TOX/2021/25

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

Alcohol in the maternal diet. The 2016 Chief Medical Officers Report

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.

2. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

3. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice. This subject was initially discussed during the horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee in July 2020. This included background information on a provisional list of chemicals proposed by SACN. It was noted that the provisional list of chemicals was subject to change following discussion by COT who would be guiding the toxicological risk assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate.

4. An initial paper discussing and prioritising the proposed chemicals for review was considered at the February COT meeting and the second part is on the agenda for this meeting. During the February discussions, it was asked whether alcohol should be considered. Alcohol per se is not within the SACN remit but the maternal health working group scope states: *wider health issues outside the remit of this risk assessment may also be considered in the background section…such as non-food related toxicological issues, such as alcohol consumption and smoking…* Alcohol could be considered by SACN in relation to energy intake, depending on the data available.

5. As the database for the potential effects of alcohol in pregnancy is extensive, the Secretariat agreed to identify what the most recent recommendations were and what data they had been based on in order to establish whether further work in this area would be of value.

Current recommendations and how they were derived.

6. The UK Government (NHS, 2021) suggests that women who are pregnant or trying to become pregnant should avoid alcohol altogether. However, the NHS website notes that "Experts are still unsure exactly how much- if any- alcohol is completely safe to have while you are pregnant".

7. The advice is based on recommendations from the 2016 Low Risk Drinking Guidelines produced by the UK Chief Medical Officers in 2016 (DH, 2016) which covered numerous health and societal outcomes. This report states that if a woman is pregnant or planning a pregnancy, the safest approach is not to drink alcohol at all. It is noted that drinking during pregnancy could result in harm to the baby with the risk increasing with the amount consumed. The guidelines further note that the risk to the baby is likely to be low if only small amounts of alcohol have been drunk before a woman knew she was pregnant or during pregnancy. This advice replaced the 2007 guidance which stated "Women who are pregnant or trying to conceive should avoid alcohol altogether. However, if they do choose to drink, to minimise the risk to the baby, we recommend they should not drink more than 1-2 units once or twice a week and should not get drunk" (quoted Jones and Bellis, 2016).

8. Supporting detail on the CMO low risk drinking guidelines is given in the Alcohol Guidelines review report (DH, 2016). This explains that the guidelines were based on reports commissioned by the CMOs from the Health Evidence Expert Group and the Behavioural Expert Group (this latter considering evidence for the impact of guidelines on changing behaviour which has not been considered further). For the health outcomes it was noted that, the Health Evidence Expert Group considered the evidence from 44 systematic reviews and meta analyses published since 1995 when the previous Sensible Drinking report had been published. Experts from Australia and Canada were also consulted who had recently updated their guidelines.

9. In the rationale for the recommendation on pregnancy made by the Health Evidence Expert Group report, it is noted that "Despite some new studies concerning the effects of alcohol in pregnancy…definitive evidence particularly on the effects of low levels of consumption remains elusive".

10. The evidence considered by the Health Evidence Expert Group report is mapped in an overview document (Jones and Bellis, 2016) which states the following.

> "The recent guidelines on the consumption of alcohol during pregnancy took into account the findings of a systematic review that evaluated the foetal effects of low to moderate prenatal alcohol exposure (equivalent to maximum 1.5 units or 12 g of alcohol daily) and binge drinking (most often defined as five or more drinks on any one occasion). The review did not find consistent evidence of adverse effects from low-to-moderate prenatal alcohol consumption, however the authors noted that the evidence was not strong enough to rule out any risk. Most of the studies included in the review that examined risk of preterm birth, stillbirth and miscarriage found no association with low to moderate alcohol intake, and studies that did report increased risk

had significant limitations. Gray and Henderson also examined the foetal effects of binge drinking finding that there were no consistently significant effects; with the exception of an indication of generally small effects on neurodevelopmental outcomes. They concluded that "at relatively low amounts of alcohol and infrequent occasions of binge-drinking, there is no consistent evidence of adverse effects. However, greater frequency of bingeing or higher levels of alcohol consumption may increase the risk of adverse foetal effects". Taken together the evidence appears to suggest that the risk of foetal effects arising from single or rare episodes of binge-drinking not associated with a consistently high intake of alcohol may be small.

Since 2008, a meta-analysis has been published that investigated the effect of alcohol consumption during pregnancy on the risk of low birth weight, preterm birth and small for gestational age. Alcohol consumption during pregnancy was associated with higher risk of developing all three complications. The meta-analysis shows that risk was elevated at consumption greater than 1-2 units per day and increased in a dose-dependence fashion thereafter. Both Henderson et al. and Patra et al. acknowledge weaknesses in the evidence base which preclude the assumption that consumption below these levels during pregnancy may be considered 'safe'. Henderson et al. suggest that one possible explanation for a lack of evidence of harm from small amounts of alcohol may be related to the 'healthy drinker effect'. That is, much like the sick quitter hypothesis (as discussed in Section 3), women with a poor obstetric history may be more likely to abstain from alcohol".

