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Can resveratrol in wine protect against the carcinogenicity of ethanol? A probabilistic dose-response assessment

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Resveratrol, which may occur in wine, was suggested to act as a chemopreventive agent against the carcinogenic effects of ethanol. The assumption was based on data from experimental animals, which have shown that resveratrol above certain thresholds may reduce the incidence of tumours in several of the alcohol-related cancer sites (colon, liver and female breast). Using a probabilistic Monte Carlo type methodology, we estimated daily intake based on chemical analysis of resveratrol (n = 672) and ethanol (n = 867). Benchmark dose (BMD)-response modelling was conducted for resveratrol based on eight animal experiments, whereas BMD data for ethanol were taken from the literature. The margin of exposure (MOE) was calculated for both substances as an indicator if the intake may reach effective dosages. For intake of one 100-mL glass of wine, the average MOE was found to be 4.1 for ethanol and 459,937 for resveratrol. In the best-case scenario for resveratrol (*e.g.*, very high contents and assuming a low effective dosage), the minimum MOE would be 111, which means that 111 glasses of wine need to be consumed daily to reach the BMD. The MOE ratio between resveratrol and ethanol is 166,128 on average, meaning that per glass of wine, ethanol is more than 100,000 times more potent than resveratrol. As resveratrol intake may not optimally reach the effective dosage, our study excludes a preventive effect of this substance on alcohol-related cancer. Commercial information about cancer-preventive or -protective effects of resveratrol in wine is misleading and must be prohibited.

Since its discovery in *Vitis vinifera* in 1976,[1] resveratrol (3,5,4′-trihydroxy-*trans*-stilbene, CAS # 501-36-0) has become known as "the red wine chemical" and has received much attention for its multitude of purported positive effects on health.[2] Siemann and Creasy suggested in 1992[3] that resveratrol in wine may be responsible for the "French paradox," *i.e.*, a reduced risk of coronary heart disease for light to moderate drinkers. Besides cardioprotective effects, resveratrol may act as a chemopreventive agent leading researchers of the German Cancer Research Center to ask the question if it is possible to "fight cancer with red wine."[4] The National Cancer Institute (NCI) at the U.S. National Institutes of Health went a step further and has published a fact sheet on "red wine and cancer prevention," which suggests that resveratrol is present in red wine at "high levels" and that it has been shown to reduce tumour incidence in animals.[5]

Interestingly, several studies purporting *in vitro* and *in vivo* evidence about the connection between cardioprotective and cancer-preventive effects and resveratrol were recently retracted (see list in Supporting Information). On the other hand, there still remains sufficient evidence in animal models to suggest that resveratrol reduces the incidence of hypertension, heart failure and ischaemic heart disease and that there are some promising results on the reduction of colon cancer in animals.[6]

Our interest in the connection between resveratrol and potential protective effects against ethanol-induced carcinogenesis was induced by a press inquiry following our recent study on the comparative risk assessment of 15 known and suspected human carcinogens in alcoholic beverages.[7] Despite having convincingly shown that ethanol was the major carcinogen, we were asked if the possibility of differences in carcinogenicity between beverage types may remain because protective compounds such as resveratrol occurring in some alcoholic beverages may lower the risk.[8] Although we found this to be unlikely based on epidemiological meta analyses that did not detect any beverage-specific effect,[9] as well as on the mechanistical unlikelihood that an antioxidant might fully counteract the oxidative stress owing to the major

Key words: wine, resveratrol, dose-response relationship, margin of exposure, epidemiology

Additional Supporting Information may be found in the online version of this article.

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What's new?

