, or prevent the oxidation of lipids such as LDL. Therefore, the antioxidative and/or other cardioprotective effects of red wine may best be observed against a 'normal' or 'higher' background diet of plant phenolic compounds, such as a Mediterranean-style diet, and may be most observed against a background diet high in fat, when oxidative stress has been observed to increase (Leighton et al. 1999, Cuevas et al. 2000, Mezzano et al. 2001, Mansvelt et al. 2002).

In conclusion:

- *A regular and moderate consumption of red wine over a four-week period does not change endothelial and vascular function or prevent lipid oxidation when combined with a diet low in plant phenolic compounds.*

- *These results also add to the growing evidence that the cardioprotective effects of wine and the wine-derived phenolic compounds are not primarily related to plasma antioxidation, but may be primarily related to other effects, such as on haemostasis or inflammation.*

- *The protective effects of wine consumption, may therefore, be best observed against a combined diet of high fat, and high fruit and vegetable consumption.*

Questions arising from this study include:

- Are the same effects on plasma antioxidant capacity and other plasma lipids, and on endothelial function observed when the background diet is not low or is high in plant phenolic compounds or, conversely, is high fat?

- What dose of red wine, regularly consumed, would counteract the 'oxidative' and other negative nutrient effects of a diet is low in plant phenolic compounds;

- What is the minimal duration of a regular red wine consumption for antioxidant or other cardioprotective effects to be observed? and

- Is amount of red wine consumed (200 mL) sufficient to observe a change in physiological and biochemical markers of cardiovascular disease?

Limitations of this study include:

- Background diet low in plant phenolic compounds;

- Relatively short-term duration (four-weeks) of each treatment; and

- Cannot pool three studies re cardiovascular markers.

Suggestions for further studies include:

- Confirmation of these results of this study in a study, which considers a background ‘normal’ diet versus a diet low in plant phenolic compounds for a longer treatment period.

- A similar study but where the subjects have cardiovascular disease, such as increased blood pressure and a high and unbalanced lipid concentration.

6.2.4 John Dixon, Monash University Department of Surgery, The Alfred (hospital)

Wine consumers have a reduced cardiovascular risk through improved insulin sensitivity and a reduced plasma concentration of homocysteine

Risk factors for cardiovascular disease include a high body mass index (BMI; being overweight or obese), a poor diet (including an excessive dietary intake of animal fats and salt) and lack of exercise, cigarette smoking, excessive alcohol consumption, a high and unbalanced blood cholesterol concentration and a high blood pressure, as well as genetic predisposition and certain diseases and disorders, such as diabetes mellitus (Hunter et al. 1995, Norrish et al. 1995, Wieslisbach et al. 1997). Another recently recognized risk factor is a high concentration of the amino acid, homocysteine, in plasma (Welsh et al. 1998). A high level of risk factors for cardiovascular disease can mitigate any cardioprotective effects of moderate alcohol and wine consumption. In addition, above moderate consumption, the effects of the excessive consumption of alcohol are additive to any other risk factors for cardiovascular disease, increasing the risk by two to three-times (Beilin and Puddey 1996, Puddey et al. 1998, Yusuf et al. 1998). Therefore, there are some moderate consumers of wine, such as diabetics, whose risk of cardiovascular disease may be increased rather than decreased.

In Australia, over 50% of men and women are overweight and 20% are actually obese, having a BMI greater than 30 kg/m^2. 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, 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. Another potential beneficial health effect of alcohol is the improvement of insulin sensitivity, possibly by reducing the concentration of free fatty acids in blood (Avogaro et al. 2002). In turn, the improved insulin sensitivity lowers the concentration of insulin, glucose and triglycerides in the blood, and increases that of HDL. Additionally, LDL particles become less dense, less adherent and less easily oxidized. Altogether, this reduces the risk of developing type 2 diabetes, as well as improving control of blood glucose and reducing the risk of cardiovascular disease in type 2 diabetics, who have a greater risk of cardiovascular disease compared with healthy individuals (Ajani et al. 2000a, Solomon et al. 2000). Indeed, epidemiological studies suggest that regular and moderate alcohol consumption significantly reduces the risk of developing type 2 diabetes (Ajani et al. 2000b, Hu et al. 2001). The American Diabetes Association now advises that moderate alcohol consumption by type 2 diabetics should not be routinely discouraged (Solomon et al. 2000).

The American Heart Association recommends that the concentration of homocysteine in plasma should be maintained below 10 µmol/L. Homocysteine is closely linked to the metabolism of the essential amino acid, methionine. It has a direct toxic effect on the lining of blood vessels that alters their function (Bellamy et al. 1998) and leads to key early steps in the atherogenic process. Three micronutrients are important cofactors in homocysteine metabolism. Folate and vitamin B12 are cofactors for the methylation of homocysteine to methionine, and vitamin B6 is involved in its breakdown. Deficiency of any of these micronutrients leads to a higher concentration of homocysteine and increased risk. It has recently been proposed that the presence of folate and vitamin B6 in beer may lead to a beverage-specific advantage through lowering of homocysteine concentration (van der Gaag et al. 2000). While high or abusive alcohol consumption is associated with an increased plasma concentration of homocysteine (Cravo et al. 1996, Bleich et al. 2001), but the effect of low to moderate consumption on the concentration of homocysteine has been inconsistent (Ayaori et al. 2000, Cuevas et al. 2000).

The severely obese (BMI >35 kg/m^2) are at increased risk of type 2 diabetes, cardiovascular morbidity and mortality. In a study of 486 severely obese subjects, their pattern of alcohol consumption was monitored and their risk of cardiovascular disease determined. Alcohol consumers showed a marked reduction in the prevalence of type 2 diabetes compared with non-consumers. 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. In this group, comprising predominantly women consumers of less than 100 g/week had more favorable insulin measures, with insulin sensitivity best in those consuming 20 to 100 g of alcohol/week, that is, 2 to 10 standard drinks/week, which is considered to be light alcohol consumption. Of the alcohol consumers, 165 nominated wine and 111 spirits or beer as the alcoholic beverage most frequently drunk. Wine consumers had a significantly lower fasting insulin level and improved insulin sensitivity.

These patients went on to have a laparoscopic adjustable gastric band placed to help them lose weight. Those patients consuming more than 100 g/week of alcohol, 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 demonstrate that light to moderate alcohol consumption, 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 (Dixon et al. 2002).

The same 416 severely obese patients were also studied for any relationship between both the amount and type of alcohol consumption and concentration of fasting plasma homocysteine. A U-shaped relationship was observed whereby light to moderate alcohol consumption was associated with a lower and more favorable plasma concentration of homocysteine. 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 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 weight, and plasma concentration of folate and vitamin B12.

The mechanisms for the beneficial effect of red wine are 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). An alteration in the relationship between the concentration of homocysteine concentration, 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 the dose-response curve in the other direction with a lower plasma concentration of homocysteine achieved with an equivalent micronutrient concentration.

In conclusion:

- *These studies of obese patients show that those consuming wine regularly are far less likely to be diabetic, have significantly better insulin sensitivity and a healthier blood lipid profile, with a lower plasma concentration of triglyceride and a higher plasma concentration of HDL.*

- *In addition, red wine consumers have a significantly lower plasma concentration of homocysteine.*

- *Given these benefits, health professionals should reconsider the advice to abstain from all alcohol generally given to obese patients, type 2 diabetics and others at high risk.*

Limitations observed with these studies include:

- smoking is a confounder as is nutrient/micronutrient intake;

- did not observe effect of very high versus low to moderate alcohol consumption; and

- did not observe effects in platelet activity/function.

Questions arising from these studies include:

- Should and how should alcohol intake be modified for those losing weight?

- Are the non-ethanol or phenolic compound components important for weight loss? and

- There may be other lifestyle or dietary factors that differ with the choice of beverage, although the timing of alcohol consumption was not observed to affect the plasma concentration of homocysteine, for example, wine consumers generally drink with food compared to drinkers of beer and spirits.

Suggestions for further studies include:

- A large intervention study, which should include beer, wine, dealcoholised wine and water as a control, to confirm the results of the effect of red wine consumption on the plasma concentration of homocysteine. Subsequent studies should be undertaken in other population groups. For example, patients with a laparoscopic adjustable gastric band have food remaining in their stomach longer due to changes in gastric motility and hence emptying (gastric stasis) which may influence the effect of alcohol on the concentration of homocysteine.

6.2.5 Trevor Mori and Ian Puddey, Department of Medicine, The University of Western Australia

Diabetes mellitus affects a large proportion of Australians and the prevalence of this disorder is escalating. The prevalence of diagnosed diabetes in the Australian population has trebled since 1981, to 7.5% of the population in 1998. There are now about 940,000 people over the age of 25 years with diabetes in Australia, approximately half of which are undiagnosed. Cases are expected to increase to 1.2 million by 2010. Worldwide cases are projected to increase from about 135 million in 1995 to 300 million in 2025. Type 2 diabetes, which accounts for more than 85% of all cases of diabetes, is a disorder characterised by resistance to the effects of circulating insulin. Cardiovascular disease remains the major cause of mortality and morbidity in diabetes. Approximately 30 to 60% of diabetic patients have high blood pressure (hypertension). In addition, patients with type 2 diabetes have coexistent lipid disorders characterised by increased blood triglycerides and reduced HDL-cholesterol, as well as haemostatic and fibrinolytic (blood clotting) abnormalities.

This disorder leads to a substantial increase in risk of cardiovascular diseases (strokes and heart attacks) as well as blindness and kidney failure. In individuals with type 2 diabetes, cardiovascular disease is the major cause of mortality, accounting for up to 80% of all deaths. The age-adjusted relative risk of death due to cardiovascular events in type 2 diabetic patients is approximately 3-fold higher than in the general population.

Apart from overweight and physical inactivity there are few well-established modifiable risk factors for type 2 diabetes mellitus. However, recent evidence suggests that alcohol may be a potentially modifiable risk factor for type 2 diabetes mellitus. A strong relationship has been observed between alcohol consumption and blood pressure in populations drinking predominantly wine, beer or sake. There are suggestions, however, that red wine has a lesser effect on blood pressure, with speculation that this may reflect the higher concentration of phenolic compounds in red wine. As in the general population, there is also a decrease in cardiovascular risk with mild-to-moderate alcohol consumption in type 2 diabetic subjects. To date, there has been no intervention study confined to type 2 diabetic patients alone, which has determined the exact direction and magnitude of any effects of red wine or alcohol, on blood pressure or blood lipids.

