

## Alcohol and Coronary Heart Disease

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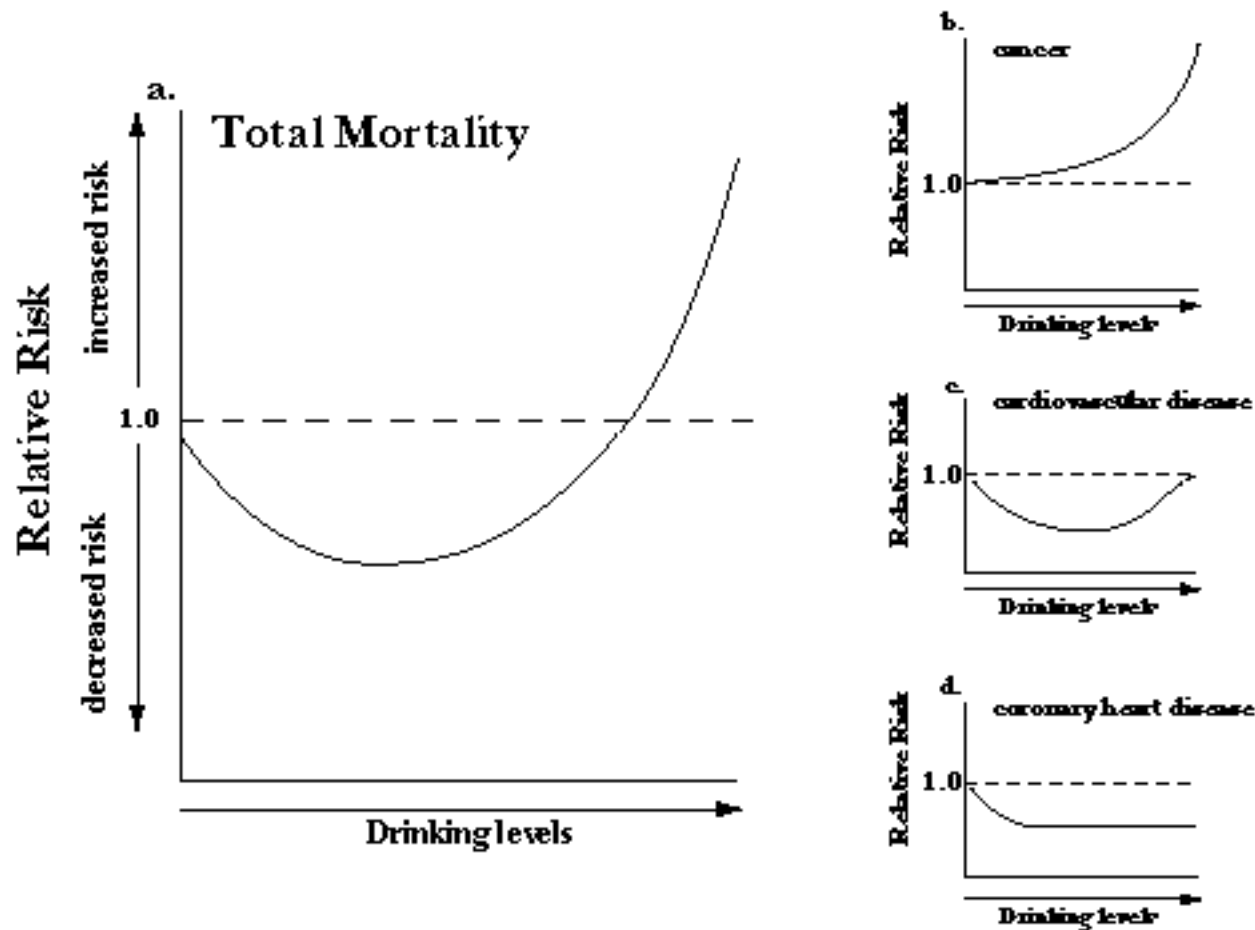
### Introduction