Resveratrol is a polyphenol found in red wine. Animal studies have suggested that resveratrol might protect wine drinkers from the carcinogenic effects of ethanol, reducing the incidence of cancers linked to alcohol consumption. In this study, the authors quantitatively estimated the resveratrol intake required to achieve a protective effect in humans. They concluded that a wine drinker would need to consume more than 100 glasses of wine per day in order to reach effective dosages of resveratrol, and that assumptions regarding resveratrol's chemoprotective effects with regard to ethanol are therefore invalid.

compound ethanol and its metabolite acetaldehyde, the literature did not contain reliable data to prove or disprove an influence of resveratrol. Some researchers claimed that plasma concentrations achieved after ingestion of some wines are "not too far from those concentrations at which resveratrol has demonstrated its biological activity."[10] In contrast, other research found that even optimistic estimates of the amount of resveratrol consumed in red wine would be "much lower than the low doses used in cell culture experiments."[11]

Therefore, the primary question centres around the human exposure to resveratrol from alcohol consumption, and if it may reach or exceed effective levels on the dose-response curve, and secondary, if the effect of resveratrol could counteract the one of ethanol. To answer these questions, this study will quantitatively calculate the margin of exposure (MOE) for both resveratrol and ethanol based on a probabilistic exposure assessment for moderate wine consumers.

Methods

The benchmark dose (BMD)/MOE approach was used for comparative risk-benefit assessment between the carcinogenicity of ethanol and the possible anticarcinogenicity of resveratrol. The methodological approach was similar to a previous comparative assessment of different carcinogenic compounds in alcoholic beverages.[7]

The starting point of the approach is the BMD, which is the dose of a substance that produces a predetermined change in response rate (benchmark response, BMR) of an effect compared to background based on dose-response modelling.[12]

The result of BMD-response modelling can then be used in combination with exposure data to calculate a MOE. The MOE is defined as the ratio between the lower one-sided confidence limit of the BMD (BMDL) and estimated human intake of the same compound. It can be used to compare the health effects of different compounds and in turn prioritise risk management actions.[7] By definition, the lower the MOE, the closer the human intake gets to the BMD. Although for adverse effects such as carcinogenicity, the MOE should be as large as possible (values above 10,000 are normally demanded for carcinogenic contaminants in foods if the assessment is based on animal experiments[13]), for compounds with pharmacological activity in humans such as medicinal compounds a MOE below 1 is expected.[14]

For ethanol, BMD modelling results are available in the literature (see review in Ref. 13). For resveratrol, no BMD values were available so that own dose-response modelling was conducted. Animal experiments and human studies suitable for dose-response modelling were identified in a review of Vang *et al.*[6] and own literature search in PubMed (U.S. National Library of Medicine, Bethesda, MD), Web of Science (Thomson Reuters, Philadelphia, PA) and Google Scholar (Google, Mountain View, CA).

The BMD modelling was conducted as previously described,[14] adhering to international guidelines.[12,15,16] In addition to the BMD, the BMDL was calculated. The BMDL is a statistical lower confidence bound on the true value of the BMD at the selected BMR and at a 95% confidence level. All calculations were conducted using the US EPA's BMDS 2.2 software (available for free at the U.S. Environmental Protection Agency website: http://www.epa.gov/ncea/bmds/index.html). The calculations were conducted in accordance with the International Programme on Chemical Safety document Principles for Modelling Dose-Response for the risk assessment of chemicals[15] as well as the recent guidance from EFSA.[16] All parameters were set at default values (*e.g.*, for slope and intercept). The best-fitting model was selected according to *p*-value and Akaike's information criterion. The goodness-of-fit was also visually confirmed in the model graphs. The BMR type was set to one standard deviation for continuous models and to 10% for dichotomous models. According to Crump[17] these BMR types give comparable results as change in the mean equal to one control standard deviation from the control mean in continuous data corresponds to an excess effect of ~10% for the proportion of individuals below the second percentile or above the 98th percentile of controls for normally distributed effects.

For exposure assessment, the resveratrol content of wine was primarily taken from the phenol explorer 2.0 database,[18] which tabulated 597 values of individual wine analysis results summarised from 36 studies on red wine ($n = 478$), 14 studies on white wine ($n = 101$) and four studies on rosé wine ($n = 18$). We have additionally included 75 values from three studies not included in the phenol explorer database,[3,19,20] so that a total of 672 values was available for the analysis.