Proposed trial to examine the effect of red wine on cardiovascular risk in type 2 diabetics

Pharmacological strategies in type 2 diabetics that target glycaemic control alone are inadequate to minimise their high risk for cardiovascular disease. The approach that has been taken by the Department of Medicine, of the University of Western Australia and the Western Australian Institute for Medical Research, has been to complement drug treatment of type 2 diabetes by targeting nutrition and lifestyle factors that may not only improve glycaemic control, but also reduce blood pressure and overall cardiovascular risk. In this regard, they have previously examined and shown benefits of a combination of dietary fish and aerobic exercise (Dunstan et al. 1997), and the purified marine ω3 fatty acids, EPA and DHA (Woodman et al. 2002), in patients with type 2 diabetes. Such approaches in modifying cardiovascular disease risk clearly requires further evaluation to determine the optimal nutrition and lifestyle advice that should be provided.

While epidemiological studies clearly suggest that light to moderate alcohol consumption reduces the risk of cardiovascular disease in diabetics by antioxidative and antithrombotic mechanisms, concerning insulin sensitivity, where target tissues are more resistant to the effects of insulin, the literature is less clear-cut. Some studies suggest that while acute alcohol consumption impairs insulin sensitivity, regular alcohol consumption lowers target tissue resistance to insulin (Flanagan et al.

2000). Sustained abstinence of alcohol for four weeks, however, did not affect insulin sensitivity (Flanagan et al. 2002). It has also been suggested that there is a J-shaped relationship between insulin sensitivity and level of alcohol consumption, as well as a J-shaped relationship between level of alcohol consumption and risk of developing diabetics (de Vegt et al. 2002, Wannamethee et al. 2002). For example, in males, the risk only increases when more than 21 standards per 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).

The aim of the current program in the Department is to examine the balance of potential risks and benefits of the regular consumption of red wine on cardiovascular risk factors in Type 2 diabetic patients who are moderate alcohol drinkers. A cross-over study has been initiated that will focus on the overall effects of red wine on blood pressure, and the plasma concentration of lipids, glucose and insulin in these subjects. Thirty-five type 2 diabetic patients who are moderate consumers of alcohol will be recruited and randomly allocated into a three groups where they will consume, for four weeks, either red wine, dealcoholised red wine or water. There will be a washout period between each of the three phases. The precise amount of red wine and de-alcoholised red wine is dictated by their usual level of alcohol consumption at entry into the study, but is between 20 to 30 g/day for women and 30 to 40 g/day for men. Subjects will consume their normal diet during the study.

Seeding funding for the study was received from the Australian Health Management Group Medical Research Fund, and the wines were donated by the Orlando Wyndham Group, dealcoholised by the Austvin Loxton Winery and bottled by Vinpac International.

6.2.6 Sebeley Pal , Department of Nutrition, School Of Public Health, Curtin University

Effect of wine and wine-derived phenolic compounds on risk factors for cardiovascular disease

Fats or lipids are required for cell functions. Lipoprotein particles serve as stable packaging to allow the efficient transport of lipids through the aqueous environment of the bloodstream. Lipoproteins are spherical particles containing hydrophobic non-polar lipids in the core that are predominantly cholesterol esters and triglycerides, and polar lipids on the surface, predominantly phospholipids and small amounts of unesterified cholesterol. The protein moiety residing on the surface of the lipoprotein, termed apoprotein(s), play a functional role in the packaging and secretion, as well as metabolism, of the particle.

The plasma lipoprotein spectrum is broad and heterogeneous. In humans, lipoproteins can be classified as either intestinally or hepatically derived. The intestinal-derived lipoproteins, called chylomicrons, transport all dietary fats from the intestine to peripheral tissues in the body. In addition to dietary lipids, chylomicrons also transport many ingested compounds into the blood stream. These lipoproteins are converted to chylomicron remanants once in circulation. Conversely, the liver-derived lipoproteins, called very low density lipoprotein (VLDL) are packaged in the liver and once in circulation, are converted into low density lipoproteins (LDL). Central to the pathology of atherosclerosis and cardiovascular disease is the accumulation of cholesterol in arterial walls. Both LDL and chylomicron remnants can penetrate the arterial wall and deposit their cholesterol and instigate the development of atherosclerotic plaque.

The Department of Nutrition in the School of Public Health at Curtin University has shown that intestinally-derived chylomicron remnants are preferentially trapped in arterial walls (Pal et al. 2002). This suggests that, similiar to LDL-induced atherogenesis, cardiovascular disease is also dependent on arterial exposure to these pro-atherogenic chylomicron remnants (Dane-Stewart et al. 2001), where, over a 24-hour period, more cholesterol is transported as chylomicron remnants than as LDL. Pharmacological strategies, such as 'lipid lowering drugs', generally reduce the plasma concentration of LDL and chylomicron remnants by increasing the hepatic clearance of LDL and inhibiting the hepatic secretion of VLDL, the precursor of LDL. It was then proposed that the wine-derived phenolic compounds may also act by reducing production and secretion of lipoproteins from the liver and intestines, and by increasing the hepatic clearance of lipoproteins by stimulating the LDL receptor.

Cell culture (*in vitro*) experiments demonstrated that human liver cells exposed to physiological concentration of wine-derived phenolic compounds, either individually or in combination, secreted less VLDL, comparable to the lipid-lowering drug, atorvastatin. Similarly, the wine-derived phenolic compounds also significantly decreased the number of chylomicrons secreted from cultured human intestinal epithelial cells (CaCo2). It was also demonstrated that these compounds could increase the activity of the enzyme HMG-CoA reductase in cultured human liver cells, which overweight (BMI greater than 25) women subjects aged between 50 and 70 years, where subjects randomized to consumed 400 mL red wine, dealcoholised red wine or water after a meal; there was a two week washout period between each study day. Red wine significantly reduced the plasma concentration of chylomicron remnants, (that is the absorption of lipids) postprandially compared with dealcoholised wine or water, but there were no changes in the plasma concentration of the other lipoproteins. Red wine consumption, however, also significantly increased the plasma concentration of insulin and triglycerides compared to that of water at 6 hours postprandially; the effect of dealcoholised red wine was intermediate.

A short-term *in vivo* study was undertaken again in 12 hyperlipidemic postmenopausal overweight women subjects over 12 weeks, where subjects consumed 400 mL dealcoholised red wine for four

weeks; there was a two-week abstinent washout period at the commencement of the study. The plasma concentration of fasting total cholesterol and LDL decreased from baseline after four weeks by 30% and 18%, respectively. The concentration of fasting triglycerides continuously increased from baseline thoughout the study, but there were no other changes in the plasma concentration of the lipoproteins. Diet and activity records would suggest that there was no change in either activity level or the nature of their diet from the start of the study to the end of the intervention period. This study suggests that dealcoholised wine consumption may decrease the plasma concentration of total cholesterol and LDL in hyperlipidemic women, but needs to be repeated with control groups.

In conclusion:

- *The results of the in vitro study implied that the consumption of dealcoholised red wine may reduce the plasma concentration of total cholesterol, LDL and the chylomicron remnants by acting at their site of production and elimination in the body.*

- *The short-term in vivo study confirmed cell culture results and showed that chylomicron production is significantly reduced by the consumption of red wine.*

- *No conclusions could be drawn from the chronic in vivo study in hyperlipidemic subjects.*

Limitations of these studies include:

- The acute *in vivo* study did not control for background diet/meal, as baseline measures of lipid parameters may be dependent on previous meals;

- The acute *in vivo* study did not include an ethanol control group to differentiate between effect(s) of ethanol vs wine-derived phenolic compounds;

- The acute *in vivo* study did not examine parameters beyond 6 hours postprandially; and

- The short-term study did not include any control group.

Questions arising from these studies include:

- Why did the baseline plasma concentration of cholesterol fall and continue to fall and not return to the pre-intervention concentration at washout? Did this reflect their background diet and pattern of exercise?

Suggestions for further studies include:

- Inclusion of normo-lipidemic control subjects matched for age and BMI parameters in a repeat study; and

- Control for background diet and pattern of exercise in a repeat study.

6.2.7 Pierre-Louis Tiessedre and Jean-Claude Ruf, Faculté de Pharmacie, Centre d'Oenologie, University of Montpellier and Office International de la Vigne et du Vin, respectively

Wine and health ¾ existing data and future research prospects

In France, the Office Interprofessional des Vins created a program on wine and health in 1994 entitled *Wine and health: biology and vascular pathology*. The program is overseen by a Scientific Council of 12 expert and a chairman comprised of medical doctors, pharmacists, epidemiologists, pharmacologists, nutritionists and research directors. A call for submission of project applications is annual and only nine or ten applications are selected and funded after peer-review. The amount of funds distributed and shared among the selected projects is 305 000 Euros/year and since 1994, a total of 2 440 000 Euros have gone towards wine and health research. Attached is a list of 27 research papers ensuing from the selected projects.

In the European Union, there is a program entitled *Quality of life and management of living resources*, and in 1997 they funded one wine and health project entitled *Wine and cardiovascular diseases* for 2 000 000 Euros, which was a collaboration between seven French, Italian and Spanish research groups. The theme of project was investigation of the effects of red wine phenolic extracts on factors contributing to atherosclerosis and thrombosis, and the results indicate that the wine-derived phenolic compounds can improve vascular function, and down-regulate lipid oxidation (Rotondo and de Gaetano 2000).

Furthermore, in 2001, the Institute Européan Vin et Santé des Régions Viticoles established funding of 40 000 Euros/year to be divided among approximately eight projects related to phenolic biomarkers and action mechanisms for cardiovascular disease and cancer *in vivo*.

Briefly, the epidemiological studies undertaken since 1979 (St Leger et al. 1979) it has been well established that the moderate consumption of alcohol, approximately 10–30 g/day, is correlated with a reduced risk of, and death from, cardiovascular disease. The correlation is described in a j-shaped curve. Certain cohort studies suggest that the correlation is strongest for wine in comparison to that for beer and spirits, where the risk of death from cardiovascular disease may be reduced by 55 to 78% for moderate consumers of wine (Gronbaek et al. 1995). These studies suggest that there is also a reduced risk of death from all-causes with moderate alcohol and wine consumption, and additionally there may be a reduced risk of Alzeheimer's disease (Orgogozo et al. 1997), age-related macular degeneration (Obisesan and Hirsh 1998), gall stones (Leitzman et al. 1999), kidney stones (Hirvonen et al. 1999) and rectal cancer (Tavani et al. 1998).

Some European studies have looked at the dietary consumption of specific phenolic compounds and shown that the addition of wine boosts the plasma concentration of these compounds compared with the consumption of fruits and vegetables alone (Ruidavets et al. 2000). *In vitro* studies have assessed the antioxidant activity of wine-derived phenolic compounds, but the results from these studies have not necessarily been confirmed in subsequent in vivo studies, and it is becoming accepted that the ethanol component of wine has a countering plasma peroxidative effect to any antioxidative effects of the phenolic component, such that the cardioprotective mechanism of wine may not be primarily related to the prevention of plasma lipid oxidation. Indeed, recent animal and human *in vivo* studies suggest that the wine-derived phenolic compounds are vasoactive, reducing platelet aggregation and restoring endothelial function.

