

# COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## STATEMENT ON EVIDENCE FOR ASSOCIATION BETWEEN CONSUMPTION OF ALCOHOLIC BEVERAGES AND BREAST CANCER: UPDATE OF INFORMATION PUBLISHED BETWEEN 1995-1999

### Introduction

1. Breast cancer is the most common cancer in women and the most common cause of cancer mortality in women. Each year there are approximately 30,000 cases registered in England and approximately 11,000 deaths from breast cancer.<sup>1</sup> The aetiology of breast cancer is very complex (see paragraph 5 below). The most clearly established risk factors which are reproductive (e.g. age at first full term pregnancy, parity, age at menarche) offer limited scope for prevention. The reason for the interest in further consideration of the association between alcohol and breast cancer is that even a small risk, if causally associated with alcohol, could have serious public health implications in terms of the number of breast cancer cases attributable to drinking alcoholic beverages. An extensive literature on the association between alcohol and breast cancer was reviewed by the World Health Organisation's International Agency for Research on Cancer in 1988<sup>2</sup> and by this Committee in 1995<sup>3</sup> but both groups were unable to establish a causal association between drinking alcoholic beverages and breast cancer. The factors which prevented definite conclusions from being drawn are considered in detail in a section of this statement. As a large number of research publications have become available since 1995, including some recent studies investigating the potential mechanism by which alcohol could induce breast cancer, it is now timely for the Committee to update its assessment.

### Background to COC consideration

#### *Statement for the Interdepartmental Working Group on Alcohol (1995)*

2. The Committee first considered the epidemiological evidence for an association between alcohol and breast cancer in 1995 at the request of the Interdepartmental Working Group (IDWG) on Sensible Drinking<sup>4</sup> as part of the review of medical and scientific evidence and its interpretation of the long term effects of drinking alcoholic beverages. The Committee provided a statement to the IDWG on the evidence for alcohol and cancer at all sites and concluded that drinking alcoholic beverages causes a dose-related increase in the risk of squamous carcinomas of the upper aerodigestive tract as a whole, and for cancers of the oral cavity, pharynx, larynx, and oesophagus which was independent of the effect of smoking tobacco. There was a substantial amount of information available to members who were able to draw conclusions on dosimetry, duration and frequency of drinking alcoholic beverages and the effect of abstinence and of smoking.<sup>3</sup>

3. A substantial amount of research was available to the Committee on drinking alcoholic beverages and breast cancer in 1995. Members reviewed the 1988 IARC monograph, which provides an evaluation of four large prospective and 13 case-control studies. The Committee also reviewed seven additional prospective studies<sup>5</sup>

<sup>11</sup>, 17 new case control studies<sup>12-28</sup> and two meta-analyses<sup>29,30</sup>. In addition a number of reviews of the available information were also considered.<sup>31-33</sup> The Committee agreed that the adequacy of control for confounding by known and/or alleged risk factors for breast cancer varied in the different accounts. A dose-related association was reported in most cohort studies and in some hospital-based case-control studies. The results of population-based case-control studies did not generally support an association. A statistically significant dose-related increase in relative risk (RR) was reported in the two meta-analyses (RR at 3 drinks/day 1.38 (95% CI 1.23-1.55)). The Committee noted that the small increases in relative risk documented in epidemiological studies ranging between approximately 1.2-3 were associated with highly variable estimates of consumption (*ca* 1-60g ethanol/day). It was agreed that clear evidence of causality had not been demonstrated.<sup>3,4</sup>

4. The Committee concluded "...that while there is no decisive evidence that breast cancer is causally related to drinking alcoholic beverages, the potential significance, for public health, of even a weak association between alcohol and breast cancer is such that we recommend, in particular, that this matter be kept under review."<sup>3</sup> The Interdepartmental Working Group endorsed the COC's conclusions and the recommendation that the relationship between alcohol and breast cancer should be kept under review.<sup>4</sup>