The alcoholic strength of wine was based on own analytical results ($n = 867$) using Fourier transform infrared spectroscopy (Foss WineScan, FT 120, Foss, Hamburg, Germany).[21]

For the probabilistic intake and MOE assessment, best-fit distributions were applied to the analytical data of alcohol and resveratrol content as well as to the available range of BMDL values. From the available distribution types, the best fit was determined according to chi-squared and Anderson–Darling statistics. For calculation per kg of bodyweight, a normal distribution with average of 73.9 kg and standard deviation of 12 kg for males and females was assumed.[22] The distribution fitting for resveratrol was conducted with a fixed lower bound of zero because negative values are factually impossible. For the risk outputs [*i.e.*, intake per glass of ethanol (100 mL) and MOE], Monte Carlo simulations were performed with 50,000 iterations using Latin Hypercube sampling and Mersenne Twister random number generator. Calculations were conducted using the software package @Risk for Excel Version 5.5.0 (Palisade Corporation, Ithaca, NY). The calculation formulae and exact distribution functions are provided in the Supporting Information.

Results

Dose-response modelling

For resveratrol, we have selected eight animal studies, which have considered at least two dose levels *vs.* placebo, and are therefore suitable for BMD-response modelling (Table 1).[23–30] For the alcohol-relevant cancer sites, animal models are available for intestinal carcinogenesis, hepatocellular carcinoma and mammary tumours. We have not identified any animal study on the other human sites for alcohol-related carcinogenesis (oral cavity, pharynx, larynx and oesophagus). One animal study about the coadministration of ethanol and resveratrol is notable, because resveratrol decreased the levels of liver malondialdehyde in mice fed ethanol with a BMDL of 168 mg/kg bw/day.[25] In a model for human intestinal carcinogenesis (Apc^{Min+} mice), a dose-related inhibition of adenoma in the small intestine and colon was detected. A clear threshold appears to exist for resveratrol in this case, as in a study with dose levels up to 90 mg/kg bw/day no effect was detected,[24] whereas in another study with the same model at higher doses, a significant inhibitory effect was seen.[23] The BMDL for this endpoint would range around 61–115 mg/kg bw/day. For liver cancer, two studies in mice with implanted carcinoma cells H22 were conducted in the low-dose[26] and high-dose range.[27] However, in both cases, resveratrol was injected making the transferability of results questionable for comparison with oral administration. Only one oral study about diethylnitrosamine-induced hepatocarcinogenesis was conducted, resulting in a BMDL of 35 mg/kg bw/day.[29] For the two studies on mammary tumour models in rats and mice, the BMDL was 34 or 1.7 mg/kg bw/day.[28,30]

The data in humans about resveratrol administration are currently extremely limited (Table 1).[31–35] Significant BMD models could be established for effects on cerebral blood flow[32] and on glucose and insulin levels in diabetics.[34] No studies in humans on cancer endpoints are available. Therefore, our assessment was based on the animal dose-response modelling data. The combined BMDL values of the animal experiments are normally distributed and vary widely between 1.7 and 206 mg/kg bw/day. As low-dose effects of resveratrol cannot be completely excluded,[36] we use the complete normal distribution of the BMDL values rather than an average value as input for the probabilistic estimation of the MOE.

For ethanol, BMD modelling results from long-term animal experiments as well as from large human epidemiological studies are available in the literature (Table 2).[13,14,37–43] We additionally provide BMD modelling of a study on breast cancer.[44] The BMDL for ethanol ranges from 0.7 to 0.9 g/kg bw/day in animal experiments and between 0.05 and 1.6 g/kg bw/day for noncancer effects in humans. The BMDL for female breast cancer was determined to be 0.06 g/kg bw/day. Similar to the rationale for resveratrol, we decided to input the distribution of combined animal and human BMDL values for cancer endpoint (range 0.06–0.9 g/kg bw/day) into the probabilistic analysis rather than a single average value.

Probabilistic intake estimation

The resveratrol content in wine is distributed non-normally, and a Pareto distribution best fitted the data. The distribution is heavy-tailed on the left tail of the distribution (*i.e.*, the lower resveratrol contents predominate). The contents are highly variable and depend on wine type, but most specifically on grape variety with the highest contents usually found in Pinot Noir.[20] Because of this extremely skewed distribution, it is difficult to define an average resveratrol content of wine, so that we decided to probabilistically estimate the intake rather than to calculate with point estimates.