Other European studies have looked at the anti-tumoral effects of the wine-derived phenolic compounds and have observed that the compounds can suppress the growth of certain human colon

cancer cells, although these effects are controversial given that alcohol consumption per se increases the risk of breast cancer.

Future research prospects elaborated on include:

- Bioavailability (absorption and metabolism) of the wine-derived phenolic compounds, including in the absence and presence of the ethanol component in humans;

- Mechanisms of action of the wine-derived phenolic compounds and their effects on disease states;

- Focus on the ethanol and phenolic components of wine on common chronic disease states such as diabetes, hypertension, obesity, on cancers, on degenerative diseases—all of which are increasing in frequency in western and developing countries as these populations live to advanced ages;

- Further epidemiological studies to compare the effects of beer, spirit and wine consumption on these diseases, in relation to amount and pattern of consumption;

- Further *in vitro* and *in vivo* studies to compare the effects of red versus white wine to determine the significance, if any, between their cardioprotective and other beneficial health effects;

- Studies to determine the dose response curve to elucidate the 'optimum' consumption of wine-derived phenolic compounds to have cardioprotective and other beneficial health effects;

- Further analytical studies on factors affecting the concentration of phenolic compounds in grapes and wine, and methods of analysis;

- Further *in vitro* and *in vivo* studies to compare the effects of the different phenolic compounds, individually and in combination, for 'optimum' antioxidant and haemostatic effects, as well as the optimum combination of phenolic compounds and ethanol component; and

- Collaborative studies to determine reliable, repeatable and reproducible methods of analysis for the evaluation of the concentration of phenolic compounds and antioxidant measures in lipids, plasma and tissues, as well as for the evaluation of phenolic compounds in grapes and wine.

6.3 Summary of post-presentation discussion on day 1

- Would the industry consider developing a low alcohol wine for a niche market? Such markets include an aging population where the alcohol component has been observed to have increasing harmful physiological and pharmacological effects with increasing age, and where another sub-population does not have the ability to breakdown alcohol efficiently (lack of an alcohol dehydrogenase enzyme), and consequently generally abstainers, but would still like the cardioprotective effects of light to moderate wine consumption. The brewing industry has developed 'light' beer thus could the wine industry develop 'light' wine, given that reducing the alcohol component in wine is achievable?

- Should, and how should, the wine industry use the information from the research results? Product liability suggests that the information should not be used to promote a competitive advantage, but as part of a healthy lifestyle choice; from Arthur Klatsky's US research, wine consumers already make other healthy lifestyle choices in comparison to those of beer and spirit consumers.

- The Australian wine industry and researchers are duty bound to publish the results of all research, positive and negative, irrespective of the consequences in the marketplace, although the consequences may mainly depend on how the results are presented.

- The current public image of red wine is that it is 'healthy' and an acceptable alcoholic beverage.

- Can wine be considered as a functional food concerning the delivery of a health benefit and consequent health claims? Australian consumers appear to be quite health conscious from the enquiries fielded by the AWRI and other industry associations, as are US consumers according to the significantly increased red wine sales (34%) immediately following the *Sixty Minutes* program on the French paradox on 17 November 1991.

- How does this health benefit, however, effect dollars? Does it or can it pay for the required research? Is there any research to show that such information has changed dietary habits in the longer term, that is, are the benefits tangible?

- How can you make wine to better meet the market, that is, be market driven, or should you drive the market?

- Should research be investigator or market driven? The most significant advances in any field of research have been investigator driven. Scientific credibility is also important for the marketplace. The present perception and promotion of wine as a healthy alcoholic beverage comes from relatively independent research published in prestigious medical and nutritional journals.

- The alcohol component of wine is protective against cardiovascular disease by mechanisms including increasing the plasma concentration of HDL and anti-clotting. This component, however, also has harmful effects on blood pressure over a certain concentration or amount with increases in blood pressure evident from 20 to 30 g/day.

- Animal and human research is inconsistent in demonstrating that the beneficial effects of the wine and the wine-derived phenolic compounds are based on antioxidation. The alcohol component is also a pro-oxidant in the same physiological systems which any antioxidant effects of the wine-derived phenolic compounds may merely counteract or neutralize; this suggests, however, that

wine a 'less toxic' alcoholic beverage than beer and spirits. This is suggested by the results of the GWRDC-funded projects.

- More recent research suggests that the wine-derived phenolic compounds have additional anti-atherosclerotic effect or mechanisms to antioxidation, such as anti-clotting mechanisms that are complementary and/or different to those of the alcohol component.

- A role identified for research that compares the beneficial and harmful effects on the different types of alcoholic beverages on biomarkers for cardiovascular disease, such as blood pressure.

- Research results from The University of Western Australia (unpublished) demonstrate that the alcohol component also up-regulates the cytochrome P450 2E enzyme system in the liver that metabolises the alcohol but the phenolic compounds can 'switch off' this enzyme system, which has implications for BAC and tissue toxicity.

- The bioavailability (absorption and metabolism) and efficacy of phenolic compounds from grapes versus wine needs addressing, given the extent of wine-derived phenolic compound products entering the OTC marketplace.

- Foster collaboration between researchers, for example, The University of Western Australia is collaborating with Johns Hopkins University (Baltimore, Maryland, USA) and the Heart Research Institute.

- There is no specific program in the current five-year plan to develop wine and health; there was in the previous plan.

- The wine industry supports research and subsequent innovation that can value-add, such that researchers need to convince the wine industry of the tangible benefits of research into the health effects of wine by undertaking market research.

- The social responsibility of the wine industry must also be considered in any application, and the potential benefits and risks of research evaluated. The GWRDC and wine industry must be transparent regarding the identification of any potential health and societal risks of wine consumption to individuals and the community.

- The American Vineyard Foundation is seeking to fund international as well as US research. Could an international collaboration be established to take advantage of this funding? How would the US and Australian wine industries be benefited, respectively, by the outcomes? Alternatively, this could be used as an additional source of funds to supplement other funding sources, such as the GWRDC, which has limited funds to distribute to researchers, and is not necessarily focused on longer-term outcomes.

- Government is establishing joint industry and government research initiatives, whereby new small grants are designed to actively forge non-traditional linkages between industry and government—small grants supply seed funding to initiate research programs which may become competitive within the NH&MRC as they have an established two to three track record by then.

- In preparing a GWRDC new project application need to consider: scientific merit of research project; feasibility of research methodology; alignment of research outcomes with GWRDC priorities; previous research undertaken by researchers; linkage of research with other projects or

researchers; potential and methods for adoption of research outcomes; and industry interest and relevance. In addition, community impact and social effects should be addressed, which is generally a government and general public issue rather than a GWRDC and wine industry issue.

- In 1990, however, the wine industry, via the WFA, attempted to address responsible amounts and patterns of alcohol consumption by preparing and implementing, in conjunction with the government, a standard drinks policy and complementary campaign.

- Political pressure on the alcoholic beverage industry per se re health and social responsibility, but this primarily relates to ready-to-drink younger age group market.

- Recent WHO health policy links alcohol and tobacco consumption.

- Global wine and health advocate the separation of wine from the other alcoholic beverages on economic, health and social issues.

- Need research undertaken at both a regional and international level for applicability of research results.

- Bottom line: should the Australian wine industry foster and sustain wine and health research?

6.4 Summary of Affinity Diagram exercise

Summary of key issues and opportunities associated with industry-funded research from the Affinity Diagram exercise.

Participants were asked to write the issues and opportunities associated with industry-funded research that they considered most important on small pieces of paper, one per piece. This exercise was performed in silence, without any discussion. The items were then grouped. Appendix 5(1) contains the raw grouping of items which are be summarised as follows:

Issues or risks

- Independence of research
- Relevance of project aim and objectives to both researchers and the wine industry
- Credibility of industry-funded research nationally and internationally
- Negative as well as positive project outcomes
- Limited availability of funds

Opportunities or benefits

- Competitive advantage for the wine industry
- Economic and social benefits for the wine industry
- Partnerships between research groups and between funding groups
- Wine industry funding, albeit limited, may entice more national researchers to initiate wine and health-related research and hence narrow the knowledge gap earlier
- The wine industry has a duty of care to consumers and must provide balanced information on the benefits and harms of wine consumption
- Research may provide information for consumers on how to consume wine healthily and responsibly
- Active monitoring (collection and collation) and communication of balanced information for the individual and community on wine and wine consumption is essential

6.5 Summary of criteria for selection

From discussion and summation of the Affinity diagram, the following criteria for the evaluation and selection of research projects for funding by the GWRDC were determined by the participants. As there were differences perceived between the importance of the selection criteria between industry and the researchers, two columns were included in the following table.

Table 1: Criteria for evaluation, selection and the priorities for researchers and industry

Criteria	Research priority	Industry priority
Industry outcomes/priorities— · Product differentiation—wine versus others alcoholic beverages · Social responsibility · Reduction of amount and consequences of alcohol abuse	*	**1**
Export potential		*
Health effects—balance and impact of benefits and risks	*	*
Scientific excellence and innovation /novelty	**1**	
Feasibility of, and to perform, the research	*	*
Relevance to national and international governments' health policy	*	
Resources—facilities and researchers		
Extension—Communication and dissemination of results to wider community	*	*
Collaboration—research groups		
Partnership funding		*

Key: * denotes top six separate priorities for researchers and industry
1 denotes the most important priority

The following paragraphs prepared from the discussion during the exercise elaborate on the brief criteria listed above:

1. Industry outcomes
The Australian wine industry has a duty of care to its consumers, the demonstration of which must be deemed appropriate as well as visible. In addition, the industry must appear sincere concerning its commitment to reduce the amount and harmful consequences of alcohol abuse, where any research and other projects should produce tangible benefits for the community. Industry must always strive to balance the market and social aspects of its products.

2. Export potential
The impact of research in export markets is a key issue, in particular any research which may facilitate new markets or expand existing ones, such as in Asia.

3. Health effects¾ positive and negative
Any communication of beneficial health effects from wine consumption must be balanced against the accepted negative effects. This relates to the credibility and social responsibility of the industry, as well as that of researchers.

4. Scientific excellence
Any industry-allied research will be seen by some to be biased. This allegation can be countered by credible science published in peer-reviewed forums and journals. In addition, industry-allied research should be researcher-initiated and driven rather than industry-initiated and driven.

5. Feasibility
Any research should be achievable and, where appropriate and possible, build on previous research. An assessment of feasibility also includes the researcher's track record.

6. Relevance to health priorities
Any research outcomes should be consistent with or relevant to the alcohol and allied health policy and priorities of national and international legislators and lobbyists, such as the World Health Organisation. That is, research should focus on issues relevant to the health of the community per se, for example, issues of national importance include cancer, cardiovascular disease, diabetes and obesity. Relevance impacts on the potential dissemination and uptake of the research results as well as the potential for future/further research.