#### *Evaluation of epidemiological data on alcohol and breast cancer*

5. The factors which may affect the adequacy and interpretation of any epidemiological studies, such as bias, confounding and errors of measurement have been discussed in detail in the Committee's guidelines for the evaluation of chemicals for carcinogenicity.<sup>34</sup> The assessment of the available epidemiological literature on drinking alcoholic beverages and breast cancer is particularly difficult as the size of the relative risk estimates reported in the literature (*ca* 1-3) are within the range where it is difficult to exclude bias and/or confounding as explanations for the results. It is therefore important to highlight the relevant factors of particular concern in interpreting studies of drinking alcoholic beverages:

*Estimating alcohol consumption data:* The difficulty in obtaining an accurate drinking history is an important cause of the observed variation in estimates of the consumption of alcohol and of relative risks for breast cancer at particular levels of drinking alcoholic beverages. Factors which affect the collection and interpretation of alcohol consumption data include inaccurate recall of drinking alcoholic beverages, leading to under reporting, changes in drinking patterns over time, cultural and regional variations in drinking habits, and differences in quantifying alcohol intakes between studies. The inadequate and inconsistent stratification of exposure groups further complicates the assessment of epidemiological data.

*Confounding:* Adequate measurement or control for confounding breast cancer risk factors is also difficult to achieve. Known risk factors for breast cancer include age, ethnic group, family history of the disease, age at birth of first child, at menarche and at menopause, history of biopsy for benign breast

disease, socio-economic status, obesity and, in pre menopausal breast cancer, history of lactation.<sup>1</sup> Other proposed risk factors have been cited, such as parity (in addition to age at birth of first child), use of oral contraceptives and hormone replacement therapy

### **Introduction to current review**

8. The Department of Health commissioned three discussion papers from its Toxicology Unit based at Imperial College of Science, Technology and Medicine to assist the Committee in its review. The first paper considered an update of the epidemiological literature from 1995 to March 1999<sup>35</sup> and the second paper was a review of the evidence (up to June 1999) on possible mechanism(s) by which drinking alcoholic beverages could induce breast cancer.<sup>36</sup> The third paper was requested by the Committee following an initial consideration of the evidence on possible mechanisms, and presented a tabulation of data on plasma and urinary sex hormones following consumption of alcohol.<sup>37</sup> The full evaluation of confounding and the demonstration of a plausible mechanism between drinking alcoholic beverages and breast cancer would be significant steps towards establishing a causal relationship. A summary of the literature reviewed in these papers is given below:

9. All of the information was evaluated in accordance with the Committee's guidelines<sup>34</sup> and also with regard to the criteria proposed by Sir Austin Bradford-Hill.<sup>38</sup> These latter criteria, which are listed below, are generally regarded as being valuable in the consideration as to whether or not an association between an outcome (in this case breast cancer) and a putative risk factor (drinking alcoholic beverages) is causal.<sup>39</sup>

#### Bradford-Hill criteria

Strength  
Consistency  
Specificity  
Temporality  
Biological gradient  
Plausibility  
Coherence  
Experiment  
Analogy

### *Objectives of current review*

10. The primary objectives of the current COC review were;
- i) To update the assessment of breast cancer in relation to alcohol consumption; to assess this risk in relation to the level and type of alcohol consumption; to examine any differences in risk between pre menopausal and postmenopausal women and/or between women using or not using exogenous hormones (oral contraceptives (OCs) and hormone replacement therapy (HRT)).
  - ii) To review the evidence relating to the mechanistic basis for an association between alcohol consumption and breast cancer.
  - iii) To assess whether any association between alcohol consumption and the risk of breast cancer can be considered as causal.
  - iv) If a conclusion regarding causality cannot be reached, to identify the nature of any additional research required to reach a definite conclusion.