In contrast to resveratrol, the alcoholic strength of wine in our sample of commercially traded wine in Germany was normally distributed with an average content of 12.0 vol %, which corresponds to 9.4 g pure alcohol (ethanol) per 100 mL. This is in excellent agreement with the "standard glass" of the German guidelines for low-risk drinking, which specifies that a standard wine glass of 100 mL contains 9 g of pure alcohol.[45] The guideline also specifies that not more than one standard glass for women and two standard glasses for men should be consumed per day.[46] For this reason, we have conducted our intake estimation for a 100-mL glass of wine. The results from our probabilistic intake estimation for ethanol and resveratrol are shown in Figure 1.

Using the distribution of the BMDL values, the MOE can be estimated for both compounds (Table 3). After calculation of 50,000 iterations of random combinations of the BMDL distributions and resveratrol/ethanol content distributions, the average MOE was found to be 4.1 for ethanol and 459,937 for resveratrol (Table 3). The full distribution of MOE values for ethanol and resveratrol for daily consumption of one 100-mL glass of wine is shown in Figure 2. In the best-case scenario for resveratrol (*e.g.*, very high contents

Table 1. Summary of own dose-response modelling results for resveratrol

Study type and data source	Sex	Investigated dose levels (mg/kg bw/day)[1] and vehicle	Endpoint for modelling	Model[2]	*p*-Value[3]	BMD[4] (mg/kg bw/day)	BMDL[5] (mg/kg bw/day)
Animal studies							
Three-week feeding study in C57BL/6J Apc^{Min+} mice as model of human intestinal carcinogenesis[23]	Males/females (n = 10–12 per dose group)	0/60/240 in diet	Inhibition of adenoma development in small intestine	Linear	0.4866	197	128
			Inhibition of adenoma development in colon	Exponential	0.3875	95	61
			Inhibition of adenoma development overall	Linear	0.5057	171	115
Seven-week feeding study in C57BL/6J Apc^{Min+} mice as model of human intestinal carcinogenesis[24]	Males (n = 25)	0/4/20/90 in diet	Intestinal tumours	(No effect)	–	–	–
Four-week study in ethanol-fed C57BL/6J mice[25]	Males (n = 4–8 per dose group)	0/200/400 in diet	Decrease in liver malondialdehyde in mice fed ethanol	Linear	0.8256	280	168
Ten-day ip injected study in Balb/c mice with implanted tumour of hepatocellular carcinoma cells H22[26]	Sex not stated (n = 40)	0/5/10/15 in DMSO/RPMI 1640	Decrease in tumour size	Exponential	0.6976	6.0	3.9
Ip injected, 10-day study in Balb/c mice with implanted tumour of hepatocellular carcinoma cells H22[27]	Sex not stated (n = 40)	0/500/1000/1500 (vehicle not clearly stated, probably DMSO and normal saline)	Decrease in tumour weight	Exponential	0.9498	549	206
4 + 20-week feeding study in Sprague Dawley rats with diethylnitrosamine-induced hepatocarcinogenesis[29]	Female (n = 6–10 per dose group)	0/50/100/300 in diet	Decrease in average number of nodules per nodule-bearing liver (nodule multiplicity)	Polynomial	0.5889	50	35
120-day i.g. study in Sprague Dawley rats with *N*-methyl-*N*-nitrosourea-induced mammary tumours[28]	Female (n = 120)	0/10/100 in 6.5% ethanol	Decrease in mammary tumours[6]	Exponential	0.8494	47	34

Table 1. Summary of own dose-response modelling results for resveratrol (Continued)