It may be possible to develop a process for funding of wine and health projects whereby the project applications are assessed and endorsed by the Winemakers' Federation of Australia and other stakeholders such as the Australian Medical Association prior to seeking GWRDC funding.

7. Resources

Resources include funding and physical resources to ensure the feasibility of the research project. Research positions rather than entire research projects may be funded to support developing expertise.

8. Communication and dissemination
Anticipated research results must be able to be translated into preferably tangible benefits that can be readily packaged, disseminated and/or communicated to key stakeholders, including the community and government

9. Collaboration
Synergistic or complementary collaboration is cost effective and projects potentially powerful, where outcomes can be quickly achieved if a project is multi-centre. CRC for wine and health?

10. Partnership funding

The GWRDC is not the core funding provider but merely a contributor of funds. Partnership funding reduces the risk to the Australian wine industry concerning bias allegations, by decreasing the reliance of the researcher on a funding body. It also has the potential to value-add if a secondary wine consumption component is added onto an existing primary protocol. Potential partners include the Anti-cancer Foundation, Australian Diabetes Association, Australian Research Council, National Heart Foundation, National Health and Medical Research Council and the Australian Associated Brewers.

6.6 Summary of areas requiring further research and potential new projects

Following determination of the evaluation and selection criteria for potential research projects, there was debate and discussion on alcohol/wine and health areas requiring further research from the previous days' presentations or potential new areas for research.

Thus, in addition to the questions arising from the initial GWRDC-funded and other studies presented on the previous day, the primary gaps in current knowledge that need to be addressed include:

- Issues of bioavailability and metabolism of wine-derived phenolic compounds concerning efficacy and effect;
- Alcoholic beverage differentiation concerning risk of cardiovascular and other diseases
- Relationship between diet/food and wine;
- Dose-response relationships of the alcohol and wine-derived phenolic compound components for the beneficial and harmful effects of wine;
- Relationship between alcohol and wine-derived phenolic compounds on the threshold of the beneficial versus harmful effects of wine;
- Relationship between the alcohol and phenolic compound components of wine in different physiological systems, such as lipid oxidation, inflammatory responses related to atherosclerosis, and coagulation/fibrinolysis/haemostasis;
- Diabetes and beverage preference;
- Obesity and beverage preference; and
- Role of alcohol and phenolic compounds in protecting against Alzheimer's Disease and other aging or degenerative diseases.

The general ethos was that targeted research, which addresses gaps in current knowledge should preferentially be performed, and similarly *in vivo* studies should be preferentially performed to *in vitro* studies, unless the *in vitro* support the *in vivo.*

Research should, where appropriate and possible, be evidence-based in order to prepare accurate advice and guidelines for consumers, for example, such as those already with cancer, cardiovascular disease and diabetes. While epidemiology gives an indication of the effects of alcoholic beverages in/on physiological systems, this research must be supported and subsequently validated by *in vitro* and *in vivo* studies, to determine whether the epidemiology was anomalous or erroneous. This is also because epidemiological studies are many and varied, with significantly different study designs and analytical methodology employed, which can bias outcomes.

6.7 Summary of potential research directions and considerations ensuing from the initial GWRDC-funded and other research projects presented on day 1

The following is a summary of potential research directions and considerations, ensuing from the initial GWRDC-funded and other research projects presented on day 1. They are categorised according to study type, study design, pharmacology of the wine-derived phenolic compounds and mechanisms of wine-derived phenolic compounds and/or ethanol component. The majority of the directions proposed build-on or extend the research that was undertaken in the initial GWRDC-funded wine and health research, and two are completely new and novel research directions **(N)**. Inclusion of the considerations in new project applications and protocols would strengthen project outcomes.

1. Study type

- Longer-term human intervention studies to determine whether acute and short-term studies accurately reflect the effects of regular and long-term wine consumption on lipid oxidation and risk factors for cardiovascular disease.

- Mouse intervention studies repeated in other animal models and in humans with cardiovascular disease, with particular emphasis on any non-antioxidative anti-atherosclerotic effects of the wine-derived phenolic compounds. This would address the question as to how similar is the mice atherosclerotic model, where atherosclerosis is accelerated, to the human atherosclerotic model?

2. Study design

- All intervention studies should include beer, wine, dealcoholised wine and water as a control to differentiate between the effects of the ethanol and wine-derived phenolic compound components.

- Determine whether amount of red wine consumed (200 mL) sufficient to observe a change in physiological and biochemical markers of cardiovascular disease?

- Comparison of cigarette smoking and non-cigarette smoking populations groups to determined heir respective difference if any, regarding the efficacy of the wine-derived phenolic compounds?

- Human intervention study, which considers a background 'normal' diet versus a diet low or high in plant phenolic compounds, supplemented with wine and other alcoholic beverages, and also considers other dietary and lifestyle factors regarding biomarkers for cardiovascular disease.

- Human intervention study where the subjects have measurable risk factors of cardiovascular disease, such as increased blood pressure and a high and unbalanced lipid concentration. For example, do the ethanol and wine-derived phenolic compound components of wine have a different effect in humans with an increased risk of cardiovascular disease?

- Studies in hyper-lipidemic obese patients should be undertaken in other patient/population groups, for example, patients with a laparoscopic adjustable gastric band have food remaining in their stomach longer due to changes in gastric motility and hence emptying (gastric stasis) which may influence the effect of alcohol on the concentration of homocysteine. Normo-lipidemic

control subjects should be included in the study, matched for age and BMI parameters, and background diet and pattern of exercise should also be controlled for.

- The effects of wine consumption need to be investigated on other forms of cellular/DNA damage than gamma radiation and hydrogen peroxide.

3. Pharmacology of wine-derived phenolic compounds

- Determine the factors influencing the absorption and metabolism of the wine-derived phenolic compounds **(N).**

- Determine whether the metabolism of the wine-derived phenolic compounds affect or alter their antioxidation efficacy as compared to *in vitro*.

- Determine whether there is a dose-dependent relationship between ethanol and pro-oxidation and phenolic compounds and antioxidation.

- Determine at what plasma, tissue or cellular concentration the wine-derived phenolic compound anti-oxidation effects completely counter the pro-oxidant effects of ethanol.

- Determine whether the presence of other phenolic compound classes or the ethanol component influences activity.

- Determine what dose of red wine, regularly consumed, would counteract the 'oxidative' and other negative nutrient effects of a diet is low in plant phenolic compounds.

- Determine the minimal duration of a regular red wine consumption for antioxidant or other cardioprotective effects to be observed.

4. Mechanisms of wine-derived phenolic compounds and/or ethanol component

- Determine the mechanism of the non-antioxidative anti-atherosclerotic effects of the wine-derived phenolic compounds **(N).**

- Determine how the wine-derived phenolic compounds reduce or prevent the deposition of lipids in the aorta.

- Determine whether the non-ethanol or phenolic compound components important for weight loss.

6.8 Summary of potential research directions from independent international and Australian researchers

The following is a summary of future directions for wine and health-related research from four independent international researchers (see Appendix 5.2), who expressed interest in, but were unable to attend for various reasons, this workshop. Also included are the top five priority areas for research suggested by a further six independent researchers, two of whom attended the workshop. These suggestions were sought from outside the workshop as certain workshop participants were reluctant to discuss and prioritise their own research projects at the workshop. The views of the 10 researchers were generally similar, and also consistent with those of the workshop research participants, both Australian and European, which are summarised in Sections 6.6. and 6.1.6, respectively.

From the large number of epidemiological studies that have been undertaken over the past decade, most researchers agree that there is a beneficial or protective effect of light to moderate alcohol consumption on cardiovascular disease. The main effect is attributable to ethanol and wine may not offer significant cardioprotective benefits to the other alcoholic beverages. Epidemiological studies, however, have also considered all-cause mortality and, together with animal and *in vitro* studies, suggest that wine may have a beneficial effect in, for example, protecting against certain cancers and degenerative diseases.

Specifically, further research projects should consider:

- *In vivo* studies, as the epidemiological studies merely observe a population group and find an association, which needs to be supported by plausible pharmacological/physiological mechanisms;

- Metabolism of the wine-derived phenolic compounds;

- Effects of various gene polymorphisms, such as those for alcohol/acetaldehyde metabolism, on the beneficial and adverse health effects of alcoholic beverages;

- Gene expression (molecular mechanisms) of wine-derived phenolic compounds that underlie the beneficial health effects, For example, apolipoprotein (APOE) is the gene that is an important determinant of serum concentration of LDL. Ordovas et al. 2001 observed that the group receiving the most cholesterol lowering benefit were men with the APOE gene type 2 who were moderate consumers of alcohol rather than abstainers or excessive consumers. However, for a subset of men with the APOE gene type 4—an estimated 12% of the US population—even moderate alcohol intake had a negative effect, increasing the concentration of LDL;

- Differentiation needs to be made between the effects of the ethanol component and that of the phenolic compounds, whereby human intervention studies should include beer, spirits and wine, both alcoholised and dealcoholised, where possible;

- Effects of moderate wine consumption of atherosclerosis-related conditions and diseases such as obesity, hypertension and type II diabetes, and on post-myocardial infarction patients;

- Differentiation of effects of moderate wine consumption on early versus late disease development, on early versus late-stages of disease and on progression versus regression of disease;

- Effects of moderate wine consumption on other causes of death and disability, such as cancer and Alzheimer's Disease, that is, the anti-carcinogenic/anti-mutagenic effects of wine and the individual wine-derived phenolic compounds;

- Supplementation of wine via diet with folate to confirm any protective effects of this supplementation on the development of breast cancer and colon cancer;

- Effects of moderate wine consumption on different population groups, for example, young adults (18–25 year old) on their physiological biomarkers for risk of diseases, such as cardiovascular disease and type II diabetes (which may provide information to help change the drinking patterns of young adults);

- Effects of drinking patterns, for example, occasional binge drinking versus regular moderate drinking on cardiovascular as well as overall health—a recent epidemiological study by Mukamal et al. (2003) suggests that it is the frequency of consumption rather than amount and type of alcoholic beverage that improves cardiovascular health;

- Concerning epidemiological studies, an Australian epidemiological study could be established in conjunction with the Centre for Alcohol Research in Denmark, which specializes in epidemiological studies. This study could be of Australian doctors and nurses, and conducted via electronic or postal questionnaires, to determine differences between the alcoholic beverages and their effects on, for example, cardiovascular disease and all-cause mortality. To date, the major Australian epidemiological study on the effects of alcohol consumption on human health has been undertaken in Dubbo, New South Wales (Simons et al. 1996, 2000).