The relationship of alcohol consumption with various diseases has been explored for centuries. A number of issues complicate the study of these relationships. The issue is first complicated by the fact that, with the exception of violent deaths attributable to intoxication, risks and benefits of alcohol consumption are likely to accrue over years or even decades. Second, quantitative assessment of drinking is generally based on self report and this may lead to some degree of misclassification. Third, drinking habits change over time, and thus, it may be important to update drinking habits periodically during a longitudinal study. Fourth, consumption of alcoholic beverages tends to be embedded in cultural practices and associated with a number of lifestyle factors making it difficult to tease out the specific effects of alcohol on a given disease versus those of other related factors. Age, sex, race, smoking, ethnic background, and education are examples of factors which are related to alcohol intake and may confound relationships with disease. Fifth, ethanol is derived from a number of different beverages and other components in these beverages may increase or decrease risk of disease aside from, or in addition to, the specific ethanol effect.

In addition, most studies tend to take into account average daily intake disregarding the specifics about how or when the alcoholic beverage was consumed. For example, southern Europeans tend to drink wine with meals while northern Europeans tend to drink distilled spirits often at times other than mealtime. The risks and benefits of alcohol consumption may be quite different for an individual who consumes seven beers on a Saturday night compared to an individual who consumes a half of a glass of wine with lunch and dinner every day, despite the fact that average weekly alcohol consumption will be similar for each individual. Finally, the precise mechanisms by which alcohol raises or lowers risks of various diseases are only now beginning to be understood.

## Epidemiologic Studies

Despite these inherent methodologic difficulties in assessing the risks and benefits of alcohol consumption, data from various epidemiologic studies are surprisingly consistent. Dose seems to play a role in the development of various chronic diseases. There is little debate over the causal relationship of heavy alcohol intake with increased risk of death from all causes (1-5). With respect to total mortality there seems to be a J-shaped association, with a significant increased hazard among heavy drinkers (Figure 1). At higher doses there is a clear and consistent increase in all causes of mortality, which is likely to be comprised of increased risk of liver disease, certain cancers, particularly of the head and neck, and some types of cardiovascular disease such as cardiomyopathy and hemorrhagic stroke. The balance of risk and benefit appears to shift dramatically at more modest drinking levels such that moderate drinkers tend to have lower total mortality rates than those who are nondrinkers. While there is some disagreement as to the precise nadir of the curve there is general agreement that the relationship is in fact J-shaped. Variability in the location of the nadir may be the result of chance but also could reflect differences in how, what and when alcoholic beverages are consumed as well as differences in disease risk among various study populations. The basis of this association is likely to be the effect of summing the cause-specific effects.



**Figure 1.** The relationship between alcohol consumption and total mortality is a J-shaped curve (a); for cancer there is no apparent increase until higher drinking levels (b); for all cardiovascular causes the relationship is U-shaped (c); and for coronary heart disease there appears to be an L-shaped threshold effect (d).

The reduction in risk in total mortality at light to moderate levels is likely to be due to a reduction in cardiovascular disease (CVD) without dramatic increases in other causes of death. The association of alcohol consumption with CVD has been widely studied using a variety of methodologies (6-23). For cardiovascular mortality there appears to be a U-shaped association of alcohol consumption with lowest levels among moderate drinkers and increased risks

among heavy drinkers. Most studies suggest a nadir from 1 to 3 drinks per day. The reduction in CVD death at light to moderate levels appears to be largely driven by a reduction in coronary heart disease (CHD) mortality. With few exceptions, cohort studies using a diversity of methods and populations, have confirmed an inverse association between CHD and moderate alcohol consumption. A dose response relationship exists in most studies in the range of light to moderate drinking and the benefit appears to persist at higher drinking levels. In a recent meta analysis, Maclure (24) suggests an L-shaped threshold effect for nonfatal CHD with reduced risks beginning at three drinks per week and no additional benefit for more than one drink per day. This is supported by several autopsy studies which suggest that the burden of atherosclerosis at autopsy among heavy drinkers is lower than controls (25).

At higher drinking levels there appears to be an increase in noncoronary causes of cardiovascular death (cardiomyopathy, sudden death, hemorrhagic stroke) which tend to offset any benefit in terms of CHD. This then causes the cardiovascular disease curve to turn upward yielding a "U" shaped relationship.