11. The following table is also provided:

Summary of risk relationship between alcohol consumption in pregnancy and conditions originating in the perinatal period

Condition	**Risk relationship[a] based on average volume of consumption[b] per day**	**Source(s)**
Low birth weight	Threshold; harmful effects >1 unit; monotonic thereafter. Inadequate evidence for a causation of alcohol during pregnancy at levels of consumption below this	Patra et al., 2011; Henderson et al, 2007 a,b
Preterm birth	Threshold; harmful effects >2 units. Inadequate evidence for a causation of alcohol during pregnancy at levels of consumption below this.	Patra et al., 2011; Henderson, et al 2007, a,b

Small for gestational age/Intrauterine growth restriction	Threshold; evidence of harmful effects >1 unit. Inadequate evidence for a causation of alcohol during pregnancy at levels of consumption below this.	Patra et al., 2011; Henderson et al, 2007 a,b
Miscarriage	Inadequate evidence for a causation of alcohol during pregnancy at low to moderate levels of consumption.	Henderson et al, 2007 a,b
Stillbirth	Inadequate evidence for a causation of alcohol during pregnancy at low to moderate levels of consumption.	Gray & Henderson, 2007
Malformations	Inadequate evidence for a causation of alcohol during pregnancy at low to moderate levels of consumption	Gray & Henderson, 2007 a,b
Neurodevelopmental outcomes	Some evidence of a possible effect of binge drinking (five or more drinks on a single occasion; equivalent to 60g / 7.5 units).	Henderson et al., 2007

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a *Monotonic* = increasing risk as the average volume of alcohol consumption increases. *Nadir* = lowest point of the curve for conditions with a U or J-shaped relationship. *Reversion point* = point on the curve where alcohol consumption becomes detrimental.

b Number of units approximated from grams of alcohol (1 unit ≈ 8 grams). Based on risk estimates presented in the document *Mapping systematic review level evidence* for conditions with sufficient evidence of an association with alcohol consumption from Rehm et al (2010).

12. The key references used by the Health Evidence Expert Group are described below:

Gray and Henderson (2006)

13. Gray and Henderson (2006) is the report of a systematic review commissioned by the Department of Health which focussed on the effects of low-moderate pre-natal alcohol exposure (up to 12 g (approximately 1.5 units) alcohol/day) and binge drinking (5 or more drinks on a single occasion). The search period covered 1970-2005 and from 3630 papers subsequently narrowed down to 395 papers read in full by 2 independent researchers, 74 were included (of which 8 were unobtainable). The studies were case-control, cohort or cross-sectional. The papers were assessed for quality using the Newcastle-Ottawa Quality Assessment scales. Where authors had not provided effect measures with confidence intervals or had not tested statistical significance for their findings these were calculated from the summary statistics where possible.

14. The overall conclusion of the report was that "for most outcomes there was no consistent evidence of adverse effects from low-to moderate prenatal alcohol consumption. Nevertheless, the evidence is probably not strong enough to rule out any risk. There was some evidence of adverse effects on neurodevelopment of binge drinking during pregnancy". Binge drinking has not been considered in this paper.

15. For low-moderate pre-natal alcohol exposure, the conclusions for individual endpoints are reproduced below:

- *Spontaneous abortion - There were eight studies which examined the effect of low-to moderate alcohol consumption on this outcome. Although five of these reported a significant effect, two had significant limitations, and in one paper the only significant result was amongst heavy smokers. The remaining two studies reported results of borderline statistical significance.*

- *Stillbirth - None of the five studies which examined this outcome found a significant effect of low-to-moderate drinking in pregnancy. Three studies reported higher rates of stillbirth in women who abstained but these were not statistically significant differences and were unadjusted for potential confounders.*

- *Antepartum haemorrhage - There was only one study which examined this outcome and no significant differences were found.*

- *Intrauterine growth restriction - Only one of the seven studies which examined this found a significant association and that was unadjusted for potential confounders. Three studies found low-to-moderate alcohol consumption to be mildly protective but, although of borderline statistical significance, two may have been subject to recall bias.*

- *Birth weight - Of the 20 studies which included birth weight as an outcome, only one reported a significant excess of low birth weight associated with low-to-moderate alcohol consumption in pregnancy. This result was inconsistent in that higher levels of consumption were not associated with increased risk. Small amounts of alcohol appeared to exert a mildly protective effect.*