7. Conclusions/outcomes

7.1 Conclusions of recent wine and health-related research undertaken in Australia

The main conclusions that can be drawn from the workshop presentations and hence the initial GWRDC-funded and other related wine and health research are as follows:

Concerning the potential cardioprotective effects of wine and wine-derived phenolic compounds:

- Wine-derived phenolic compounds are absorbed into, and are detectable in, human plasma following the consumption of wine, whether wine consumption is on one acute occasion or is regular for a short or longer period of time;

- The evidence in animal and human studies to date, consistently suggests the consumption of dealcoholised red wine can exert antioxidative effects on LDL and plasma in humans on a 'western' diet, when consumed regularly for a short or longer period of time, and in both cigarette smoking and non-smoking population groups; the results following consumption of red wine with its associated ethanol component have been mixed. This may be because of contrasting or countering anti-oxidative effects of wine-derived phenolic compounds with the established pro-oxidative effects of ethanol metabolism per se. Whether the presence of such antioxidant compounds in red wine offers a relative advantage for red wine compared to other alcoholic beverages in terms of the potential to cause less injury or even confer specific benefits (especially in terms of cardiovascular disease and cancer risk) requires considerably more basic, clinical and epidemiological research.

- The wine-derived phenolic compounds may act synergistically with endogenous antioxidant, vitamin E, in LDL and plasma;

- The wine-derived phenolic compounds may also reduce the plasma concentration of total cholesterol, the liver-derived lipoprotein LDL, and intestinal-derived lipoprotein chylomicron remnant, by acting at their site of production and elimination in the body; a high plasma concentration of these lipids is a risk factor for cardiovascular disease;

- The consumption of dealcoholised red wine reduces the deposition of LDL in the blood vessel walls of genetically modified mice, which have developed atherosclerosis similar to that developed by, and observed in, humans;

- Background diet, in particular of phenolic-rich fruit and vegetables, may either enhance or suppress any antioxidative effects of the wine-derived phenolic compounds; and

- The primary cardioprotective effects of whole red and white wine consumption may be related to effects other than antioxidation;

- Obese individuals are at high risk of cardiovascular disease predominantly because of the associated high prevalence of reduced insulin sensitivity or the development of type 2 diabetes. Given current knowledge of the mitigating effects of moderate alcohol and red wine consumption on cardiovascular risk, however, those who regularly consume alcohol and, in particular, wine in moderation may have a relative reduction in risk for cardiovascular disease. For example, they have been observed to be significantly less likely to be diabetic having a significantly better insulin sensitivity than abstainers, and observed to have a lower plasma

Comment: This refers to the work presented by Sebeley Pal at the workshop which you will remember wasseverely criticized because of major ainadequacies in scientific design. It should therefore not be a "conclusion" of the workshop.

concentration of the fat, triglyceride, and a higher concentration of HDL, the lipid that removes fat from the body. Those consuming red wine have also been observed to have a significantly lower plasma concentration of homocysteine, a high plasma concentration of which is another risk factor for cardiovascular disease. These possibilities deserve further investigation given the rapidly increasing prevalence of obesity and type 2 diabetes in Australia.

Concerning the potential cancer-protective effects of wine and the wine-derived phenolic compounds:

- The acute consumption of dealcoholised and whole red wine may protect DNA from induced and spontaneous oxidative damage, but ethanol exacerbates DNA damage; and

- The effect of the whole red wine is observed to be intermediate to that of ethanol and dealcoholised red wine, which implies that the antioxidant wine-derived phenolic compounds may counter the peroxidative effects of the ethanol component in cells;

Specifically, the questions raised at the Wolf Blass Foundation International Wine and Health Conference of 1996 regarding the bioavailability and differential effects of the wine-derived phenolic compounds on the blood lipid profile as compared to ethanol have been answered. The wine-derived phenolic compounds are bioavailable and exhibit antioxidative effects in plasma, LDL and cells as compared to ethanol, which exhibits peroxidative effects. The antioxidant effects of the wine-derived phenolic compounds, however, were observed in all three GWRDC-funded research projects to merely counteract the peroxidative effects of the ethanol component, when consumed together. Whether this is important for cardio- and cancer-protection remains to be answered.

7.2 Questions arising from the Australian research

From these three research projects, the major questions arising are:

- whether there is a dose dependent relationship between ethanol and peroxidation and the wine-derived phenolic compounds and antioxidation. An ethanol-containing wine manipulated to have a higher concentration of phenolic compounds and a lower concentration of ethanol may, therefore, be potentially antioxidative rather than neutral or peroxidative in plasma, LDL and cells (DNA) *in vivo*;

- whether the baseline or existing oxidative stress of the body, from diet or cigarette smoking or disease, influences the antioxidative effect of the wine-derived phenolic compounds; and

- whether wine consumption mitigates other forms of cellular/DNA damage than gamma radiation and hydrogen peroxide, such as …

The primary cardioprotective effects of wine and the wine-derived phenolic compounds may, however, be related to a reduction in the plasma concentration of the LDL and chylomicron remnants, which would also prevent or reduce the development of atherosclerosis, or may be related more to haemostatic, inflammatory and/or thrombotic mechanisms.

In addition to researching healthy subjects, it is becoming as important to research subjects at greater risk of developing cardiovascular disease and cancer, such as type 2 diabetics and the obese, as both diseases affect a great and growing proportion of the Australian (and western world) adult population. This could further foster the adoption of regular and moderate consumption of wine as

part of a healthy diet and lifestyle, where abstinence has been traditionally advised by medical practitioners.

7.3 Are any Australian or international researchers undertaking this research?

From a detailed review of the literature, few researchers have been identified in Australia or internationally as currently undertaking the research outlined above and in Section 6.5

For example, there are two groups of Italian researchers at the Department of Pharmacology, The University of Florence and the Istituto di Patologia Generale, Catholic University, Rome, examining the effect of specific wine-derived phenolic compounds on DNA damage but neither of the groups have examined effects *ex vivo* or with ionising radiation in humans or human cells.

In addition, while there is epidemiological data on the potential cardioprotective effects of wine consumption in type 2 diabetic patients, no clinical studies have been conducted in this patient group, such that the research outlined by Mori and Puddey of the Department of Medicine, The University of Western Australia, in Section 6.1.5 is unique.

Furthermore, only the Monash University Department of Surgery at The Alfred (hospital) in conjunction with specifically examining alcohol consumption in the severely obese and as a confounding variable in weight loss, and the Department of Nutrition at the School of Public Health, Curtin University was the first research group to establish, with the National Heart Foundation, that subjects groups with increased lipids needed to be examined if any lipid lowering effects of red wine was to be observed. No other research group in Australia or internationally is examining post-prandial fat uptake and oxidation when food is consumed with red wine, as a potential therapeutic for obesity. These areas are under-researched area given the high prevalence of obesity and type 2 diabetes in the western world.

Concerning the effect of diet in conjunction with wine consumption on the antioxidant status of plasma and LDL, two groups at the Universidad Catolica de Chile, Santiago, Chile and the Departments of Haematological Pathology and Family Medicine and Health Care, Faculty of Health Sciences, The University of Stellenbosch, South Africa, have examined the antioxidative and other haemostatic effects of wine against a high or low fat background diet, but neither group has considered different background disease states or the dose response relationship between the phenolic compound and ethanol components. In addition, another research group at TNO Nutrition and Food Research Institute, The Netherlands, has examined the effect of different alcoholic beverages on the total antioxidant capacity of plasma against a controlled background diet, but did not examine other antioxidant parameters. Other research groups with common interests include: UC Davis, California and Tufts University, Boston, USA; University of Montpellier, France; and Rambam Medical Center and Technion Faculty of Medicine, Haifa, Israel. The expertise of, and materials and methodologies used by, these research groups, however, are different but complementary to that of the Australian research groups.

While it is a prerequisite for research projects to have one or more unique components, if multiple research groups are undertaking inter-related projects, any similar conclusions drawn will be given more credibility and credence, and any different conclusions drawn will provide further debate, discussion and directions for further research projects.

7.4 Is the Australian research relevant to Australian and international alcohol/wine and health policies and positions?

Irrespective of the substantial epidemiological data and increasing clinical data that the moderate consumption of wine reduces the risk of death from cardiovascular disease and certain cancers ion many population groups, where cardiovascular disease and cancer account for approx. 25 and 20%, respectively, of all deaths in Australia, and up to 50% in developed countries, wine consumption remains vilified by a proportion of health and medical professionals, government officials and academics associated with alcohol reform per se.

The most internationally influential inter-government body is the World Health Organisation (WHO), which establishes policy on all areas impacting on the health of the world, that is either adopted by a government or influences its policies. The WHO policy on alcohol has recently been revised in the World Health Report 2002 *Preventing Risks, Promoting Healthy Life.* While the Report states that " globally, 140 million people are suffering from alcohol dependence" and that "alcohol is responsible for four percent of all disease worldwide", it also states that "alcohol has been consumed in human populations for millennia, but the considerable and varied adverse health effects, as well as some benefits, have only been characterized recently." Furthermore, the Report acknowledges that despite causal relationships between volume of alcohol consumption and diseases and injury, "…there are beneficial relationships with coronary heart disease, stroke and diabetes mellitus, provided low-to-moderate average volume of consumption is combined with non-binge patterns of drinking."

Therefore, any credible clinical research, such as that being undertaken in Australia, that demonstrates that there are significant beneficial health effects from regular and moderate wine consumption that can help further characterize the health benefits of regular and moderate wine consumption, thus providing perspective for health/medical professionals, government policymakers and, importantly, the general population, is relevant to wine and health policy.

The current Australian policy on alcohol, and thus wine, can be demonstrated in the new NH&MRC *Australian Alcohol Guidelines: health risks and benefits* (1991). These Guidelines are more relaxed and realistic concerning the amount of alcohol that can be safely consumed by the population per se and various population groups as compared to the former NH&MRC *Is there a safe level of daily consumption of alcohol for men and women?* (1987). These Guidelines acknowledge that alcohol has "potential health and social benefits", and these include cardioprotection. They do not, however, differentiate between the health and societal effects of wine consumption and those of beer or spirits, despite substantial data demonstrating significant differences between the alcoholic beverages. In addition, the influential Alcohol and Other Drugs Council of Australia, a lobby group allied with Professor Tim Stockwell of the National Drug Research Institute and the Independent Wineries Association, has recently released its Alcohol Taxation Statement. This Statement only focuses on the harmful effects of alcohol consumption per se discounting any beneficial health effects from moderate wine consumption, and hence advocating significantly increased taxation on wine, broadly based on alcohol content; wine is deemed to be closely substitutable with beer and spirits.

Thus, the results from the Australian research on the potential cardio- and cancer-protective effects of regular and moderate wine consumption in a variety of population groups will be an invaluable source of data for an Australian wine industry. This data can be used, for example, to demonstrate that wine may afford more cardio- and cancer-protective effects than the other alcoholic beverages, and may even mitigate the harmful or negative pharmacological and physiological effects of the common ethanol component that promotes cardiovascular disease and cancer. This is in addition to

existing data that demonstrates that wine is generally consumed in a less abusive pattern to beer and spirits, by consumers with healthier lifestyle patterns to those of beer and spirits, whereby wine consumers generally have a greater life expectancy than consumers of beer and spirits.