Shaper has suggested that the inverse association of alcohol with CHD is due to the contamination of the nondrinking category with those who have reduced drinking due to pre existing coronary heart disease (26). However, this would not explain the apparent dose response relationship reported in most studies. In addition, most recent studies exclude recent ex-drinkers from the analysis and the relationship persisted, so it is unlikely that this potential bias had any impact on estimates.

The consistency of the epidemiologic data suggests more than just a chance finding. Prospective studies which reduce selection and recall bias suggest that the findings are not the result of bias but cannot eliminate the possibility of confounding which may result in an overestimation or underestimation of the true effect. Since most of the recent observational studies have controlled for the major predictors of CHD with little effect on the relationship, it is unlikely that residual confounding fully explains the association.

## **Mechanisms**

Establishing causal relationships in human disease where the size of the effect is small to moderate can be made much easier if mechanistic explanations for the association are available. A number of mechanistic possibilities has emerged from both experimental and observational epidemiologic studies of the past two decades. Alterations in plasma lipoproteins, particularly increases in high density lipoprotein (HDL) cholesterol, represent the most plausible

mechanism of the apparent protective effect of alcohol consumption on coronary heart disease. HDL cholesterol is produced primarily in the liver and intestines and is released into the blood stream. Commonly referred to as the "good" cholesterol, HDL binds with cholesterol and brings it back to the liver for elimination or reprocessing, thereby lowering total cholesterol levels in body tissues. In this way, the HDL reduces the cholesterol build-up on the arterial wall, in a sense reversing the atherosclerotic process. In addition, HDL may play a role in rendering the LDL less harmful by preventing it from becoming oxidized.

Alcohol intake clearly raises HDL cholesterol levels (27-33), but until recently it was felt that this may not be the mechanism by which alcohol exerts its protective effect. HDL cholesterol is comprised of two principal types, or subfractions: HDL2 and HDL3, each of which have a slightly different function. Early experimental studies of small sample size suggested that moderate alcohol consumption raised HDL3 but not HDL2 (34-36). The protective effect of HDL2 in reducing risk of myocardial infarction has been well documented, but data on the role of HDL3 have been less consistent (37-39). The effect of alcohol on each subfraction of HDL was recently explored in a large case-control study (40). Total HDL, as well as both HDL2 and HDL3 levels, were strongly associated with alcohol consumption (Table 1). Both subfractions were associated with a reduction in risk of myocardial infarction (Table 2). The addition of HDL, or each of its subfractions, to a multivariate model substantially reduced the association of alcohol and myocardial infarction, suggesting that the inverse association is mediated, in large part, by increases in both HDL2 and HDL3 subfractions.

**Table 1.** Level of HDL and its subfractions (mg/dL) among nondrinkers\* and those who consume three or more drinks per day.

Lipoprotein	Nondrinkers	3 or more drinks/day	P value
HDL	36.5	42.8	<0.001
HDL2	13.4	16.3	<0.001
HDL3	22.9	26.6	<0.001

\* Nondrinkers are those who drink less than one drink per month

**Table** Level of HDL and its subfractions (mg/dL) among cases of myocardial infarction and controls.

Lipoprotein	Cases	Controls	P value
HDL	35.0	43.3	<0.001
HDL2	12.1	17.7	<0.001
HDL3	22.9	25.6	<0.001

Other potential mechanisms which may contribute to the cardioprotective effect of light to moderate alcohol consumption include alterations in factors affecting blood clotting. Clot formation is an important step in the development of a myocardial infarction. A number of factors involved in maintaining the delicate balance between clot formation to protect against bleeding and clot dissolution to prevent blood clots from forming in arteries have been implicated as risk factors for myocardial infarction. Alcohol seems to affect several of these factors. One recent study suggests that alcohol consumption increases the levels of a clot dissolving enzyme, tissue plasminogen activator (t-PA) (41). Acute ingestion of alcohol can prolong bleeding time and reduce platelet aggregation (42, 43). These data are consistent with the hypothesis that alcohol consumption may reduce the chance of clot formation by enhancing the clot dissolving system or reducing the stickiness of platelets. While hemostatic factors represent a theoretical mechanism by which alcohol may reduce the risk of CHD mortality, the extent to which they contribute to lower risk beyond that of the lipid effect remains unclear.

