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# Biogenic Amines: A Claim for Wines

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## Abstract

Many possible factors influence the accumulation of biogenic amines in wines, correlated both to agronomical practices in the vineyard and during the winemaking process. In the literature, it is reported that the quantities of biogenic amines found in many wines are not alarming, especially with regard to those of toxicological interest (histamine and tyramine). For subjects in specific physiological conditions (histamine intolerance, taking class of drugs that inhibit monoamine oxidase enzymes), the risk of creating toxic reactions is related to the composition of the whole meal, not only the consumption of wine. It would be desirable to establish a regulatory system, as already existing for sulphites, allowing to read a label with the claim specifying their absence (e.g., histamine free) in order to enhance the quality of wines that would be a priori forbidden.

**Keywords:** biogenic amines, wine, winemaking process, quality, safety

## 1. Introduction

The level of biogenic amines (BA) in wines is an important quality and safety parameter, in addition to the composition in polyphenols and polysaccharides [1, 2].

The presence of biogenic amines in wine is quite frequent and inevitable; they are naturally present in grapes but also deriving from the decarboxylation of amino acids by enzymes of microbial origin, or even produced by transamination of aldehydes by amino acid transaminase [3–6].

In most of the studies carried out, more amines have been observed in red wine than either white or rosé ones [7]. There is a high correlation among chemical and microbiological characteristics of grape variety, winemaking process conditions, and amount of the biogenic amines in wines [5, 8].

Histamine, tyramine, and cadaverine biogenic amines are most representative of the wine; other amines such as putrescine, ethylamine, 2-phenylethylamine, spermine, and spermidine are also present in the grape must [9].

Some factors of agronomic practice as well as of the winemaking process can cause discrete levels of biogenic amines in the wine: fertilization of the soil (nitrogen level), poor state of health of the grapes and presence of molds, nonregular lowering of the pH of the must and development of non-*Saccharomyces* yeasts, and activity of lactic acid bacteria responsible for secondary fermentation (malolactic fermentation, MLF) [8, 10].

Many technological, biological, and environmental factors can affect the occurrence of biogenic amines in wine such as skin maceration or post-fermentative maceration or contact with the lees [11–13].

The occurrence of biogenic amines in wines is also a consequence of the various treatments applied in winemaking process, some of them favoring the amines synthesis (wine and must treatments with yeast mannoproteins or proteolytic enzymes) [14, 15], and others, such as the use of clarification substances and oenological adjuvants (bentonite and polyvinylpolypyrrolidone), are instead able to absorb biogenic amines and then lower their levels in the final products [4].

In addition, mold infections of grapes display significant impacts on the initial content of biogenic amines in grape must, and their level is not efficiently reduced from fining agents currently available for the wine industry [16].

## 2. Why know the biogenic amines level in wines?

The knowledge of the biogenic amine levels in wines is important to both consumers and producers. Some authors proposed biogenic amine content as markers for authentication of origin in addition to other chemical compounds as polyphenols [3, 17].

Biogenic amines are present as salts but, at the pH prevailing of mouth, they are partly in free form, becoming reactive with other compounds responsible for the aroma of the wine so to impart aromatic notes own or even indirectly; they can be responsible of sensory changes and occult (e.g., loss of varietal character) and overt (musty smell of tuna) [18, 19].

But what makes it very useful to know the level of amines in wines is related to the fact that they are generally recognized among the most important causes for the intolerance to wine originating intoxication symptoms as nausea, cardiac palpitations, headaches, flushing, and increase or decrease blood pressure, as also reported by European Food Safety Authority [20, 21]. High sensitivity toward biogenic amines ingested with the diet depends on insufficient amino oxidase activity caused by drugs, genetic predisposition (histamine intolerance), gastrointestinal disease, inhibition by alcohol, acetaldehyde, and other amines (e.g., putrescine and cadaverine) [7].

Monitoring of the amine levels in wines can be an important marketing advantage. A large data set (from various production sites, vintage years, etc.) is necessary to establish BA profiles as wine fingerprint and provide scientific basis for safety and quality control in winemaking process.

### 2.1 Occurrence of biogenic amines in the red, white, and rosé wines

Different processes are applied for the production of red, white, or rosé wines, in which the chemical and physico-chemical characteristics result different and differently correlated with their biogenic amine content [22].