7.5 How can wine and health research be made more relevant?

Any research outcomes should be consistent with the general health and alcohol and health policies and priorities of the Australian government and international bodies such as the World Health Organisation (WHO), as well as with those of the Winemakers' Federation of Australia (WFA) (see Appendix 5.3). Issues of national and international importance include cancer, cardiovascular disease, diabetes and obesity. Thus, any research that increases understanding of both the positive and negative pharmacological and physiological effects of wine consumption and thus fosters the safe consumption of wine in moderation by the general population as well as various population groups, is relevant to current government and industry policies and priorities on alcohol and health.

In addition, any research results must be able to be translated into preferably tangible benefits that can be readily packaged, disseminated and/or communicated to all stakeholders—industry, government, health and allied-health professionals and the community.

7.6 Should industry via the GWRDC continue to fund wine and health research?

In Australia, over the last decade, the domestic per capita consumption of wine has declined from approximately 21.5 L/year and plateaued at approximately 20 L/year. This change in consumption has been accompanied by a repositioning of wine in the diet and in the lifestyle of Australians, approximately 20% of whom consume wine in preference to the other alcoholic beverages. The regular and moderate consumption of wine is also allied to tourism. This is projected onto a background where the domestic consumption of alcohol per se in Australia has declined over the last decade by approximately 15% and is continuing to decline. Interestingly, in November 1991, when the US *Sixty Minutes* television program aired a story entitled "The French Paradox", which effectively said that red wine consumption halves an individual's risk of cardiovascular disease, red wine sales in the US tripled, and a similar increase in sales was seen in Australia when the story was aired here. The sale of red wine has remained relatively high a decade later.

The objectives in Strategy 2025 of the Australian wine industry, which are related, directly or indirectly, to wine and health issues are:

1. Progress and sustain the community acceptance positioning of wine (health, environment and lifestyle);
3. Extend the influence of Australia in world wine forums and institutions; and
26. Continue, in partnership with government, alcohol and health programmes to reduce alcohol abuse.

Correspondingly, Program 4 of the GRWDC 5-Year Plan 2002–2007 refers to the impact of wine on the community in a social context, and specific strategies include:

- Evaluate and quantify the costs and benefits of…social…effects on the Australian community by the wine industry;
- Monitor current scientific research findings on the health aspects of wine; and

- Increase Australian influence in the agendas and access to the information resources of global wine forums.

Funding from the Australian wine industry will help demonstrate the industry's duty of care to its consumers regarding the appropriate amount and pattern of wine consumption, which minimises the harmful effects of wine whilst maximising the potential benefits to human health. Community and consumer perception of the social benefits will also be improved by a rigorous scientific approach to the evaluation of the health benefits associated with the regular and moderate consumption of wine. Indeed, in a society where health has assumed a high profile, the consumer is being progressively educated by the media to question the 'healthiness' of food/beverage products irrespective of their quality, where a major aim of the Australian wine industry is to position wine as a healthy lifestyle beverage.

In addition, there are few funding bodies available to provide all the funds required to undertake a research project, and universities and related research organisations, such as the CSIRO, are being actively encouraged to seek some funding from industry; New GWRDC project applications from CSIRO Plant Industry, Horticulture Unit exemplify this. This has an effect of making the research projects more industry relevant, where tangible outcomes are an important criteria, as is the communication and dissemination of the outcomes. As the harmful health and societal effects of alcohol have prominence over any beneficial effects, funding bodies have not given research into beneficial health effects a high priority, and hence have not encouraged other Australian researchers to actively participate in this area. Therefore, the funding or co-funding with other independent funding bodies, of wine and health-related research will ensure that the research undertaken will be relevant to government AND Australian wine industry policy on wine and health, and provide information that can be used by the industry in discourse with government and consumers. Indeed, before the GWRDC began funding wine and health research approximately five years ago, the industry was reliant on the Federal government and internationally-generated information in debates on alcohol and health policy. In recent reviews conducted by the Federal government, however, the industry has been able to usefully cite the emerging outcomes of this research in it submissions. These reviews include: the *National Drug Strategy—Alcohol Action Plan 1999; National Alcohol Strategy¾a plan for action 2001 to 2003-2007*; the *National Alcohol Research Agenda*; the *draft National Youth Alcohol Strategy*; the NH&MRC recommendations and guidelines regarding responsible drinking behaviour; Dietary Guidelines for Australians; *Proposal P167—the review of nutritional labelling: further consultation, Proposal P153: Review of Australian Food Standard Code Clause A1(19)—Health and medical claims*, and Application 359—*Labelling of alcoholic beverages "This product contains alcohol. Alcohol is a dangerous drug*".

Concerning the influence of the Australian wine industry in international forums, the emerging outcomes of the GWRDC funded wine and health research have enabled greater participation of the industry in international forums, such as the Office de la Vigne et du Vin (OIV). The OIV Nutrition and Health Sub-commission is the only regular and permanent inter-governmental organisation devoted exclusively to the health and nutrition issues of wine and wine consumption. The Health and Regulatory Information Manager of The Australian Wine Research Institute was elected as Vice President of the Nutrition and Wine Expert Group in 2001 and prepares Australia's position on wine and health resolutions for the annual OIV General Assembly and biannual Expert Group meetings, again often usefully cited the GWRDC funded wine and health research.

7.7 How can the risks of industry funding wine and health research be decreased and the benefits increased?

A primary risk of industry funding wine and health research is the allegation of bias and credibility. This risk can be largely dispelled or minimised by choosing credible researchers that are established, and nationally and internationally recognized in their field of research, and by allowing the research to be researcher rather than industry driven. In addition, publishment of complete research results in credible peer-reviewed journals and forums and by actively acknowledging the harmful health and societal impacts of excessive wine consumption, will minimise this risk.

This risk can also be minimised by co-funding the research with independent funding bodies, such as the Anti-Cancer Foundation, Australian Diabetes Association, Australian Research Council and the National Health and Medical Research Council, National Heart Foundation and the Australian Associated Brewers. Co-funding also permits value-adding if a secondary wine consumption component is added onto an established or existing primary protocol. Synergistic or complementary collaboration is also cost-effective where the outcomes of research projects are more powerful and can be more quickly achieved if the research project is multi-centre.

Another risk is negative rather than positive outcomes from a research project. This risk can be managed by undertaking evidence-based research, by balancing any negative research results observed in the project against positive research results, as well as by placing all research results in context with other health benefits, risks and observations.

In conclusion, more benefits and opportunities for the Australian wine industry were identified by workshop participants as associated with industry-funded wine and health research than were risks, and all the risks could be managed

8. Recommendations

The primary recommendation from this Workshop is that the GWRDC continue to support and fund or co-fund wine and health research undertaken by Australian researchers, which will ultimately strengthen the positioning of wine as a healthy lifestyle beverage, which corresponds to objectives of Strategy 2025 of the Australian Wine Industry and the GWRDC 5-Year Plan 2002–2007.

The GWRDC should also be encourage collaboration between Australian and, where relevant, international research groups with complementary projects, aims and objectives.

Prioritised list of potential wine and health projects for the next three to five years

From the workshop discussions and canvassed comments from international and Australian researchers, the following is a prioritized list of potential wine and health projects, which address gaps in current knowledge and understanding. Projects 1–8, build immediately on from the initial GWRDC-funded projects and hence are cost and time effective as the research groups already have methodologies and protocols established and in place, as well as trained clinical and research staff, and project 9 is an extension into other degenerative disease states. These studies would also confirm and strengthen the outcomes from the initial GWRDC-funded projects. Researchers should also incorporate the study design considerations outlined in Section 6.7 in any new project application protocols.

1. A clinical intervention (*in vivo*) study to determine whether there is a dose dependent relationship between the ethanol component of wine and per-oxidation and the phenolic component of wine and anti-oxidation in plasma and lipids such as LDL. Utilization of a similar protocol to those used in the initial GWRDC-funded studies UWA 97/1, CSN 97/1 and HRI 97/2, which also addresses any weaknesses in the protocols of the initial studies, would confirm and strengthen the results of the initial studies.

2. A clinical intervention (*in vivo)* study to determine whether the baseline or existing oxidative stress of the body, from background diet or cigarette smoking, influences the antioxidative and non-antioxidative effects of the wine-derived phenolic compounds. Utilization of a similar protocol to those used in the initial GWRDC-funded studies UWA 97/2, CSN 97/2 and HRI 97/2, which also addresses any weaknesses in the protocols of the initial studies, would confirm and strengthen the results of the initial studies.

3. A clinical study in diabetic and obese patient populations that are at increased risk of cardiovascular disease. This is an extension of priority 2. concerning the effect of background disease state on the antioxidative and non-antioxidative effects of the wine-derived phenolic compounds; two such projects are merely seeking co-funding from the GWRDC to include a wine component in their protocol (see Appendix 15), and build on existing protocols with established patient population groups.

4. A comparative clinical intervention (*in vitro* and *in vivo*) study on the potential effects of the wine-derived phenolic and ethanol components on other forms of cellular/DNA damage than gamma radiation and hydrogen peroxide, again to access any dose dependent an countering effects between the two wine components. Utilization of a similar protocol to those used in the initial GWRDC-funded study CSN 97/1, which also addresses any weaknesses in the protocols of the initial studies, would confirm and strengthen the results of the initial study, and would also

5. An extension of project 4. is a comparative clinical intervention study on the potential protective effects of the wine derived phenolic compounds against DNA and alcohol damage in population groups with susceptible genetic backgrounds, such as, BRCA1, BRCA2, SOD2 and aldehyde dehydrogenase (ALDH) mutants, respectively, which predispose individuals to developing certain cancers. This study could potentially determine whether genome damage would occur when these individuals consumed wine according to the 'safe' levels annotated in the NH&MRC Australian Alcohol Guidelines. A wine could then be developed for optimal prevention of oxidative and alcohol damage to DNA in susceptible genotypes by manipulating the phenolic and ethanol components.

6. *In vivo* study investigating the absorption and metabolism of specific wine-derived phenolic compounds, and in particular, what influence these pharmacokinetic parameters and whether metabolism modifies their perceived antioxidant and non-antioxidant cardioprotective effects in addition to their efficacy. This would demonstrate differences between clinical and test tube results and thus the applicability or relevance of test tube data to clinical conditions, which is oft debated and discussed.

7. Animal study of the cardiovascular effects of de-alcoholised and whole red wine on early and late stages of atherosclerosis (progression versus regression of disease), using established animal models in addition to apolipoprotein E gene knock-out animals, such as LDLr-/- mice, Watanabe Heritable Hypercholesterolemic rabbits, to confirm the observations of the initial GWRDC-funded research project HRI 97/2 and subsequent studies undertaken by The University of Western Australia.

