Epidemiology-based risk assessment using the benchmark dose/margin of exposure approach: the example of ethanol and liver cirrhosis

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Accepted 22 July 2010

Background A novel approach to derive a threshold dose with respect to alcohol-related harm, the benchmark dose (BMD) methodology, is introduced to provide a basis for evidence-based drinking guidelines. This study is the first to calculate a BMD for alcohol exposure using epidemiological cohort data. With this BMD we will be able to calculate the margin of exposure (MOE) for alcohol consumption, which can be used for comparative risk assessment and applied to setting public health policy.

Methods Benchmark dose–response modelling of epidemiological data gathered during a recent systematic review and meta-analysis of alcohol consumption as a risk factor for liver cirrhosis morbidity and mortality.

Results For a benchmark response (BMR) of 1.5%, the resulting BMD values were 30.9 g/day for males and 29.7 g/day for females; the corresponding lower one-sided confidence values were 25.7 and 27.2 g/day, respectively. The intake scenario for the Canadian population resulted in an MOE of 1.23. Intake scenarios for individuals as based on the Canadian drinking guidelines led to MOE values between 0.96 and 1.91. Using an uncertainty factor of 10, the acceptable daily intake for alcohol would be 2.6 g/day.

Conclusions The BMD approach was feasible in developing evidence-based guidelines for low-risk drinking. As our calculated MOEs result around unity (i.e. 1) for moderate drinking, it is evident that the current guidelines correspond very well to low risk on the dose–response curve. The BMD methodology therefore validates current guidelines. The results again highlight the health risk associated with alcohol consumption.

Keywords Alcohol, ethanol, alcoholic beverages, liver cirrhosis, risk assessment, dose–response relationship, margin of exposure, benchmark dose, epidemiological methods
Introduction

In the public health-risk assessment of alcoholic beverages, the derivation of a threshold dose or a tolerable upper alcohol intake level is fundamental in providing scientifically founded drinking guidelines. Previous approaches include interpretations of single epidemiological dose-response studies on all-cause mortality (e.g. Hoffmeister and colleagues defined the threshold as the point within a dose-response model at which the response starts to rise\(^1\)), non-formal attempts to interpret the literature by expert committees,\(^2\) the use of cumulated lifetime risk\(^3\) and use of the more formal ‘no observed adverse effect level’ (NOAEL) methodology with an uncertainty factor for deriving an ‘acceptable daily intake’ (ADI) level.\(^4\)-\(^6\)

All of these methods have substantial limitations. The single-article approach is problematic as it is based on one underlying distribution of deaths and is fraught with measurement problems of exposure, especially since most cohort studies have only one baseline measurement.\(^7\) Any intuitive or non-formal interpretations are subjective, as a consequence different committees using this method have had vastly different results.\(^8\) The lifetime method has often been based on models that do not allow for variation in drinking over an entire lifespan, essentially disregarding the potential problem of differential impact of drinking patterns:\(^9\) the effect of one standard drink per day in a week is different when consumed as all seven on a single day as opposed to one per day. Finally, the NOAEL/ADI is problematic when there is a dose-response relationship with no apparent threshold, as is the case for some alcohol-attributable endpoints, such as certain cancers\(^10\) (for breast cancer, as an example, the largest pooled study on breast cancer shows significant effects for lower than one drink daily\(^11\)). In such a situation, the NOAEL and subsequent threshold dose for the minimal risk value will be very low, possibly even 0. However, from a public health perspective, the risk of cancer at higher levels may be in fact counterbalanced by the protective effects of alcohol on ischemic disease and diabetes (for an overview of the effects of alcohol on disease see Rehm et al.\(^12\)).

One of the most promising alternatives to the NOAEL/ADI approach is the benchmark dose (BMD) methodology.\(^13\) Based on dose-response modelling, the BMD is the point on the dose-response curve that characterizes adverse effects. This value can then be used in combination with exposure data to calculate a margin of exposure (MOE) for quantitative risk assessment. The MOE is defined as the ratio between the BMD and estimated human intake of the same compound. It can be used to compare the health risk of different compounds and in turn prioritize risk management actions. By definition, the lower the MOE, the larger the risk for humans; generally, a value <10,000 is used to define public health risks.