### **Review of new information**

#### Update on epidemiological evidence<sup>35</sup>

11. Three new prospective studies were identified in the DH Toxicology Unit discussion paper.<sup>40-42</sup> These investigations found a small but statistically significant association between drinking alcoholic beverages and increased risk of breast cancer and thus confirmed the findings of prospective studies reviewed by the COC in 1995. A further 22 case-control studies were reported.<sup>43-64</sup> A statistically significant association between drinking alcoholic beverages and increased risk of breast cancer was reported in 17 of these studies with relative risks in drinkers estimated to be between 1.2 and 2.5. A dose-related trend for the association between drinking alcoholic beverages and breast cancer was reported in the two cohort studies where this aspect was considered<sup>40,42</sup> and in the majority of the case-control studies reviewed.<sup>45,47,50,53,57,64</sup> A significant trend between increasing alcohol consumption and relative risk of breast cancer was documented in a pooled analysis of six prospective studies.<sup>65</sup> The extent of correction for potential confounding risk factors varied between the different studies and a number of different methods for estimating alcohol consumption were used. An analysis of risks in pre menopausal and post menopausal women separately was undertaken in nine case-control studies<sup>43,45,46,48-50,59,62,64</sup> and in one pooled analysis of six prospective studies<sup>65</sup> but no conclusions could be drawn regarding these data in view of the variation in quality and results between the individual investigations. Other important variables, such as beverage type and duration and frequency of drinking alcoholic beverages were considered in a number of the epidemiology studies but no clear conclusions could be drawn from the narrative review provided.

### *COC consideration of epidemiological data*

12. The Committee noted that the DH Toxicology Unit had considered dose-response and duration of drinking alcoholic beverages and had come to similar conclusions to that reached by the COC in its 1995 review; namely that there was evidence for an association between drinking alcoholic beverages and breast cancer. Overall, there were no definitive data on an effect of beverage type on relative risk and thus the authors had concluded that most information pointed to an effect of alcohol itself rather than any congeners or other ingredients. The Committee agreed that a more comprehensive review of all the epidemiological data was required, particularly with respect to the quality assessment of the individual investigations, and suggested that the epidemiological papers should be assessed for quality using a scoring method and that a formal systematic review, and where appropriate, meta-analyses of all the epidemiological data should be undertaken. Two further epidemiological studies published after the DH Toxicology Unit report considered the evidence for a risk of breast cancer in pre menopausal women.<sup>66,67</sup> The Committee agreed that the results of these studies needed further consideration as part of the systematic review.

### Possible mechanisms for association between drinking alcoholic beverages and Breast Cancer<sup>36,37</sup>

13. The discussion paper drafted by the Department of Health Toxicology Unit identified sparse evidence for a number of potential mechanisms by which alcohol could induce breast cancer including enhanced metabolism of carcinogens<sup>68-70</sup>, increased cellular permeability to potential carcinogens<sup>71</sup>, impaired immune responsiveness<sup>72</sup>, and abnormal differentiation of mammary tissue.<sup>73</sup> A further published paper presented a hypothesis that alcohol could induce tissue and DNA damage via the formation of reactive oxygen species in breast tissue.<sup>74</sup> However, most of the available studies on mechanism examined the effects of drinking alcoholic beverages on oestrogen metabolism in humans. There was evidence from both cross-sectional and intervention studies that alcohol consumption affected oestrogen metabolism in premenopausal<sup>75,76</sup> and postmenopausal<sup>77-83</sup> women. The mechanism by which alcohol affected oestrogen metabolism was not readily apparent from these studies particularly in view of the evidence for confounding and interaction by other possible breast cancer risk factors such as obesity<sup>77</sup>, the use of oral contraceptives<sup>84</sup> and hormone replacement therapy.<sup>82</sup> One small study published after the DH Toxicology Unit review<sup>86</sup> provided evidence suggesting that among pre menopausal women there may be a group which is more susceptible to the effect of alcohol consumption on breast cancer, because of genetic differences in alcohol metabolism. The results obtained in this latter study need to be confirmed before any definite conclusions can be reached.