Study type and data source	Sex	Investigated dose levels (mg/kg bw/day)[1] and vehicle	Endpoint for modelling	Model[2]	*p*-Value[3]	BMD[4] (mg/kg bw/day)	BMDL[5] (mg/kg bw/day)
20-day ip injected study in Swiss albino mice inoculated with Ehrlich ascites carcinoma (EAC) cells of mammary origin[30]	Female (n = 8–10 per dose group)	0/20/40 in carboxymethylcellulose/NaCl	Decrease in tumour size[7]	Gamma	0.9677	2.8	1.7
Human studies							
Oral single-dose, double-blind, randomised cross-over comparison in obese humans[31]	Males/females (n = 19)	0/0.3/1.0/3.0 as capsule	Increase in flow-mediated dilatation of the brachial artery (FMD)	Hill	(0.01)[8]	(0.08)	(0.02)
Oral single-dose, randomised, double-blind, placebo-controlled, crossover study of cerebral blood flow in healthy humans[32]	Males (n = 22)	0/4.2/8.3 as capsule	Increase in total haemoglobin[9]	Linear	0.766	5.3	3.9
			Increase in deoxyhaemoglobin[9]	Linear	0.1434	4.2	3.3
Repeat oral dose (29 day) in healthy humans (not double-blind, not placebo-controlled)[33]	Males/females (n = 40)	0/8.3/16.7/41.7/83.3 as caplet	Decrease in insulin-like growth factor-1 (IGF-1)[10]	Linear	(0.08)[8]	(18)	(12)
Oral 28-day, randomised, placebo-controlled study in type 2 diabetic humans[34]	Males (n = 214)	0/41.7/83.3 as proprietary formulation SRT501	Decrease in fasting glucose	Linear	0.5039	33	27
			Decrease in postprandial glucose	Linear	0.9622	18	16
			Decrease in fasting insulin	Linear	(0.04)[8]	(75)	(54)
			Decrease in postprandial insulin	Linear	0.7389	38	31
Prospective population-based cohort tested for prebronchodilator lung function[35]	Males/females (n = 3,224)	Estimation of resveratrol intake based on content in 11 food items including wine[11]	Increase of forced vital capacity	Exponential	(<0.01)[8]	(0.0010)	(0.0009)

[1]If necessary, the dose in mg/kg bw/day was calculated from dose in mg/day using the bodyweight provided in the study or if unavailable using 60 kg for humans. [2]Data from best-fitting models selected with BMDS 2.2 software according to US EPA criteria are presented. The benchmark response (BMR) type was set to one standard deviation for continuous models and to 10% for dichotomous models. [3]A *p*-value greater than 0.1 indicates that the model fits the data (*p*-value 1.0 = perfect fit). [4]BMD: benchmark dose for the BMR. [5]BMDL: The BMDL is a statistical lower confidence bound on the true value of the BMD at the selected BMR and at a 95% confidence level. [6]The raw data did not provide standard deviations, which were estimated based on data on tumours per rat and total tumours (Figs. 5C and 5D in Ref. 28). [7]Only relative values were stated, so that the percent tumour reduction was used for dichotomous modelling. [8]Not significant dose response. Values are shown in brackets for information. [9]The average of eight values obtained during a 36-min period of cognitive task performance was used for modelling. [10]Calculation excluding 83.3 mg/kg bw/day group. [11]The resveratrol intake was provided in tertiles (minimum/maximum range). The following average intakes were estimated for the three groups: 0.43, 3.11 and 6.89 μg/kg bw/day.

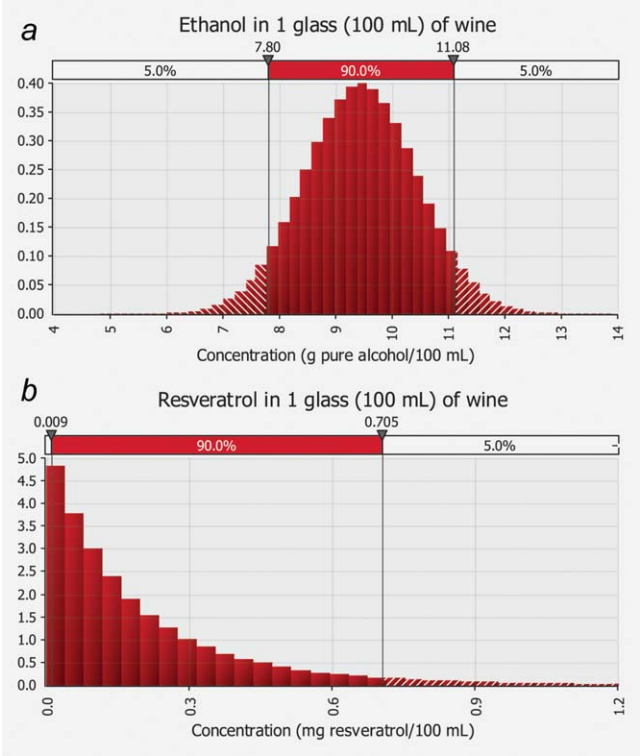

Figure 1. Histograms showing the probability density of estimated concentrations of ethanol (*a*) and resveratrol (*b*) in one 100-mL glass of wine using probabilistic simulation with 50,000 iterations (*y*-axis shows the relative frequency of a value in the range of a bin occurring). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