It is well known that SO<sub>2</sub> is added in higher concentration in white wine to ensure color stabilization, particularly in the post-malolactic fermentation and before bottling, therefore the total SO<sub>2</sub> value can be rather variable, but it must be in any case below the legal limits. In red wines, higher pH values than white or rosé ones are a consequence of malolactic fermentation in which lactic acid bacteria degrade malic acid to lactic acid and CO<sub>2</sub> (biological deacidification). A parameter of wine very useful for predicting the amino biogenic activity can be pH, especially considering that one of the explanations is that microorganisms use the biogenic amines synthesis as a metabolic strategy in response to environmental acidity or as a source of alternative energy [23].

As regard alcohol degree that is considered one of the parameters affecting the activities of amino acid decarboxylating bacteria involved in MLF, it is lower in white and rosé wines compared to red ones [24]. Generally, red wines with maximum alcohol content (about 14.5%) belong to the Reserve “Controlled Designation of Origin” (CDO) wines.

According to Bauer and Dicks [25], the malic acid content indicates a complete MLF (occurring in all red wines) or an incomplete/absent MLF (in white and rosé wines). Many studies were carried out on the role of MLF on the content of biogenic amines in wines and on the factors that can affect their production [11, 24, 26–28]. The variability of the biogenic amines distribution in red, rosé, and white wines is remarkable and could be attributed to the numerous variables affecting biogenic amine formation by bacteria during vinification and wine storage.

High amounts of diamine putrescine as well as the biologically active amines histamine and tyramine are determined in red wines, higher than those found in rosé and white wine [2, 29–32]. Generally, red wine vinification is carried out in the presence of grape skin and pulp, and putrescine could be released from these into the must [33].

The presence of putrescine has been associated with the secondary fermentation (MLF) and in particular with the activity of *O. oeni* strains although it has been demonstrated that *L. hilgardii* and *L. plantarum* are able to produce putrescine during alcoholic fermentation, using substrates from autolysis of yeast wine strains [34–36].

During vinification, putrescine can also originate from the microbial decarboxylation of ornithine or from arginine via agmatine [37]. Furthermore, some study demonstrated that amines are formed during alcoholic fermentation, even from the very beginning, involving yeasts and molds [38].

Moreover, high histamine and cadaverine levels in wines in which oak barrels were employed for secondary fermentation MLF [22].

In wines, polyamines might originate from grapes and/or from yeast lysis [33]; therefore the low amount of spermidine in rosé wines could be explained taking into account that yeasts are able to liberate polyamines in significant amount. A significantly decreasing of endogenous spermidine can be observed during winemaking, due to the growth of lactic acid bacteria, to potential consumption by alcoholic fermentative yeasts or to spontaneous chemical degradation [30, 31].

Moreover, higher levels of biogenic amines in the CDO reserve wines could be explained by the influence of the aging treatments [2, 12]. Cells of some lactic bacteria surviving aging are still able to decarboxylate amino acids and, due to the increase in pH value, multiply giving rise to the biogenic amine accumulation [26]. A relative high amount of biogenic amines in a Sherry-like wine as Vernaccia di Oristano could be explained with the long aging process, respect to those of newly made white wines [2, 39].

A separate case is the liqueurs, whose process is completely different from that of winemaking [40]; however, being counted among the alcoholic beverages consumed in a meal or in any case during the day, it could be useful to know the case also with respect to these products. For example, in [41], it is reported that high levels of BA in coffee, honey, and fruits liqueurs are significantly higher than those occurred in milk and herb liqueurs. The variability observed between samples was influenced by the type of components as well as by the different modes of production (homemade or industrial). Indeed, homemade sample had significantly higher amounts of BA than industrial samples. To date, no studies have been reported on the content of biogenic amines in homemade wines. Since this practice is still widely used in many regions of Italy, it would be desirable to collect data on the matter.



Significant seems to be the effect of the winery, regardless of the geographic area where it is located, in according to the results of other authors [15]. A predominance of decarboxylating positive microbiota can occur in some wineries, even if the fermentation is carried out by commercial starter strains [9].

However, great efforts are made in recent years by winemakers to reduce the content of amines and improve the quality and safety of wines: a study carried out on about 700 samples of Spanish wine, demonstrated that the average values of the histamine content for red, rosé, and white wines decreased, from 2010 to 2015, and in any case, none of the samples exceeded  $10 \text{ mg L}^{-1}$  of histamine [1].