The BMD approach was developed by Crump in 1984,\(^14\) and has since been adopted by the US Environmental Protection Agency (EPA),\(^15\) as well as the European Food Safety Authority (EFSA),\(^16\) mainly in the area of risk assessment of genotoxic carcinogens. In later years, the BMD approach was broadened to other agents with a wide range of effects (e.g. pesticides, mycotoxins and natural toxins),\(^17\) as well as macroconstituents in food such as sugar and fat.\(^13\) Originally and traditionally in regulatory toxicology, data from animal experiments were used for BMD modelling: \(^14,17-21\) only more recently has the approach been applied with epidemiological data (e.g. for risk assessment of mercury,\(^22\) methylmercury,\(^23,24\) arsenic,\(^25,26\) cadmium,\(^27\) chromium,\(^28\) lead,\(^29\) styrene\(^30\) or respirable coal mine dust\(^31\)). It should be noted that calculations generally use the lower one-sided confidence limit of the BMD (BMDL) as the point of departure.

In the alcohol field, the BMD methodology was applied in a study of 1100 Japanese salesmen to find thresholds for the effect of alcohol on blood pressure and biochemical markers for liver injury.\(^32,33\) The BMD/MOE model was also used to evaluate the carcinogenic substances acetaldehyde and ethyl carbamate in alcoholic beverages.\(^34-37\) In the carcinogenic potency project, a large-scale cancer risk assessment utilizing analyses of animal cancer tests, Gold et al.\(^38\) based on rodent data, estimated an MOE of 3 for alcoholic beverages (daily consumption of 22.8 ml ethanol), which was the highest risk for non-occupational exposures in the entire project.

In this study, we will be the first to calculate a BMD and BMDL for daily alcohol consumption based on epidemiological (cohort) data, specifically the excess lifetime risk for liver cirrhosis, which is the most important single fatal chronic disease condition attributable to alcohol globally.\(^39,40\) Plausibility will be assessed by comparison with the other previously discussed approaches as well as comparison with BMD modelling of animal experiments. With this BMD we will be able to calculate the first MOE for alcohol consumption based on epidemiology, which can be used for comparative risk assessment (e.g. between ethanol itself and other health-relevant substances contained in alcoholic beverages) and applied to setting public health policy.

Methods

Epidemiological and animal data

The epidemiological data gathered during a recent systematic review and meta-analysis of alcohol consumption as a risk factor for liver cirrhosis morbidity and mortality in humans was re-evaluated to allow for benchmark modelling.\(^40\) According to the methodology of Morales and Ryan\(^25\) for BMD estimation based on epidemiological cohort data, a dose-response
model between dose and excess lifetime risk should be used to calculate the BMD. In this case the risk relations from the meta-analysis were re-calculated to estimate the excess lifetime risk for the Canadian population for several average volumes of daily average drinking (see Rehm et al. for details of the general methodology of calculating excess risk).

Additionally, as a sensitivity analysis, animal experiments regarding the effect of ethanol on the liver and suitable for dose–response modelling, were identified using the recent literature review of the International Agency for Research on Cancer. Most animal studies demonstrating the causal relationship between ethanol ingestion and liver injury were unfortunately unsuitable for dose–response modelling, as only single dose levels were compared with controls. A notable lifetime carcinogenicity study by Soffritti et al. again did not meet the criteria, as it also only researched a single dose level. Only the 2004 National Toxicology Program (NTP) 2-year rodent bioassay contained data meeting the criteria for the modelling of the dose–response relationship for lifetime exposure to ethanol.

**BMD and MOE calculation**

The BMD and BMDL were calculated for the epidemiological data using the methodology presented in Morales and Ryan. A benchmark response (BMR) of 1.5% referring to excess risk was selected as this response was in the experimental range for both sexes. The BMD was then found by backsolving from an excess risk of 1.5% to the corresponding alcohol intake. The BMDL was estimated in the same way as BMD by finding the exposure that corresponded to 1.5% on the upper confidence limit for BMD. For comparability, we also calculated BMD and BMDL values using the US EPA’s BMDS 2.1.1 software (available for free at the US Environmental Protection Agency website: http://www.epa.gov/ncea/bmds/index.html). The data from animal experiments were also evaluated using this software.