such as in Pinot Noir), the minimum MOE would be 111, which means in other words that 111 glasses of wine need to be daily consumed to reach the BMD. The MOE ratio between resveratrol and ethanol is 166,128 on average, meaning that per glass of wine, ethanol is more than 100,000 times more potent than resveratrol.

Discussion

Our study provides the first comprehensive comparison of the risks and benefits related to ethanol and resveratrol in wine. We use the BMD approach, which was originally established for risk assessment, but has recently shown to be also suitable to provide thresholds for substances with beneficial effects in foods and beverages.[14] In light of this research, a substance must have a MOE value of around 1 or lower when a pharmacological effect may be assumed. A therapeutic or preventive dosage in the sense of a medicinal product would require an even larger dosage.

The first caveat in our assessment of resveratrol is the underlying data for establishing the threshold of pharmacological action (*i.e.*, the minimum dose to ingest daily to achieve an effect). First, no human data on cancer are available for resveratrol, and second, the animal data were all established for model cancer systems, meaning that they may have proven a therapeutic effect of resveratrol against certain cancer types including some of the alcohol-related cancers, but it cannot necessarily be deduced that a preventive effect similarly exists. Nevertheless, our results also uphold considering recent mechanistical *in vitro* data, which show that resveratrol may be an allosteric activator of SIRT1, an enzyme with roles in many biological processes including DNA repair, metabolism, programmed cell death and inflammation.[47,48] However, the tested *in vitro* concentrations (40 μM,[47] which is about 9 mg/L) were considerably higher than the concentrations in wine itself, and physiological concentrations this high cannot be reached even in heavy wine drinkers. The *in vitro* research also did not provide evidence about dose-response information for resveratrol necessary for BMD calculation.

For all these reasons, we think that the fact sheet of the NCI mentioned in the introduction is not only factually incorrect but also irresponsible as it purports a preventive effect of resveratrol on cancer that appears not to be scientifically proven. Second, we think that the NCI claim of "high resveratrol" contents of wine must also be put into perspective, when even in best case assessments the concentrations in wine are factors of 100 or more away from the minimum effective dosage (for the therapeutic effects in animals).

Some researchers in the past have claimed that resveratrol may have "abnormal" dose-response behaviour, meaning that it may be more effective in the extreme low-dose range than at higher dosages, sometimes referred to as "hormetic" biphasis dose-response behaviour.[36] One of the pivotal study, which claimed to have proven this effect, was recently retracted because of falsified or fabricated data [see Dudley *et al.* (2009) in list of retracted references in Supporting Information]. In none of our dose-response models we did observe such behaviour for the cancer endpoints. In all cases (see Table 1), the data were best fitted by linear or exponential models, which had a monotonous increase. For these reasons, we believe that it is highly unlikely that we have underestimated the effect of resveratrol. Even if resveratrol was effective at doses more than 100 times below our current BMD range, these would only barely be reached by the human intake with Pinot Noir wine but clearly not for average drinking scenarios.

Based on a regular consumption of 200 mL/day of Monastrell wine, Moreno-Labanda *et al.*[10] estimated an average daily intake of resveratrol in the range of 1.7–3.8 mg/day (0.9–1.9 mg/day for 100-mL consumption, own recalculation). In contrast, Marques and Morris[11] have found in "an optimistic estimate" that the intake of 185 mL of red wine would lead to an intake of 13.5 μg/kg in a 70-kg person (about 0.5 mg/day for 100-mL consumption, own recalculation). Both estimates are higher than our average (0.22 mg/day for 100-mL consumption), but are in reasonable agreement with our distribution (*e.g.*, our P95, which could be interpreted as "optimistic estimate" was 0.7 mg/day for 100-mL consumption). The major difference is that these previous intake estimations were usually conducted using point estimates combining wine types high in resveratrol, which are not realistic in a real-world scenario where all types of wine are consumed (as resveratrol