## 2.2 Exposure to biogenic amine human intake via wine consumption: a case study in China

The first study at the national level to assess and link the BA contents to potential health risks for the largest group of wine consumers was recently carried out in China by Ke et al. [42]. Average annual per capita wine consumption in China is 0.75–1.2 L, whereas it is 54 and 49 L in France and Italy, respectively [43]; so, two different exposure scenarios can be designed: chronic and acute exposures. A general physiologically based pharmacokinetic (PBPK) model was used in order to estimate the tissue concentrations of biogenic amines in humans after intake via wine consumption [42]. In this study, the chronic exposure scenario was equivalent of consumption per person of 150 mL (one glass) of wine per day through a whole year (365 days). This corresponded to 54.8 L of wine in a year. In the acute exposure scenario, it was assumed that the person intakes 750 mL of wine (one bottle) in a single oral dose; the BA fate in the human body was simulated for 30 days. The dietary intake amount of biogenic amines in both exposure scenarios was calculated by using the median concentrations of BAs (putrescine, cadaverine, histamine, tyramine, phenylethylamine, spermidine, and spermine) detected in 456 wines sold in China (>90% of wine brands in a three-year span). The simulation considers the simultaneous uptake of a group of BAs together with alcohol, a situation that may inhibit BA metabolism. The PBPK model simulations were carried out by assuming no metabolism/transformation of BAs, simulating the pharmacokinetic fate of BAs for the most sensitive population in a critical exposure scenario. Results of this study demonstrated that in a chronic exposure scenario, the steady-state mass fractions of phenylethylamine and tyramine present in the adipose tissues are 77 and 65%, respectively, remarkably higher than those of other biogenic amines. The highest steady-state mass fractions of the other biogenic amines were found in the muscle tissues, with a 40% of the total body mass, while the mass fractions of blood, adipose, and liver tissues are 7.4, 21 and 2.6%, respectively. In the acute exposure scenario, the entire dose of amine was lost from the body at the end of the 30-day simulation; in particular, it took more than a week for the complete loss of phenylethylamine, and about one week was required for tyramine, whereas it was about one day for all the simulated biogenic amines. For all the simulated BAs, urinary loss accounted for >99% of the loss processes, whereas fecal and air loss were negligible (<1%).

## 2.3 Defining a biogenic amine safety threshold for wines

Actually, the European Union (EU) has not established regulations for the wine industry, but it has only suggested the “safety threshold values” [6].

Wines imported into EU are often accompanied by a certificate of analysis regarding biogenic amine content, even if there is no EU regulation about their limit in wines; however, Germany, Belgium, and France have differently recommended

not to exceed histamine levels of 2, 6, 8 mg L<sup>-1</sup>, respectively, while Switzerland has removed its official maximum histamine limit (previously set at 10 mg L<sup>-1</sup>) in imported wines [44]. The biogenic amine content in wines must be interpreted in the light of the toxicology studies on consumers [21], considering that biogenic amines have different safety threshold values depending on the physiological conditions of consumers. In general, the amines taken with the diet are metabolized by the activity of enzymes located in the intestine, the mono- and di-amino oxidases (MAO and DAO, respectively). The activity of intestinal MAO and DAO can be inhibited by alcohol and by some antidepressant and hypotensive drugs, the so-called MAO inhibitors (MAOIs). Diamine (putrescine and cadaverine) and polyamine (spermine and spermidine) are histamine, tyramine, tryptamine, and phenylethylamine toxicity enhancers, as they compete in the detoxification metabolism carried out by MAO and DAO. For subjects having histamine intolerance (genetic deficiency in diamine oxidase), patients taking MAOI drugs or patients under new generation MAOI treatment, so called RIMA (reversible inhibitors of MAO-A drugs), the risk of creating toxic reactions is related to the composition of the whole meal, not only the consumption of wine.

**Table 1** shows the amounts of biogenic amines found in 100 mL of commercial wines classified as “Controlled Designation of Origin” (CDO) and “Typical Geographical Indication” (TGI) (Commission Regulation EC No 628/2008) of different regions of South Italy. Results shown in **Table 1** demonstrate that the levels of biogenic amines can be not alarming in the commercial wines, especially with regard to histamine and tyramine, the most important cause of intolerance to wine [20].