The EFSA harmonized approach, as previously mentioned, was used to conduct the dietary intake assessment. For this, relevant substance-specific dietary intake estimates in humans are needed. Such data on alcohol consumption were obtained from the Global Information System on Alcohol and Health (GISAH) based on data primarily from the Food and Agriculture Organization for the year 2002 (averaged from 2001 to 2003) for the population >15 years of age. The data on unrecorded consumption were also based on estimated volume for the population >15 years of age. The MOEs were calculated by dividing the reference point, in this case the BMDL, by the estimated human intakes, based on either Canadian data as derived from the triangulation of survey and per capita data, or low-risk drinking guidelines for Canada (13.6 g pure alcohol per standard drink). The ADI was calculated according to the guidelines of the WHO International Programme on Chemical Safety (IPCS).

**Results**

The excess lifetime risk for alcohol-related liver cirrhosis dependent on daily alcohol consumption amount is shown in Table 1. These data were used

<table>
<thead>
<tr>
<th>Alcohol consumption (pure alcohol g/day)</th>
<th>Rate of alcohol attributable liver cirrhosis mortality for every 100 000 population</th>
<th>Excess mortality (%)</th>
<th>Excess mortality 95% CI upper boundary (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>10</td>
<td>5.5</td>
<td>6.2</td>
<td>0.60</td>
</tr>
<tr>
<td>20</td>
<td>10.0</td>
<td>7.7</td>
<td>1.09</td>
</tr>
<tr>
<td>30</td>
<td>13.6</td>
<td>8.5</td>
<td>1.48</td>
</tr>
<tr>
<td>40</td>
<td>16.4</td>
<td>9.0</td>
<td>1.79</td>
</tr>
<tr>
<td>50</td>
<td>18.7</td>
<td>9.4</td>
<td>2.03</td>
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<tr>
<td>60</td>
<td>20.4</td>
<td>9.6</td>
<td>2.22</td>
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<tr>
<td>70</td>
<td>21.8</td>
<td>9.8</td>
<td>2.36</td>
</tr>
<tr>
<td>80</td>
<td>22.8</td>
<td>10.0</td>
<td>2.48</td>
</tr>
<tr>
<td>90</td>
<td>23.6</td>
<td>10.1</td>
<td>2.56</td>
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<tr>
<td>100</td>
<td>24.2</td>
<td>10.2</td>
<td>2.63</td>
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<tr>
<td>110</td>
<td>24.6</td>
<td>10.3</td>
<td>2.68</td>
</tr>
<tr>
<td>120</td>
<td>25.0</td>
<td>10.4</td>
<td>2.72</td>
</tr>
<tr>
<td>130</td>
<td>25.3</td>
<td>10.4</td>
<td>2.74</td>
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<tr>
<td>140</td>
<td>25.5</td>
<td>10.5</td>
<td>2.77</td>
</tr>
</tbody>
</table>

CI, confidence interval; M, male; F, female.
to calculate the BMD and BMDL as shown in Figures 1 and 2. For a BMR of 1.5%, the resulting BMD1.5 values were 30.9 g/day for males and 29.7 g/day for females; the corresponding BMDL1.5 values were 25.7 and 27.2 g/day, respectively. Calculated for persons weighing 60 kg, the values were very similar for both sexes, with an average BMD1.5 of 0.52 g/kg bw/day and a BMDL1.5 of 0.43 g/kg bw/day.

Using the US EPA BMDS software, very similar values to our calculations were obtained. The dichotomous hill model had the best fit, with P-values of 0.9722 (male) and 0.9992 (female). The BMD1.5 values were 29.8 g/day for males and 27.9 g/day for females; the corresponding BMDL1.5 values were 29.0 and 25.1 g/day, respectively. As the EPA software does not calculate based on experimental confidence limits, we gave preference and used the data calculated from our own models.