- *Preterm birth - As with birth weight, only one study out of 16 reported a significantly increased risk of preterm birth. This study may be subject to residual confounding as it was unadjusted for socioeconomic status.*

- *Malformations - None of the seven studies that examined this outcome found a significant association.*

- *Head circumference and birth length - Of the five studies reporting on these outcomes, one found a higher proportion of low birth weight babies among those whose mothers drank low-to moderate amounts in pregnancy. However, the tests of statistical significance were across the whole range of exposure so interpretation of this difference was problematic. Moreover, there was no adjustment for potential confounders in this analysis. None of the other studies reported any differences at these levels of consumption.*

- *Postnatal growth - There were only two studies which examined the association between alcohol exposure and growth as measured in childhood. One of these studies, which followed children up to age 14, found that children of women who drank small amounts in pregnancy were consistently lighter with smaller head circumference. However, the other study found the opposite, 3 that children of abstainers tended to be lighter with smaller head circumference. However, neither of these studies reported the statistical significance of these findings and there were significant other problems with the second one.*

- *Neurodevelopmental outcomes - Of the seven studies which looked at this outcome, one was conducted at birth, the others were later in childhood. Only one study found small but significantly poorer results in children of low-to-moderate drinkers. However, this analysis was unadjusted for potential confounders.*

Henderson et al (2007a.b)

16. The paper by Henderson et al (2007a) is a systematic review of 46 relevant studies examining the effects of low-moderate maternal alcohol exposure (up to 84 g alcohol/week, approximately 10 units of alcohol) in the pre-natal period compared to abstainers. The search period covered 1970-2005 and the 3630 papers initially identified were narrowed down to the 46 papers included in the review). The studies considered were case-control, cohort or cross-sectional. A meta-analysis was not considered appropriate due to the heterogeneity of the methods used. The papers were assessed for quality using the Newcastle-Ottawa Quality Assessment scales. The outcomes considered were miscarriage, stillbirth, intrauterine growth restriction (IUGR), prematurity, birthweight, SGA at birth and malformations including fetal alcohol syndrome. The authors noted that at low to moderate exposure there were no consistently significant effects on any of the end points but that many of the studies had methodological flaws. The results for the individual endpoints are as below:

- Miscarriage. Eight studies were available, of these 5 reported an increased risk of miscarriage in women consuming less than 84g alcohol/week. Two of the studies had significant limitations, in a third the result was only significant in heavy smokers and in the remaining two studies, the findings were of borderline significance.

- Stillbirth. Five studies were available, of these three found an increased risk in women who did not drink. All of the studies had significant limitations. The only study not reporting results not subject to recall bias and adjusting for confounding reported that low to moderate alcohol consumption was associated with a slightly increased risk of stillbirth, but this was not statistically significant.

- Impaired growth. Seven studies considered IUGR or SGA. Only one of the studies reported an association but this was not adjusted for potential confounders and was potentially misleading.

- Birthweight. Nineteen cohort studies considered birthweight. There were few statistically significant results. Six of the studies did not adjust for smoking, which is known to be associated with birthweight. Similarly, the majority of the studies did not adjust for ethnicity which is also associated with birthweight. One study reported an increased risk at less that 2.4 g/ alcohol per day, but the extent of the risk was reduced at 2.4 to 6g/day. Other studies reported a slightly protective effect.

- Pre-term birth. Sixteen studies were available (2 case-control and 14 cohort). Different methods of age were used. Nine of the studies were adjusted for confounding although sometimes this was in analyses where alcohol consumption was more broadly grouped or when other associations were being examined. All except one study reported no effects or a reduced risk of prematurity; the one US study reporting an increased risk was not adjusted for socio-economic factors.

- Malformations. Six studies examined the association between low-moderate alcohol consumption and malformations. Only one of these reported significant associations but this included only white women and had not been adjusted for confounders.

17. The authors noted that the protective effect reported in some studies and considered that this might be due to the healthy drinker effect, since women with a poor obstetric history might be more likely to abstain from alcohol and that further work would be necessary to establish if there was a genuine protective effect.

18. Overall it was concluded that there was no convincing evidence of adverse effects form low-moderate pre-natal alcohol exposure but that weaknesses in the evidence base precluded the conclusion that it was safe.

19. Henderson et al (2007b) is a systematic review of studies related to the effects of binge drinking and has not been considered further.