### **Beverage Type**

Recently a great deal of research has focused on the benefits of specific alcoholic beverages. Many have postulated that the antioxidant value of phenolic substances or bioflavonoids in red wine render it more potent in reducing risk of cardiovascular disease. Oxidative damage has been postulated to play an important role in the development of atherosclerosis. Oxidation of low density lipoprotein (LDL) cholesterol has been implicated in several steps of atherogenesis, and several antioxidants have been shown to protect LDL against oxidation raising the possibility that they may reduce the risk of atherosclerotic disease. Both in vitro and in vivo studies have shown that red wine can protect LDL from oxidative damage.

Based on these findings, some investigators have postulated that red wine might reduce the risk of atherosclerosis beyond that of other alcoholic beverages. This has been offered as one possible explanation for the lower than expected CHD mortality rates in France as well as other Mediterranean countries. However, the evidence from available observational data does not clearly suggest greater benefit for wine compared with beer or distilled spirits. In general all three have been shown to reduce risks of CHD. While some studies have suggested greater benefit for wine consumption compared with other beverages (44), others have reported greatest benefit of beer (16) or liquor (22). Those studies which have reported a benefit for wine have not seen a more protective effect for red wine compared with white (42). In addition, since wine drinkers tend to be more educated and have higher incomes, it has been speculated that apparent benefits of wine consumption may be due at least in part to confounding. Crique and Ringle (45) recently reported that the ethanol content rather than the total volume or type of wine were better predictors of the reduction in risk of CHD death in a cross-cultural study.

At this point the totality of evidence suggests that the major beneficial component of alcoholic beverages is in fact the ethanol itself rather than some other component. Some researchers have speculated that how and when alcoholic beverages are consumed may have more to do with benefits rather than what is consumed. Wine tends to be consumed in modest amounts with meals which may have metabolic advantages. On the other hand liquor is often consumed at times other than mealtime. More analytic data will be required to better answer this question.

## **Recommendations**

The effects of alcohol consumption on chronic diseases are complex. The strength and consistency of the observational and experimental evidence strongly suggests a causal link between heavy drinking and total mortality as well as light to moderate alcoholic beverage consumption and reduced risks of CHD. Comparisons by beverage type suggest that it is the alcohol which is the major factor responsible for the protective association. The reduction in risk of CHD appears to be mediated largely by raising HDL cholesterol levels, though additional mechanisms remain possible. Maximal benefit in terms of CHD appears to be at the level of one drink per day. From a public policy standpoint, whether the benefits for CHD persist at heavy drinking levels or are attenuated is moot, since clear harm in terms of overall mortality outweighs any benefits in the reduction of heart disease.

While the association of alcohol and CHD is likely to be causal, any individual or public health recommendations must consider the complexity of alcohol's metabolic, physiologic, and psychologic effects. With alcohol, the

differences between daily intake of small-to-moderate and large quantities may be the difference between preventing and causing disease. A discussion of alcohol intake should be a part of routine preventive counseling. One drink per day appears to be safe, in general; however, counseling must be individualized. Other medical problems including coronary risk factors (particularly diabetes and hypertension), liver disease, tendency toward excess, family history of alcoholism and possibly breast and colon cancer should be taken into account when discussing alcohol consumption. In addition, the dose relationships in men and women appear to be different. Liver toxicities occur at lower levels among women compared to men, which does not appear to be entirely due to the difference in lean body weight. Given the complex nature of alcohol disease relationships, alcohol consumption should not be viewed as a primary preventive strategy nor should it necessarily be viewed as an unhealthy behavior.

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## How Regulatory Agencies View BELLE

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This paper was presented in part at the 15th Annual Meeting of the American College of Toxicology, Williamsburg, VA, October, 1994.

A number of scientists from regulatory agencies were invited to respond to a series of questions regarding the biological effects of low-level exposure to chemicals and the implications of those effects on the research and regulatory processes in the agencies.

### **Are the biological effects of low exposures of concern in your agency?**

It is recognized that dose response and threshold effects are central to the determination of the no-observed-adverse-effect-level (NOAEL). Some effects seen at low levels, particularly those that are hormetic (i.e., that give contradictory effects at lower dosages) directly affect determination of the NOAEL. Thus, a more concerted focus is needed to define and clarify the meaning of "adverse" in the NOAEL. There is little debate that the phenomenon of hormesis (defined as the stimulating effect of subinhibitory concentrations of any toxic substance on any organism) is of concern to the Food and Drug Administration's Center for Food Safety and Applied Nutrition.