The data of the NTP animal study allowed for the BMD calculation with the usual BMR of 10%, as well as 1.5% for comparison with the epidemiological results. According to the authors of the NTP study, the incidence of hepatocellular adenoma or carcinoma in male B6C3F1 mice administered ethanol in drinking water for 2 years was significant (P < 0.05) dose-related trend with respect to ethanol (% in drinking water) (Table 2). We therefore used this endpoint for dose–response modelling. From the model choices available in the US EPA software, the multistage cancer model showed the best fit with a P-value of 0.9689 (Figure 3). The BMD10 and BMDL10 were 2.07 and 0.72 g/kg bw/day, and the BMD1.5 and BMDL1.5 were 0.78 and 0.10 g/kg bw/day, respectively.

Table 3 shows the values determined in this study as compared with those found in the literature, which are in reasonable agreement (see Discussion section). The comparison therefore substantiates the
Table 3  Summary of own dose–response modelling results for ethanol in epidemiological cohort studies and animal experiments (data from Figures 1–3) and comparison with literature data

<table>
<thead>
<tr>
<th>Modelling</th>
<th>Data source</th>
<th>Endpoint</th>
<th>BMD1.5&lt;sup&gt;a&lt;/sup&gt; (g/kg bw/day)</th>
<th>BMDL1.5&lt;sup&gt;b&lt;/sup&gt; (g/kg bw/day)</th>
<th>BMD10&lt;sup&gt;a&lt;/sup&gt; (g/kg bw/day)</th>
<th>BMDL10&lt;sup&gt;b&lt;/sup&gt; (g/kg bw/day)</th>
<th>Conventional threshold dose (g/kg bw/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>Rehm et al.&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Human epidemiology, liver cirrhosis in Canadian population</td>
<td>0.5</td>
<td>0.4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>This study</td>
<td>NTP&lt;sup&gt;48,49&lt;/sup&gt;</td>
<td>Rats, hepatocellular adenoma or carcinoma</td>
<td>0.8</td>
<td>0.1</td>
<td>2.1</td>
<td>0.7</td>
<td>–</td>
</tr>
<tr>
<td>Gold et al.&lt;sup&gt;38&lt;/sup&gt;</td>
<td>(No information provided)</td>
<td>Rodent cancer dose (rats)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.93&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Dakeishi et al.&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Original data</td>
<td>Liver markers in Japanese men</td>
<td>BMD2 0.27&lt;sup&gt;d&lt;/sup&gt;</td>
<td>BMDL2 0.32&lt;sup&gt;d&lt;/sup&gt;</td>
<td>BMD5 0.60&lt;sup&gt;d&lt;/sup&gt;</td>
<td>BMDL5 0.69&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Dakeishi et al.&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Original data</td>
<td>Blood pressure in Japanese men</td>
<td>BMD2 0.56&lt;sup&gt;c&lt;/sup&gt;</td>
<td>BMDL2 0.45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Hoffmeister et al.&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Original data</td>
<td>Liver markers in the German population</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.08 (F), 0.43 (M)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sillanaukee et al.&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Original data</td>
<td>Liver markers in the Finnish population</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.14 (F), 0.18 (M)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Burger et al.&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Literature review</td>
<td>Different endpoints including liver cirrhosis and cancer</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.16–0.20 (F), 0.33–0.40 (M)&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Victorin et al.&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Literature review</td>
<td>Liver effects and cancer, low birth weight</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.2–0.4 (F)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rydberg and Skerfving&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Literature review</td>
<td>Liver cirrhosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.1&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>BMD: benchmark dose for a 1.5 or 10% incidence of health effect.

<sup>b</sup>BMDL: lower one-sided confidence limit of the BMD.

<sup>c</sup>LTD10 value, which should be comparable with BMDL10 value. LTD10 is the lower 95% confidence limit on the dose to induce tumours in 10% of animals. The LTD10 value was estimated by re-calculation from a TD50 value. See Gold et al.<sup>38</sup> for details.

<sup>d</sup>The study reported results for a BMR of 2 and 5%. The values were re-calculated from the BMR modelling for γ-glutamyltransferase (GGT) and a bodyweight of 60 kg.