8. A clinical intervention study, systematically investigating the effects of the moderate wine and alcohol consumption on surrogate markers of atherosclerosis or cardiovascular disease, such as endothelial function and carotid intima-to-media ratio to further define effects other than LDL antioxidation, of the wine-derived phenolic compounds.

9. *In vitro,* animal and human studies investigating potential protective mechanisms of moderate wine consumption and the wine-derived phenolic compounds on the development of other degenerative diseases, such as Alzheimer's disease, which has been observed from epidemiological studies.

9. Appendix 1

Communication

9.1 Outline how the outcomes of this project have been communicated during the project.

As outlined in the second Performance Target of the Outputs section of the project application, a policy paper/journal article on wine and health issues on which to base future research decisions for the Australian wine industry is currently being prepared. This paper is to be circulated to all stakeholders and published in the *Australian and New Zealand Grapegrower and Winemaker* or the *Australian and New Zealand Wine Industry Journal*. The estimated date of completion is April 2003.

9.2 If any journal articles were written or published during the conduct of the project, please list them and where possible include copies in the index.

Immediately prior to the workshop, three journal articles were published on research that has been, or is currently being, undertaken on wine and health in diabetic and obese population groups, which were presented at the workshop (see Appendix 5).

9.3 If you believe further communication activities would enhance the uptake of this project's findings, please identify them, i.e., the conduct of field days, workshops or the production of brochures or identification guides.

Further activities that were discussed at the workshop that would enhance the up take of this project's findings include:

- Development or formation of an Industry Reference Group for wine and health research;
- Presentation of the outcomes of the workshop to GWRDC Board and WFA Executive Council and other stakeholders; and
- Presentation of preliminary project applications submitted with this report to the GWRDC Board, as well as the final outcomes (and implications) of the initial GWRDC-funded research projects.
- Presentation of the research results from the initial GWRDC-funded wine and health research projects and from other relevant Australian and international research projects at a workshop attached to the Twelfth Australian Wine Industry Technical Conference, which would facilitate the attendance of industry as well as representatives from government, health/medicine and research. Effectively, it would be a workshop to counter the negative publicity on the abuse and misuse of alcoholic beverages per se and to inform the industry and other stakeholders of recent and relevant Australian and international research results on the decreased risk of cardiovascular disease and all-cause mortality in populations when wine is consumed in moderation.

10. Appendix 2

Intellectual property

11 Appendix 3

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12. Appendix 4

Staff

Creina Stockley
Health and Regulatory Information Manager
The Australian Wine Research Institute

For the workshop facilitation on Friday, 13 December 2002:
Henrietta Child and Louise Stanton
KNEEDEEP *in* PROJECT MANAGEMENT

13. Appendix 5

1. Grouping of issues (risks) and opportunities (benefits) associated with industry-funded research prepared by the workshops participants:

Risks

- How do industry researchers share common goals?
- Respond to the attendance of the industry
- Need to convince the Australian federal government of industry's responsibility
- Industry awareness and commitment
- Trade obstacles
- Responsibility for independent research—no strings attached
- Industry needs to accept negative results
- Industry needs to be active in —leadership
- Risk for industry—results of research cannot be controlled, however, supporting good ethical research paints the industry in a favourable light
- Potential problems of negative outcomes of research
- What has industry to gain—are there risks? Research may not give you the answer that industry wants
- Development of new technology
- Changing priorities in a rapidly developing industry
- Threat from other alcohol producers
- Ownership
- Credibility of outcomes if funded by beneficiaries—eg USA system
- Industry funded research—vested interest
- Research—responsibility to industry benefit?
- Well designed feasible studies
- Intangible benefits are often ignored—seeding effects of small grants— translation and dissemination of research results has huge benefits for industry

Perceptions

- To show we are on the same side—research and industry unity
- Industry view versus research view versus community view

Benefits associated with research

- Commercial benefits, for example, red wine benefits contributing to Asian sales
- Will sales increase as media picks up on any positive research that we do
- Track record establishment to foster further funding and grants
- Funding from industry will entice more researchers to get involved and thus narrow our knowledge gap
- Best research is through link between: university/CSIRO/government bodies/funding bodies such as ARC, NH&MRC, NHF/industry
- Tangible outcomes for Australian wine industry, for example, a competitive advantage for the Australian wine industry
- Facilitate a healthy lifestyle choice
- Wines that are proven to confer health benefits may be developed

Funding

- Limited industry $ for high cost research
- Funding availability
- Cost of research
- Limited funding
- Cost to Australian wine industry relative to benefit is 'economic'
- Limited funds demand strategic partnerships (government, industry, university), for sustainable and productive collaborative research programs

- It should be in the interest of the wine industry to support local research on health effects of wine
- Development of more research

International issues
- Maintaining strong international credibility
- Need to be global

Ethical issues
- Need for balanced information taking into account positive and negative results
- Ethical issues—risks and benefits
- Tools to inform customers of right and wrong ways to consume wine
- The wine industry should become more aware of the potential toxicological effects of wine and how to prevent these effects
- Health implications and consequences of a product cannot be ignored—active monitoring/research on an ongoing basis is essential

Duty of care
- Potential co-funding to assess social impacts
- Legal issues—risk to industry
- Industry needs to demonstrate duty of care
- Duty of care: of the industry for its consumers
- Duty of care to consumers
- Industry social responsibility
- Responsibility to consumer health and safety with respect to safe levels of consumption

2. Recommended research directions from international researchers

1. Morten Grønbæk, Professor, Dr. Med. Sci., Ph.D., Centre for Alcohol Research, National Institute of Public Health, Svanemoellevej 25, DK-2100.

Background

During the last decade, a large number of epidemiological studies have addressed the issue of beverage specific differences with regard to health outcomes. At this point, most researchers agree that there is a beneficial effect of a light to moderate alcohol (ethanol) intake on coronary heart disease, while the issue of beverage specific differences is still unsettled. Many have addressed the issue whether wine has beneficial effects with regard to this specific outcome, and I think there is a general agreement that the main effect is that due to ethanol itself. That is, although most of the studies show a slightly more beneficial effect of wine, there may be serious confounders, and the main effect is attributable to ethanol itself.

Yet newer studies, among those some from our centre in Copenhagen, have suggested that the lower mortality among wine drinkers may be due to the effect of wine on other health outcomes than coronary heart disease, such as several types of cancer and alcoholic cirrhosis.

Suggestions

Clinical and experimental studies

In the non-epidemiological field, such as more clinical and experimentally oriented ones, the focus ought to turn towards the anti-cancerogenic effects of substances in wine. There have been some newer suggestions of substances, such as resveratrol being such an antimutagenic substance in line with several others. Indeed, there are already quite a few such studies on mice etc., but I think there is a clear lack of human studies in this field. Hence, it would be interesting to see smaller intervention studies on the effect of wine versus beer and spirits (such as vodka) on intermediate parameters or risk factors for cancer or maybe antioxidant levels in the blood.

Epidemiological studies

An interesting topic in the epidemiological field would be to establish one or two Australian cohorts. There are many prejudices about epidemiological studies, one of them being that they take a very long time, and that they are very expensive. It has of course something to do with reality, but on the other hand it may be reasonable toestablish a cohort of, for instance, Australian doctors or nurses, whom are known to have, at least in other countries, to be responsible and to imply a high response rate on mailed questionnaires. It would be reasonably easy to establish such a cohort through their organisations, and it may be possible to ask the participants to answer electronically on the Internet. This has the advantage of being cheap (in long-distance Australia) and of securing the anonymity of the respondents. Further, the answers are easy to handle while the questionnaires are electronically based. A further argument against these prejudices about the long-term aspects of a prospective study is that with a big cohort you would have even hard outcomes such as coronary heart disease and cancers within very few years. Hence, my guess is that you have around 50,000 thousand doctors in Australia. It may be necessary to collaborate with other institutions, also in order to increase the credibility about your intentions. I would be happy to assist you with establishing such a cohort, including drawing the lines for the life-style and dietary questionnaires.

2. Dr Henk F.J. Hendriks, Nutritional Physiology, TNO Nutrition and Food Research
P.O. Box 360, 3700 AJ Zeist, The Netherlands

This short summary has been written to stimulate discussion on the directions for future research into wine and health.

Antioxidants and coronary heart disease
Most of the scientific wine research over the last several years has been focused on the antioxidant properties of non-alcoholic bioactive compounds in red wine. Results appear to indicate that wine polyphenolics are absorbed in the blood during the post-prandial phase.

It is particularly interesting to study further the interactions and overall effect of both polyphenolic antioxidants and alcohol on the oxidative stress burden after a meal. This overall measure should include measuring polyphenolic compounds in post-prandial blood but also and at the same time other parameters to have an overview of the total antioxidant capacity (e.g. TEAC and specific antioxidants such as uric acid), antioxidant activity (e.g. HDL-PON, LDL oxidation protection) and oxidative damage parameters (e.g. F2-isoprostanes, NF-kappa-B) as well as the effector molecules related to disease (e.g. vascular wall function parameters like ICAM and inflammation mediators like TNF alfa).

This work should preferentially be performed in human volunteers. The research might compare moderate drinking with other physiological conditions known to result in oxidative stress, such as physical activity and obesity. These studies should provide insight in the relevance of the effects of polyphenolic compound as compared to the alcohol effects and it will help to substantiate the antioxidant theory of coronary heart disease prevention, which has been heavily attacked and questioned during the last few years.

Polyphenolic compounds
Some important health effects of the polyphenolic compounds are independent of their antioxidant effect. The best known example is resveratrol, which is considered very promising in terms of its anticancer activities. Epidemiology however, does in general not show a highly protective effect of wine drinking on cancer incidence yet. This may be due to the low concentrations of this bioactive substance in wine.

More data are needed on the metabolism of bioactive compounds in wine and their possible health benefits. Recently new techniques have come available that allow the evaluation of all gene expression changes after an intervention. These DNA microarray techniques, which probably should be applied in experimental animals first, may help to identify new functionalities in wine, specific to bioactives in wine. These studies will help substantiate the health effects of non-alcohol wine components.

Antioxidants and diabetes mellitus type II
The epidemiological evidence for a protective effect of moderate alcohol consumption on diabetes type II is steadily increasing. First studies suggested that no beverage specific effects exist. The risk factors for diabetes type II, however, are comprised in what is referred to as “syndrome X”. Syndrome X does include many risk factors but excludes cholesterol as a risk factor. This may mean that other factors like the oxidative stress parameters or vascular wall effects are more important in causing the disease and in protecting from the disease.

Studies into the mechanism of moderate drinking being protective against diabetes type II are important and may very well include mechanisms that are independent of cholesterol and therefore not be solely alcohol-mediated.