Although the concept of hormesis has been discussed in the scientific community for a number of years, it was accorded only superficial recognition until recently. The concern centers around whether these effects occur with most toxicological endpoints, e.g., teratogenesis, mutagenesis, neurobehavioral toxicity, etc., and whether they are biologically relevant. If they occur with most toxicologic endpoints, our approaches to risk assessment will need to be

adjusted to include the concept of hormesis.

Of the types of effects that can be categorized as hormetic, the first and probably the most clear cut is that represented by damage to DNA. At high dosages of the chemical, DNA damage exceeds the rate of repair and is readily observed. At lower dosages, repair is stimulated, and as more repair than damage occurs to DNA, the net result is "protection" by the chemical, or more repair than occurs in controls. At both high and low dosages, DNA is affected.

A hormetic effect can also occur as a result of ingesting ethyl alcohol. At very high acute dosages, ethyl alcohol can affect the central nervous system and possibly cause respiratory depression. At lower dosages, it may increase the levels of high-density lipoprotein, the "good" type of cholesterol. This type of hormetic action differs from the former in that the effects of alcohol occur at various sites of action and by different mechanisms. The levels of precision used to define these hormetic effects, therefore, vary widely. The effect on DNA is at the cellular/molecular level, whereas that of alcohol is at the systemic level. Are both effects hormetic? Can our definition of the phenomenon rule out certain types of effects? This issue can be critical when we extrapolate to lower dosages, because the same site of action is assumed to be operating at the lower and higher levels of exposure. If effects are observed at one site for the high dose and at another site for the lower dose, we are not observing true hormesis. If we need to define terms, there is no better time to do so than now.

### **What are the areas of concern and what are the specific concerns?**

We are concerned about the hormesis phenomenon operating with most endpoints of toxicology, e.g., carcinogenesis, immunotoxicity, reproductive, teratogenicity, mutagenicity, and neurobehavioral toxicity. Specifically, our paradigms would need to be changed for hazard determination and risk assessment, and the basis for this change would need to be explained to industry, academia, and all regulatory agencies. Extensive discussions would be required with the international organizations we have been working with for many years. The major concern, however, would be the possible change of risk estimates, and acceptable daily exposure values. Such changes and the admission that our previous assumptions were incorrect would cause confusion and a possible loss or reduction of confidence in regulatory agencies.

### **Is the basis of concern theoretical or empirical?**

At this point, the basis of the concern is theoretical. However, that may be temporary because the information that is accumulating rapidly indicates that hormesis is operating in a number of areas of toxicology.

### **What if anything is being done to address the concern?**

Current discussions in the Division of Toxicological Research of the Center for Food Safety and Applied Nutrition have been held on whether to include this issue in the strategic issues document that is being developed. Recognizing the serious deficiency of resources for research, we decided that neither the biological effects of low-level exposure nor hormesis would be included at this time.

### **What additional proposals do you have to address these concerns?**

Regulatory agencies should initiate research by pooling ideas and resources and mounting a collaborative effort to study the existence and significance of hormetic effects in toxicology and to determine how best to respond to constituents. This approach would avoid duplication of resources and provide a cohesive and coordinated approach to a common concern, e.g., a consensus definition of "adverse" for noncarcinogenic endpoints.

### **What effect does such a response [hormesis] have on the Delaney Clause?**

Hormesis has no effect on the legislative Delaney Clause because quantitative risk assessment is not permitted for food and color additives. Thus, it does not matter that "protection" would occur at the lower dosages. As long as carcinogenesis would be shown in the study, the substance would be banned. Clearly, if the Delaney Clause is changed and the concept of threshold allowed, and if hormesis is shown to operate with some or all carcinogens, a major policy change would be needed in terms of how chemicals are regulated. As an example, risk estimates for carcinogens with thresholds would in all likelihood be set by the establishment of safety factors, as is currently done for reproductive and developmental effects. Carcinogens not known to have thresholds would undergo low-dose extrapolation to an insignificant risk. These safety factors and extrapolations would have to take into account hormetic effects at lower dosages, if they are shown to occur. It is not clear whether the Delaney Clause impacts carcinogens that may theoretically operate through thresholds, or nonlinearity on nongenotoxic mechanisms. These situations have not been tested in the courts of law.