Table 2. Summary of dose-response modelling results for ethanol (extended from summary in Ref. 13 by permission of Oxford University Press on behalf of the International Epidemiological Association)

Study type and data source	Sex	Investigated dose levels (g/kg bw/day) and vehicle	Endpoint for modelling	Model and data source for modelling	*P*-value	BMD[1] (g/kg bw/day)	BMDL[2] (g/kg bw/day)
Animal studies							
Two-year study in $B6C3F_1$ mice[37,38]	Males (n = 48 per dose group)	0/2.2/4.2 g/kg bw/day in drinking water	Increase of hepatocellular adenoma or carcinoma	Multistage cancer[13]	0.9689[3]	2.1	0.7
Rats (no further information provided)[39]	(No information provided)	(No information provided)	(No information provided)	(No information provided)[39]	(No information provided)	(No information provided)	0.93 (LTD10)[4]
Human studies							
Meta analysis of case–control or cohort design epidemiologic studies[40]	Males/females (1,477,887 individuals with 3,384 cases of liver cirrhosis)	Meta analysis of 17 studies [categories: 0 (reference group), >0–12, >12–24, >24–36, >36–48, >48–60 and >60 g/day]	Excess liver cirrhosis mortality	Polynomial[13]	<0.001[5]	0.5 (BMD1.5)	0.4 (BMDL1.5)
Observational study including biochemical analysis[41]	Males (n = 1,113)	Self-report by questionnaire (range 0–1,400 g ethanol/week)	Increase in γ-glutamyltransferase (GGT) in serum	Linear[41]	<0.001[5]	0.60 (BMD5)	0.69 (BMDL5)
Observational study including blood pressure measurement[42]	Males (n = 1,100)	Self-report by questionnaire (range 0–200 g ethanol/day)	Increase in diastolic blood pressure	Linear[42]	(No information provided)	2.1	1.6
Meta analysis of case–control or cohort design epidemiologic studies[43]	Males/females [38,627 IHD events (mortality or morbidity) among 957,684 participants]	Meta analysis of 44 studies [categorisation: lifetime abstainer, occasional drinker (less than weekly drinking or 0.1–2.49 g/day), 2.5–11.99 g/day, 12–23.99 g/day, 24–35.99 g/day]	Decrease in relative risk of ischaemic heart (IHD) disease mortality (at low-dose range)	Polynomial[14]	<0.001[5]	0.08	0.05
Collaborative reanalysis of individual data from case–control or cohort design epidemiological studies[44]	Females (58,515 women with breast cancer and 95,067 women without the disease)	Reanalysis of 53 studies (self-reported consumption 0–6 drinks per day)	Increase in relative risk of breast cancer	Linear (own dose-response modelling)	0.3676[3]	0.07	0.06

[1]BMD: benchmark dose for the benchmark response (BMR). If not otherwise stated, the BMR is one standard deviation for continuous models and 10% for dichotomous models. [2]BMDL: The BMDL is a statistical lower confidence bound on the true value of the BMD at the selected BMR and at a 95% confidence level. [3]For models calculated with US EPA BMDS 2.2 software, a *p*-value greater than 0.1 indicates that the model fits the data (*p*-value 1.0 = perfect fit). [4]LTD10 value, which should be comparable to BMDL10 value. LTD10 is the lower 95% confidence limit of the dose to induce tumours in 10% of animals. The LTD10 value was estimated by recalculation from a TD50 value. See Gold *et al.*[39] for details. [5]Conventional *p*-value indicating that the model fits the data.