Patra et al (2011)

20. The paper by Patra et al (2011) (abstract only available) is a systematic review and meta-analysis of 36 eligible case control or cohort studies examining the effect of maternal alcohol exposure on the risk of low birthweight, pre-term birth and small for gestational age (SGA). Two reviewers independently extracted the information on these endpoints using a standardised protocol. Meta-analyses on dose-response relationships were performed using linear as well as first order and second order polynomial regressions to estimate best fitting curves to the data. The main results reported were that compared with abstainers, the overall dose response relationship for SGA and low birth weight did not show any effect as up to 10 g alcohol/day (approximately one drink). For pre-term birth there was no effect at up to 18 g/day. Thereafter the dose response relationship showed a monotonically increasing risk for maternal alcohol consumption. Moderate consumption pre-pregnancy was associated with reduced risks for all outcomes. The authors concluded that heavy alcohol consumption during pregnancy increased the risks of all three outcomes, whereas light to moderate consumption had no effect

Current literature

21. The available literature on the adverse effects of alcohol is potentially extensive. For example, a limited search of PubMed suggests that since 2011, 752 papers have covered alcohol toxicity in pregnancy. Taking a similar approach, to the Health Evidence Expert Group, a number of additional systematic reviews or meta-analyses have been identified which consider low-moderate alcohol exposure. The outcomes of these are briefly summarised in the table below:

Endpoint	**Outcome**	**Comment from authors**	**Reference**
Miscarriage	Meta-analysis of 24 studies. Risk of miscarriage increased compared to abstainers. If five or less drinks/week each additional drink increases risk by 6%		Sundermann et al., 2019.
Oral clefts	Meta-analysis of 9 studies. No overall association. Association with binge drinking only in some studies.	Prudent to avoid binge drinking.	Yin et al., 2019.
Oral clefts	Systematic review and meta-analysis	Influence of design cannot be ignored. Considerable	Bell et al., 2014.

	of 33 studies. No association found	heterogeneity in studies.	
SGA	Meta-analysis of 26 studies. Limited evidence for association	Need for precautionary advice	Mamluk et al., 2017.
Low birth weight	Association found in retrospective cohort studies only. None in prospective cohort or case control studies.	High heterogeneity	Pereira et al., 2019.
Low birth weight	Pooled sample of 9 European cohorts. 6 or more drinks/week associated with lower birth weight	Analysis designed to consider bias over time. But results still indicative of bias.	Strandberg Larsen et al., 2017.
Low birth weight	Pool of 2 large European studies. No association found.		Pfinder et al., 2014
Low birth weight	Systematic review of 23 studies. Weak evidence for causal role.	Caution in interpretation needed. No studies at low risk of bias.	Mamluk et al (2021)
Pre-term birth	Pool of 2 large European studies. No association limited evidence but not pre-term birth		Pfinder et al., 2014
Pre-term birth	Meta-analysis of 26 studies. Limited evidence for association but also consistent with no association.	Need for precautionary advice	Mamluk et al 2017
Pre-term birth	Pooled sample of 9 European cohorts. 6 or more drinks/week associated with	Analysis designed to consider bias over time.	Strandberg Larsen et al., 2017

	reduced risk of pre-term birth		

22. Systematic reviews or meta analyses of other endpoints have also been performed which could be relevant; these include success with assisted reproductive techniques and in the offspring, congenital heart defects, neurodevelopmental endpoints such as language development and ADHD, and various types of cancer. In general, the findings are comparable with those above, limited evidence of associations and identified issues with study quality. Numerous primary studies have also been published. The effects of binge drinking have not been considered.

Summary and Discussion

23. The 2016 report by the UK Chief Medical Officers is the most recent review of alcohol consumption during pregnancy, either in the UK or internationally. Pregnant women, or women trying to conceive are advised that abstinence from alcohol is the safest approach but that low levels of alcohol consumption are likely to be of low risk and it is noted that the data at low levels of intake are very uncertain. Advice elsewhere in the world is consistent with this view.

24. The available literature on the adverse effects of alcohol is potentially extensive. Taking a comparable approach to the Expert Health Advisory Group, there have been a number of systematic reviews or meta-analyses conducted since 2011 covering the end points they identified, but the results appear to be inconclusive and methodological failings are generally noted. Primary studies and systematic reviews of other end points have been also published.

25. Given the work and resources that reviewing this area could involve, Members will wish to consider whether the likely outcome would materially change the current advice to women. If Members do feel it would be appropriate to undertake such work their thoughts on what the best approach would be valuable.

Questions for the Committee

26. Do Members have any comments on:

a) The CMOs 2016 report
b) The data published since 2011
c) Whether there is any value in undertaking a further review
d) If such a review was undertaken, what would the most appropriate approach be for i) endpoints to be considered, ii) types of study to include, iii) anything else that should be considered.
e) Do Members need to see any additional information before reaching a decision?
f) Do Members have any other comments.

Secretariat
2016

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