Commercial wines	grape variety/ies	Putrescine	Cadaverine	Histamine	Tyramine
Montepulciano d'Abruzzo CDO [2]	100% Montepulciano	0,789±0,602	0,012±0,030	0,311±0,275	0,551±0,493
Primitivo del Salento TGI [2]	100% Primitivo	0,870±0,128	n.d.	0,055±0,021	0,181±0,255
Negramaro TGI [2]	100% Negramaro	0,689±0,130	n.d.	0,040±0,018	0,362±0,22
Aglianico del Vulture CDO [3]	100% Aglianico	0,324±0,118	0,174±0,104	0,195±0,113	0,261±0,141
Aglianico Irpinia CDO [3]	100% Aglianico	0,223±0,070	0,321±0,124	0,022±0,009	0,114±0,004
Gaglioppo [3]	100% Gaglioppo	0,599±0,331	0,194±0,051	0,301±0,106	0,122±0,016
Montepulciano d'Abruzzo Cerasuolo CDO [2]	100% Montepulciano	0,339±0,246	0,090±0,014	0,065±0,128	0,097±0,274
Faro CDO [32]	60% Nerello Mascalese, 30% Nerello Cappuccio, 10% Corinto and Nero D'Avola	0,233±0,005	0,004±0,000	0,123±0,001	0,045±0,001
Nero D'Avola TGI [32]	100% Nero D'Avola	0,033±0,000	0,002±0,000	0,152±0,002	0,264±0,006
Chardonnay Terre di Chieti TGI [2]	100% Chardonnay	0,150±0,071	n.d.	n.d.	n.d.
Trebbiano d'Abruzzo TGI [2]	100% Trebbiano	0,267±0,334	0,100±0,000	0,025±0,087	0,008±0,029
Mamertino TGI [32]	45% Catarratto, 20% Inzolia, 15% Grillo, 20% other	0,122±0,001	n.d.	0,007±0,000	0,014±0,000
Trebbiano TGI [32]	100% Trebbiano	0,054±0,001	0,004±0,000	0,006±0,000	0,005±0,000
Inzolia TGI [32]	100% Inzolia	0,126±0,001	n.d.	0,004±0,000	n.d.
Vernaccia di Oristano CDO [39]	100% Vernaccia	1,33±0,88	0,060±0,03	1,22±0,49	0,31±0,18

**Table 1.**  
 Biogenic amine contents (mg/100 mL) in commercial wines of South Italy.

The statistical distribution of histamine in 684 samples of Spanish wines has been modeled using the  $\beta$ -content tolerance intervals [1]. Besides, copulas to obtain the joint multivariate confidence region between histamine and tyramine have been built for the first time in the oenological field. Authors demonstrated that it is necessary for the nonparametric approach to correctly analyze the distribution of BA content in wines, because the data do not follow a normal distribution nor their

relations are linear; in the univariate approach, the  $\beta$ -content tolerance interval permits to obtain the proportion of wines that meet a “possible” limit.

### 3. Conclusions

In order to evaluate the real risks of biogenic amine intake associated with the consumption of wines, it must be considered that a chronic exposure scenario can be equivalent of consumption per person of 150 mL (one glass) of wine per day; moreover, in the Mediterranean diet, the consumption of wine with meals can be about 100–200 mL (for woman and man consumer, respectively).

It should be considered that the consumer needs a positive message about the product, so that it can be encouraged to purchase. On the other hand, it is necessary that the consumer is correctly informed of the content of potentially toxic compounds, also based on its physiological and pathological status. In general, wine is forbidden a priori to sensitive consumers, regardless of its real quality and safety. Therefore, if the wine label shows information about the composition in biogenic amines, both qualitative and quantitative, it would make the consumer aware of the real risk and then a double goal would be achieved: avoiding unpleasant or even harmful effects on his health, allowing the consumption of wine low or completely free of amines with a toxic effect. It would therefore be desirable that, after extensive collection of toxicological data and following an extensive media information campaign, establish for the wines a regulatory system, as already existing for sulphites, which allows the communication of the values of amines present, or, again better, a statement that can enhance the wines in which these compounds are absent, for example, a claim “*histamine free*.”

### Conflict of interest

The author, the undersigned corresponding author, declares that we have no commercial associations that might pose a conflict of interest in connection with the submitted chapter.

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