Table 3. Results of probabilistic analysis (50,000 iterations) to compare ethanol and resveratrol for daily consumption of one glass of wine

	Mean	Minimum	P5	P95	Maximum
Ethanol intake per glass of wine (g/100 mL)	9.4	4.8	7.8	11	14
Resveratrol intake per glass of wine (mg/100 mL)	0.22	0.00	0.01	0.70	5.94
Margin of exposure for ethanol (one glass of wine per day)	4.1	0.3	0.9	7.6	13
Margin of exposure for resveratrol (one glass of wine per day)	459,937	111	4,271	741,065	5*E*+09
Margin of exposure ratio for resveratrol/ethanol	166,128	24	1,063	262,032	1*E*+09

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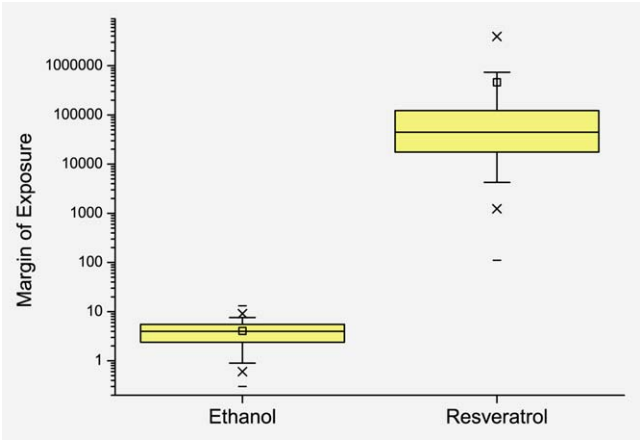

Figure 2. Margin of exposure (MOE) for ethanol and resveratrol for daily consumption of one 100-mL glass of wine (distribution from probabilistic estimation using 50,000 iterations). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

content is not known, the consumer cannot choose the wine for resveratrol content apart from the grape variety). We think that our probabilistic approach based on a summary of the complete literature of resveratrol occurrence data currently available provides a more robust intake assessment than any other study so far available. Therefore, it is likely that the average resveratrol intake from red wine consumption was considerably overestimated in the past.

On the basis of the result, that more than 100 glasses of wine would have to be consumed to reach a pharmacologically active dosage of resveratrol, our research clearly discredits any consumer recommendation to drink wine in order to indirectly ingest resveratrol for a cancer-protective effect. We agree with Vang *et al.*[6] that not even the intake of resveratrol in the form of supplements appears to be currently justified for the prevention of cancer, as experimental data and clinical evidence to indicate such a use is lacking. On the contrary, one clinical trial about resveratrol supplementation was halted because of observed adverse effects.[49] Our study at least provided evidence that the safety margin of resveratrol intake with wine (about 100) is sufficiently large, so that we do not have any safety concern about ingesting the wine types with higher contents of resveratrol. Similar to the positive effects, the threshold of the adverse effects of resveratrol (which are typically much higher[50]) cannot be reached with wine consumption. In sum, however, we do not think that the currently available data allow final conclusions for any consumer recommendations with respect to cancer. To evaluate the impact of resveratrol on ischaemic heart disease and other cardiovascular event was not the topic of this article.

Conclusion

Our initial question can clearly be answered that resveratrol in red wine is not able to protect against the carcinogenic effects of ethanol. Even at higher resveratrol concentrations (*e.g.*, due to supplementation), the scientific evidence about a protective effect of resveratrol is currently insufficient. Long-term animal experiments about the coadministration of both substances are clearly needed. Nevertheless, it is clear that resveratrol concentrations effective to protect against cancer cannot be reached solely from the natural contents in wine, so that supplementation would be necessary to obtain a positive result. Before human administration, it is obviously necessary to conduct clinical trials and to follow the guidelines required for the approval of a medicinal product. In light of the safety concern during some of the clinical studies, the sale of resveratrol as a food supplement in high or very high dosages through internet shops appears to be questionable. On the basis of our review of the evidence for this study, we do not think that human administration of resveratrol in supplement form is currently justifiable. We do not have any concerns about the ingestion of the trace amounts found in wine, apart from general concerns around alcohol ingestion.

Our study has implications for policy, as the cancer-protective effects of resveratrol have been used in commercial communications about alcohol. In Europe, such "health claims" are clearly an infringement of European law (which generally prohibits health claims even if scientifically proven) in the labelling as well as in commercial communication according to Regulation (EC) No 1924/2006, but according to our results such claims are also clearly misleading to the consumer [infringement of the general food law Regulation (EC) No 178/2002] as they are just factually incorrect.

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