<sup>e</sup>The study reported results for a BMR of 2 and 10%. The values were re-calculated from the BMR modelling for diastolic blood pressure and a bodyweight of 60 kg.

<sup>f</sup>Threshold value of GGT, re-calculated using a bodyweight of 60 kg.

<sup>g</sup>The study reports so-called tolerable upper alcohol intake levels, derived using the NOAEL combined with an uncertainty factor.

<sup>h</sup>Lowest-observed adverse effect level for reproductive effects during pregnancy (low birth weight).

<sup>i</sup>ADI based on NOAEL of 1 g/kg bw/day with uncertainty factor of 10. M, male; F, female.
plausibility of our calculated values and allows for their further use in MOE estimation. As such, we decided to use the BMDL1.5 of 0.4 g/kg bw/day (C24 26 g/day) from the epidemiological data for our further calculations.

Table 4 shows the corresponding MOEs for several scenarios. The intake scenario for the entire Canadian population resulted in an MOE of 1.23. Intake scenarios for individuals as based on the Canadian drinking guidelines led to MOE values of 1.91 or 1.49 for females (drinking one drink per day, or nine drinks per week), with lower MOEs for men at 0.96 (with drinking two drinks per day, or 14 drinks per week). For a heavy drinking scenario, the MOE was 0.48.

Finally, to calculate an ADI, the traditional default uncertainty factor (UF) of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was chosen (10), which assumes that the difference of sensitivity within the human population is in a 10-fold range.56 According to IPCS,55 the ADI based on BMD modeling is calculated as ADI = BMDL/UF. With the BMDL of 26 g/day, the ADI for ethanol would therefore be 2.6 g/day.

Discussion

For the BMD modelling of cohort data on liver cirrhosis, the suggested standard BMR of 10%, e.g. by the EFSA,16 cannot be used as it is outside the experimental range. This is typically the case for studies based on epidemiological data, for which an excess risk of 10% seldom occurs.25 To address this issue, other BMD studies based on such data used BMRs in the range of 1–5%.24–27,32,33 We decided to use a BMR of 1.5% as this was in the experimental range for both sexes; this would not have been the case for 1 or 2%. For the evaluation of the animal experiments, we used the standard BMR of 10% as well as 1.5% for better comparability.

Using this approach we observed similar results from both the epidemiological and the animal data. It must be noted that with respect to the inherent uncertainties of BMD modelling, even between different mathematical models of the same study, differences up to a factor of 3 are typically acceptable and allow for an averaging of the values. In our case, the BMDL1.5 values from epidemiological (0.5 g/kg bw/day) and animal experiment (0.8 g/kg bw/day) data did not even differ by this factor of 3. This is in line with previous research showing good agreement between these types of studies,37 which can be taken as an indicator for the concurrent validity of the approach. Even between the different studies and approaches (Table 3), the values are in good accordance. Our modelling of the animal data (BMDL10 of 0.7) is also in reasonable agreement with the modelling of Gold et al.38 (BMDL10 of 0.93), which is the only BMD for ethanol present in the literature, also based on animal experiments. Furthermore, the results from our epidemiological data on liver cirrhosis are in excellent agreement with those for liver markers and blood pressure from the Japanese studies of Dakeishi et al.32,33 Finally, our indicators are in reasonable agreement with the conventional thresholds.1,4–6,58

Notably, our approach allows for the first comparison of the overall effect of alcoholic beverages with that of minor constituents and contaminants in beverages that might additionally contribute to the health risk. For acetaldehyde directly contained in the beverages (i.e. outside ethanol metabolism), we had previously calculated an average MOE of 498.35 For ethyl carbamate, the MOE was ~5000.36 This signifies that alcoholic beverages per se (i.e. mechanistically the direct effects of ethanol and/or metabolically formed acetaldehyde) are >100 or even 1000 times more potent than the most relevant contaminants acetaldehyde and ethyl carbamate, which are regularly found in addition to ethanol. This comparison additionally provides evidence against the argument, often misleadingly exaggerated by the alcohol industry, that these minor contaminants are the main health threats of unrecorded alcohol products.59
Our results underline again that alcohol is truly no ordinary commodity.\[^{60}\] If ethanol were in fact treated like any other food ingredient, an ADI of 2.6 g/day, which could be exceeded by just a single portion per day, would be considered as outside the safety requirement for foods.