### *COC consideration of potential mechanisms*

14. The Committee agreed that there was now substantially more information on the potential effects of alcohol on oestrogen metabolism than was available in 1995. However the interpretation was complex and it was requested that the data be

reviewed by an independent expert endocrinologist who would advise on what effects alcohol might have on the metabolism of oestrogens in pre menopausal and post menopausal women. A further discussion paper<sup>37</sup> prepared by the Department of Health Toxicology Unit was considered together with a submission from Professor H S Jacobs (Emeritus Professor of Reproductive Endocrinology, University College Medical School, London) who provided an oral assessment of the data to the Committee. The Committee agreed with Professor Jacobs that there was sufficient evidence from the available studies in humans to conclude that drinking alcoholic beverages can elevate blood concentrations of oestrogens (particularly oestradiol) and that the data concerning oestrogen-receptor status in breast cancer suggested a plausible link between alcohol consumption and an increased risk of breast cancer.<sup>85</sup> Overall the available data suggested a plausible mechanistic link between consumption of alcohol and breast cancer mediated via an effect of alcohol on hormones. The interpretation of these data was particularly complicated and difficult; for example, the influence of confounding effects of other possible breast cancer risk factors such as obesity, use of oral contraceptives and hormone replacement therapy and their potential interaction with drinking alcoholic beverages needed to be considered carefully.

15. Some recent research has noted that the effects of alcohol on serum oestradiol concentrations occur in pre menopausal women using oral contraceptives.<sup>87</sup> The Committee agreed that further epidemiological work should consider a number of sub-groups, i.e. pre menopausal women who either used or did not use oral contraceptives and postmenopausal women who had or had not taken HRT. The Committee agreed that there were insufficient data available to describe a threshold of action for alcohol-induced elevation in oestrogens.

16. The Committee agreed that it was important to consider carefully all the available evidence relating to potential mechanisms and therefore asked the COM to update its conclusions, reached in 1995, on any new and relevant mutagenicity studies.

### **Consideration of causality**

17. The Committee felt it helpful to consider all the available evidence under the Bradford-Hill criteria which were outlined above in paragraph 9, in order to assess whether a definite conclusion on causality between drinking alcoholic beverages and breast cancer can be reached and, if not, to use the criteria to identify key areas where further work is required. An assessment of the available evidence has been tabulated as shown below.

Criterion	Evidence regarding alcohol and breast cancer	Comments
Strength	Limited. Magnitude of association is small	The RR in alcohol drinkers is modest and, even for heavy drinkers, rarely exceeds 3. However the RR for most other identified breast cancer risk factors also rarely exceed this value.
Consistency	Limited. Under review.	The available published meta-analysis by Longnecker MP <sup>30</sup> reported significant heterogeneity. A reason for marked variation in results across studies was not found. The pooled analysis of prospective studies published by Smith-Warner SA et al <sup>65</sup> found evidence of heterogeneity in results for pre menopausal women but not postmenopausal women. There is a need for a further systematic review, using all studies available to date, to evaluate heterogeneity more fully. (A DH funded study is in progress).
Specificity	Not relevant.	Cancer risk attributed to alcohol is not specific for breast cancer (e.g. prolonged alcohol consumption can induce cancers of the head and neck and oesophagus and liver). <sup>3</sup> The mechanism for alcohol induced causation of these cancers is unknown but is unlikely to be related to that for breast cancer.
Temporality	Yes	Association demonstrated in prospective studies where alcohol consumption can be studied before the occurrence of disease.
Biological gradient	Limited. Some evidence available	There is some evidence for a dose-response effect but the RR rarely exceeds 3 even in heavy drinkers. Assessment of potential confounding and bias required to reach a conclusion on this criterion.
Plausibility	Yes	Evidence for effect of alcohol consumption and elevations in blood levels of oestrogen metabolites (in particular oestradiol) documented. <sup>36,37</sup> Raised oestradiol is a risk factor for breast cancer. <sup>39</sup> The evidence therefore suggests a plausible mechanism in both pre menopausal and postmenopausal women.
Coherence	Limited	Evidence for an increased risk of breast cancer in alcoholics <sup>88</sup> and for a relatively low rate of breast cancer incidence among populations abstaining from alcohol (e.g. Mormons). <sup>89</sup> Difficult to assess this criterion on these data.
Experiment	Limited. Some evidence available.	No evidence that alcohol is carcinogenic in experimental animals. <sup>3</sup> Some evidence that alcohol affects breast tissue differentiation in animals. <sup>90</sup>
Analogy	Yes	Other causes of significantly increased oestradiol levels in exposed populations are suggested risk factors for breast cancer (e.g. use of oral contraceptives and HRT). <sup>39</sup>