It seems probable, however, that if hormetic effects can be demonstrated for certain carcinogens, there will be additional pressure to modify the current legislation.



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*Toxicology Excellence for Risk Assessment*

Michael Dourson gave this presentation at the American College of Toxicology in his capacity as Chief of the Systemic Toxicants Assessment Branch of the U.S. Environmental Protection Agency in Cincinnati, Ohio. The views expressed are those of the presenter and not of the U.S. EPA. Currently, Michael Dourson is the Director of Toxicology Excellence for Risk Assessment, a nonprofit corporation located in Cincinnati, Ohio.

The U.S. Environmental Protection Agency generally considers the biological effects of low level exposures in its risk assessment deliberations. In doing so, it is a common, although not exclusive, practice to divide the universe of toxicities evoked by chemical and radiation exposures into those that are thought to occur by way of a threshold (for example, noncancer effects) and those which do not (for example, cancer effects). This simple division is not exclusive, but it is useful.

In its consideration of the biological effects of low level exposures, specific concerns of the U.S. EPA encompass low dose extrapolation of toxic response, evidence of micro- or macro-nutrient needs, and hormesis. However, the primary concern of U.S. EPA is low dose extrapolation of toxic response.

For noncancer effects, the assumption that a threshold in adverse effect occurs with most individual chemicals is based primarily on theory. Low dose extrapolation occurs routinely in EPA's estimation of Reference Doses (RfDs) and Reference Concentrations (RfCs), these estimates being synonymous in practice with subthreshold doses. RfDs and RfCs have been estimated for the noncancer toxicity of hundreds of chemicals and are listed on EPA's Integrated Risk Information System.

However, evidence of an increase in toxicity at doses lower than the threshold of a chemical does exist, for example, with the macro-(e.g., water) and micro-nutrients (e.g., vitamins). In these cases, EPA estimations of RfD consider the toxicities on both sides of the threshold region, recognizing that in some individuals, such a region may be small or even absent. Examples of this balancing act can also be found in EPA's IRIS (e.g., selenium and zinc).

With noncancer toxicity risk assessment, evidence of hormesis is generally ignored. However, this might have more

to do with the current RfD or RfC model rather than a disregard of hormesis. Since the RfD or RfC is attempting to find a dose below toxicity threshold, a yet lower dose that enhances the organism's response to the toxicity of a chemical is generally irrelevant. Or perhaps another way to say this is that evidence of hormesis at doses lower than the RfD or RfC is entirely consistent with the definitions of RfD and RfC.

With cancer effects, the assumption that a threshold in adverse effect does not exist with most individual chemicals is also based primarily on theory, and more controversy exists. Low dose extrapolation occurs routinely in EPA's estimation of cancer slope factors, risk specific dose (sometimes referred to as RSDs<these estimates being associated with various upper-bound, lifetime cancer risks), and unit risks which are equivalent of the RSD in the particular environmental media of interest (e.g., drinking water). Slope factors and resulting associated quantitative values (i.e., RSDs and unit risks) have been estimated for the cancer toxicity of hundreds of chemicals and are listed on EPA's Integrated Risk Information System.

The evidence of an increase in noncancer toxicity at doses lower than a specified level of cancer risk also exists, for example, with the micro-nutrient selenium. In these cases, EPA often chooses not to estimate a cancer slope factor.

With cancer toxicity risk assessment, evidence of hormesis is often ignored or considered spurious. However, information on lower cancer incidences than control at lower doses (i.e., hormesis) may be used in the dose response model to develop the slope factor. In this situation, the hormetic response is used indirectly to affect the estimation of cancer risk.

As with many areas of science, new data force federal agencies and others to reexamine their methods for low dose extrapolations of health risk. Moreover, new models are under development that combine the estimation of health risk of both cancer and noncancer endpoints. This model development should more formally include consideration of hormesis, within the existing framework of biological effects of low level exposure.