As our calculated MOEs vary around unity (i.e. 1) even for moderate drinking, it is evident that the current guidelines correspond very well to low risk on the dose–response curve. However, as normally an uncertainty factor of at least 10 would be introduced for evaluations based on human epidemiology, they do not provide any added safety. There is also the likelihood the uncertainty factor for alcohol would have to be even larger to allow for the genetic risk associated with ADH and ALDH polymorphisms. There is currently limited evidence for increased risk of liver disease associated with carriers of these polymorphisms,\[^{61,62}\] in addition to evidence on their effect on cancer\[^{63}\] and cardiovascular risk.\[^{64}\] At least for populations with predominantly active ADH/ALDH, uncertainty factors above 10 would appear overly conservative. Victorin et al. suggested uncertainty factors in the range of 2–10 for alcohol.\[^{5}\] Rydberg and Skerfving used the default factor of 10 in their toxicity evaluation of ethanol.\[^{6}\] We agree with Vermeire et al.\[^{65}\] that until better data are available it appears to be most appropriate to remain consistent with the traditional default value of 10 and to assume that this value protects the majority of the general human population.

If we would have to suggest a ‘virtually safe guideline’ based on our ADI of 2.6 g/day, this could be for example a maximum of one drink every 5 days, or six drinks per month. In this context, the additive risk stemming from heavy drinking behaviours must be mentioned. The evidence in the literature has consistently found that heavy drinking occasions pose a risk over and above the risk of the volume of alcohol consumed,\[^{9}\] in particular for ischemic heart disease and injury, with the possibility of playing a role in other alcohol-attributable disease,\[^{12}\] possibly including liver cirrhosis.\[^{40}\] As a consequence, low-risk drinking guidelines should incorporate limits for drinking per occasion in addition to limits for average volume.\[^{2}\]

Finally, our MOE values allow for an epidemiology-based comparison of the health risk of alcoholic beverages with other risk factors of modern lifestyle. In the list of agents evaluated by this model (e.g. see refs\[^{11,38}\]), alcoholic beverages are confirmed to be at the top position. This is another proof for the major necessity, priority and relevance of risk management and policy actions for reducing alcohol consumption.\[^{60}\]

**Conclusion**

There are two main conclusions. First, the approach, derived from regulatory toxicology, was feasible for developing evidence-based guidelines for low-risk drinking. This can provide a foundation for future risk assessments using the BMD methodology with epidemiological data and for calculating an MOE. Moreover, it is recommended that this methodology be applied to potential harmful substances with applicable epidemiological data (e.g. other life style-related risk factors such as tobacco or illegal drugs), in order to more accurately assess risk for priority setting in public health policy.

Secondly, the derived lower threshold of ~26 g/day is in line with the current drinking guidelines in Canada, derived from other methods.\[^{2,54}\] This indicates that the values produced using the BMD methodology in this study are consistent with those of the other methods used in the current guidelines. Moreover, the BMD methodology and values in this study can also be considered as a validation of the current guidelines.

In conclusion, this study has provided a novel new approach to risk assessment in epidemiology, based on toxicological methodology. Furthermore, it has added to the evidence for health risks associated with alcohol consumption and provides more reason for appropriate public health measures to reduce alcohol-attributable harm.\[^{60}\]

**Conflict of interest:** None declared.

**KEY MESSAGES**

- The BMD/MOE methodology was found to be usable in evaluating epidemiological data from life style-related risk factors such as alcohol consumption.
- The BMD allows for the derivation of evidence-based low-risk drinking guidelines, which are in good agreement with previous approaches.
- The MOE allows for the comparison of the overall effect of alcoholic beverages with that of minor constituents and contaminants in the beverages that may additionally contribute to the health risk.
- The further use of this approach for assessing life style-related risk factors may allow for more accurate priority setting in public health policy in the future.
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