Antioxidants and dementia
The number of epidemiological studies describing the associations between moderate alcohol consumption and incidence of dementia is still limited. More of these studies, using populations of middle-aged individuals at the start and with state of the art diagnosis of the disease, are needed.

Studies into the mechanism of moderate drinking being protective against dementia are also important. The mechanisms may be similar to those described for coronary heart disease.

Specific population groups
Most information on the health benefits of moderate wine drinking is available for men. In some (possibly most) countries, women usually prefer to drink wine. More information on their specific health benefits will be useful.

Teenagers are considered the largest group of drinkers causing trouble. It is also believed that this group will not benefit from moderate drinking, because the disease burden is very low at this age. The majority of deaths in this age groups in relation to alcohol consumption is due to accidents.

It may be interesting to have more data available on the effects of moderate drinking on the physiological risk biomarkers for disease (coronary heart disease, diabetes type II) in young people. This may show the beneficial health effects of moderate drinking in young people. This type of information may also help to change the drinking pattern of young people.

Drinking pattern
Very little data are available on the effects of drinking pattern. Both in epidemiological studies as well as in clinical trials drinking patterns need to be compared to assess the health benefits of regularly drinking moderate amount as compared to the (lack of) benefits when binge drinking.

3. Dr Francois Booyse, Professor, Department of Medicine and Cell Biology, Director, Cardiovascular Disease Research and Molecular Cardiology, University of Alabama, Birmingham, AL 35294, USA

A few thoughts on the direction that I think wine and health research should focus on in the future:

1) We have generated more than sufficient convincing epidemiological data on the various heath-related benefits attributed to moderate wine/alcohol consumption, and should focus our attention on better identifying and defining the molecular mechanisms that underlie these potential protective benefit;

2) High-quality research should also be conducted with the principal purified wine components (i.e. polyphenolic compounds), rather than with the complex mixtures of un-fractionated wine in which the results are impossible to analyze and/or interpret, mechanistically;

3) Better characterization of newly formed wine component conjugates that are found in the blood, including identification of their biological properties;

4) If we continue on our present research path we will only continue to add more new identified metabolic functions that may be protective, but still will not understand the importance, role and/or synergistic interactions between these varied pathways/functions in overall protection. I think it is imperative that we start applying some of the new technologies to gain better insight into these complex mechanisms. For example, microarray gene analysis of ethanol/wine component-induced gene expression in the heart, blood vessels, endothelial cells, smooth muscle cells, etc. These analyses will identify new highly responsive genes (not previously described), as well as identify the coordinate expression of multiple genes and new metabolic pathways/interactions that we were unaware of and will allow us to make better sense of the importance/role of the many varied and diverse functions that have been described to date (and will continue to be described without any real focus); and

5) Finally, we must start identifying/defining the importance and role of individually identified functions or function combinations, *in vivo*, using genetically-deficient mice, deficient in one or more genes, relevant to a particular "hypothesized" protective mechanism or function.

4. Professor Roland Stocker, Centre for Thrombosis and Vascular Research, School of Medical Sciences, Faculty of Medicine, University of NSW, UNSW Sydney NSW 2052

I believe that the GWRDC should continue funding research in the cardiovascular area, with a focus on establishing any potential difference between alcohol-containing versus de-alcoholised products (highest priority) and red versus white wines. The research should be focused on *in vivo* work.

Published results, as well as our study, suggest although do not prove, a potential health benefit associated with moderate consumption of wine. Based on animal research, the limited studies available on humans, and scientific considerations, the strongest case can, arguably, be made for a beneficial effect of de-alcoholised red wine. Future studies that should be supported could include:

1. Additional testing of cardiovascular effects of de-alcoholised red wine on atherosclerosis, using established animal models in addition to apolipoprotein E gene knock-out animals (e.g., LDLr-/- mice, Watanabe Heritable Hypercholesterolemic rabbits).

2. As 1) with differentiation between early versus late disease development; progression versus regression.

3. Direct comparison between de-alcoholised and alcoholised red wine; red wine versus white wine for 1) and 2).

4. Extension of animal models to atherosclerosis-related disorders, such as hypertension (e.g. spontaneous hypertensive rats) and type-II diabetes (e.g. Zucker rats).

5. If experimental approach outlined in 1) to 4) provides clear support for beneficial effect, clearly defined mechanistic studies, at whole animal, cellular and sub-cellular level should be conducted.

6. Human studies, systematically investigating surrogate markers of CVD (such as endothelial function, carotid intima-to-media ratio), as per 3). These should be small, well-defined studies that may eventually provide the basis for large controlled intervention studies.

5. R. Curtis Ellison, MD, Professor of Medicine & Public Health, Boston University School of Medicine

Five most important priorities for future directions in wine and health research:

1. A randomized clinical trial (blinded to the extent possible) for the effects on subsequent cardiac events and mortality of the equivalent of a drink a day for subjects post-myocardial infarction or with other evidence of serious coronary disease;

2. Research into the interactions of folate and alcohol, in terms of both beneficial and adverse effects. I am very impressed by the ability of adequate folate intake to negate any potential increase in risk from moderate drinking for both breast cancer and colon cancer. Also, there are potential protective effects of folate against foetal alcohol syndrome (FAS) among alcoholic women drinking throughout pregnancy;

3. Studying the relation of wine and alcohol to obesity and diabetes. It is getting clear that alcohol improves glucose metabolism. I think that it may well help prevent obesity, as well;

4. The effects of various polymorphisms of ADH3 and other genes on beneficial and adverse effects of wine and alcohol. We need to repeat all of our epidemiologic studies looking for differential effects according to many genotypes; and

5. Looking for bio-markers, by which we can judge beneficial and adverse effects of wine and alcohol, especially in terms of cardiovascular disease and cancer. (Should everyone be required to undertake an "alcohol-tolerance test" before getting a permit to drink?)

6. Professor Erna Mansvelt, Head, Department of Haematological Pathology and Dr David van Velden, Department of Family Medicine and Health Care, Faculty of Health Sciences, University of Stellenbosch

Five most important priorities for future directions in wine and health research:

1. Metabolic syndrome: the impact of diet and alcohol/wine on the different diagnostic parameters of this syndrome;

2. Blood platelet membrane fatty acid composition and fluidity affected by diet/wine intake to explain the anti-thrombotic effect of wine;

3. Influence of alcohol/wine intake on adhesion molecules and mechanisms of the cellular interaction in relationship to the inflammatory response of atherogenesis;

4. Qualitative research: Wine consumption as part of a healthy lifestyle which inclides regular and moderate wine consumption in association with regualr excercise, Mediterranean diet, creative intellectual/ spiritual activity; and

5. Aiming to make a phenolic enriched white wine with the "ideal" synergistic combination of phytochemicals and its effect on certain clinical parameters in humans.

(We have already looked at the first two topics and would like to focus on the latter 3).

7. Dr Erik Skovenborg, MD, Ved Stranden and Founding member of the Scandinavian Medical alcohol Board (SMAB), Denmark

Five most important priorities for future directions in wine and health research:

1. the importance of drinking patterns;
2. identification and importance of confounders in cohort studies of wine and health;
3. initiating a small controlled randomized study of the effect of a moderate wine consumption in AMI-patients just released from hospital;
4. studies of the aspirin-like effect of alcohol—is there an extra benefit with wine? and
5. how to send the message of moderation to the young generation.

8. Professor Michael Aviram, Head, Lipid Research Laboratory, Rambam Medical Center and Technion Faculty of Medicine, Haifa, Israel

Five most important priorities for future directions in wine and health research:

1. Macrophage foam cell formation and the development of atherosclerosis;
2. Paraoxonase expression;
3. Monocyte–macrophage differentiation;
4. Atherosclerotic plaque stability and the extracellular matrix (ECM); and
5. Hypertension and the renin–angiotensin system.

9. Dr Michael Fenech, CSIRO Health Sciences and Nutrition and Chairman, HUMN Project, International Collaborative Project on Micronucleus Frequency in Human Populations

Five most important priorities for future directions in wine and health research:

1. Continue current research to identify most important components of wine in terms of prevention of DNA oxidation and atheroma formation;
2. Effect of wine consumption on homocysteine, folate and B12 status;
3. Effect of wine consumption on weight loss;
4. Pharmacogenomics A: what proportion of the population would experience toxic effects of alcohol even when drinking within the guidelines? and
5. Pharmacogenomics B: what proportion of the population would actually benefit from the antioxidant properties of wine phenolics when drinking within the guidelines.

10. Dr Peter Clifton, CSIRO Health Sciences and Nutrition

Three most important priorities for future directions in wine and health research:

1. *in vivo* testing to determine what components of wine are found in plasma in humans and then test those in animal models of atheroma;

2. an *in vivo* observational study of red wine, white wine and no alcohol in regular drinkers/non drinkers looking at carotid intimal medial thickening over 3 to 5 years plus plasma endothelial markers plus coronary calcium in approximately 500 subjects; and

3. controlled study in regular drinkers and non drinkers with randomized polyphenol extract as per design 2).

3. Winemakers' Federation of Australia

From Core policy: Wine and health (www.wfa.org.au)

The Australian wine industry has a long standing commitment to the consumption of wine in moderation and has initiated a number of programmes to pursue this objective including:

- The development and promotion of standard drinks labelling;
- The initiation of advertising self regulation on alcohol products;
- The promotion of appropriate levels of consumption for males and females; and
- The development of close working relations with Federal and State government agencies in the development of policies and guidelines.

This programme has been backed by a comprehensive research programme and the development of one of the world's largest databases on wine/health, located at The Australian Wine Research Institute in Adelaide [and funded by the GWRDC].

The Winemakers' Federation has consistently put the view that wine (alcohol) in moderation is not injurious and arguably beneficial to health for a normal, healthy consumer. Also, that the focus of public policy should concentrate on the individual and the choice they make to drink moderately and responsibly or to abuse the product and run the associated risks.

14. Appendix 6:

Budget reconciliation

GWRDC BUDGET SHEETS

Indicative Budget (GST Exclusive) **2003/2004**

		Agency Contribution	
	GWRDC	***eg WA Ag***	***eg CRCV***
Salaries *(List staff paid with GWRDC Funds)*			
Travel			
Domestic	3200		
International	19500		
Operating	6500	600	
Capital			
TOTAL	29200	600	0
ADD GST (10% of the Total)	2920		
TOTAL FUNDS REQUESTED FROM GWRDC	**32120**		
TOTAL PROJECT COST	**32720**		

15. Appendix 7

New GWRDC Project Applications for wine and health

1. **A controlled trial of the effect of red wine on cardiovascular risk in type II diabetic patients**
   Dr Trevor Mori and Professor Ian Puddey, The University of Western Australia

2. **The potential cardiovascular benefits of red wine polyphenolics in hyperlipidemic patients**
   Dr Sebeley Pal, Curtin University

3. **Constructing a healthier wine**
   Dr Michael Fenech, CSIRO Health Sciences and Nutrition