18. Taking all the available data into account there is evidence to satisfy three of the criteria (temporality, plausibility, and analogy) and some limited evidence to satisfy a further four of the criteria (consistency, biological gradient coherence, and experiment). The Committee agreed that there was no evidence that alcohol is carcinogenic from experimental studies in animals. The Committee considered that the criterion of specificity was not relevant to the assessment of breast cancer risk. The Committee agreed that there was considerable evidence to support an association between drinking alcoholic beverages and increased risk of breast cancer but the magnitude of the association was small (i.e. the relative risk is modest and, even for heavy drinkers, rarely exceeds 3) and it was difficult to ascertain the nature of the dose-response relationship from the available information. The small magnitude of the association between drinking alcoholic beverages and risk of breast cancer and the complex aetiology (i.e. it is not specific to a single risk factor) of breast cancer are the

main reasons for the difficulty in reaching a definite conclusion based on the Bradford-Hill criteria. The association could be due to biases in the studies or to confounding by other breast cancer risk factors.

19. The Committee conclude that in view of the difficulty in assessing the data on drinking alcoholic beverages and breast cancer, there is need for a rigorous systematic review of the epidemiological literature using appropriate methods (i.e. meta-analysis) to identify and evaluate potential biases, confounding and heterogeneity so that an assessment of causality and risk associated with drinking alcoholic beverages can be facilitated. The Committee agreed that it would be important for any further analyses of the data to provide a population-attributable risk estimate for the U.K. The Committee subsequently agreed an outline proposal for a meta-analysis study prepared by a research team from Imperial College of Science, Technology and Medicine. The study has been commissioned by the Department of Health and was initiated in December 1999. A draft report should be available for scrutiny by the Committee in approximately 18 months time. The Committee was also aware that additional relevant data on alcohol consumption and risk of breast cancer from the Oxford Collaborative Group on Hormonal factors in Breast Cancer would be forthcoming and should be reviewed when available.

### **Conclusions of current review**

20. The Committee reached the following interim conclusions based on its updated review of the published literature since 1995.

i) There is an association between drinking alcoholic beverages and increased risk of breast cancer. It is difficult to resolve whether this is causal. The magnitude of the observed association is small (i.e. the relative risk is modest and, even for heavy drinkers, rarely exceeds 3) and within the range where it is difficult to exclude bias and/or confounding as explanations for the observed results in epidemiological studies. It is difficult to derive a quantitative relationship from the dose-response data available in the literature.

ii) Further epidemiological studies have been published since 1995. There is a need for further systematic review of the epidemiological literature to assess fully the influence of bias, confounding and effect modification. This will contribute to a conclusion on causality and population attributable risk associated with drinking alcoholic beverages.

iii) Studies of possible mechanisms provide evidence for a plausible basis for the causation of breast cancer by consumption of alcohol. Alcohol increases blood levels of oestrogens and in particular oestradiol in both pre menopausal and postmenopausal women. These data suggest a similar mechanism to other known breast cancer risk factors.

iv) The COM should be asked to update its opinion of 1995 on the mutagenicity data on alcohol.

**April 2000**

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