Estimates of maximum tolerable levels of tyramine content in foods in Austria

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Summary

Tyramine is one of the most relevant vasoactive ("pressor") amines present in foods. This paper suggests risk-based tolerable levels of this compound for certain food commodities. Dose-response data indicate that the "no observed adverse effect level" (NOAEL) for healthy individuals is 200 mg per single oral administration. Based on this NOAEL and Austrian food consumption data, maximum tolerable levels for foods (high consumption scenario: female user, 60 kg body mass, 95 percentile) are 1 000 mg·kg^{-1} for cheese; 2 000 mg·kg^{-1} for fermented / raw cured meats; 950 mg·kg^{-1} for fish (raw or processed) and 800 mg·kg^{-1} for sauerkraut. Reduced bioavailability of amines when ingested with solid foods was considered, susceptible consumers and interactions with other dietary amines were not considered. Literature data indicate that, at least for cheese, these limits may be exceeded in practice. However, surveys on market samples in Austria (2000–2008) report maximum tyramine contents well below the estimated tolerable contents (440 mg·kg^{-1}, 240 mg·kg^{-1} and 430 mg·kg^{-1} for cheese, fish and fermented meats, respectively). Under medication with monoaminooxidases inhibitors, a "safe-side" NOAEL of 5 mg per meal can be assumed, which may easily be exceeded even under "normal" nutrition conditions that requires some degree of consumer awareness.

Keywords

tyramine; "no observed adverse effect level"; exposure assessment; tolerable content

Tyramine and β-phenylethylamine belong to the most relevant vasoactive ("pressor") biogenic amines [1]. Tyramine is present in particular in foods rich in protein. An increase of tyramine contents during aging of raw meat [2], fermentation and ripening of meats [3] as well as dairy products [1] has been observed. Thus, tyramine contents, either alone or in combination, have been proposed as freshness and quality indicators [e.g. 4, 5]. Heat treatment as such seems to have little, if any, effect on tyramine concentration, but during boiling of pork, tyramine concentrations decrease, most likely because tyramine will leak into the surrounding liquid [6]. In vitro studies have demonstrated that the tyramine-forming ability is common in contaminant bacteria found on meat and dairy products. For example, pseudomonads [2] and enterococci [7] possess this ability, whereas it has been shown that for *Enterobacteriaceae* [7–9] and lactobacilli [7, 10] this ability is strain-dependent rather than characteristic for certain species or genera. Strategies to reduce biogenic amine accumulation during fermentation processes include, inter alia, selection or initial treatment of raw materials, use of starter cultures, use of additives (acidulants) or changes in process parameters [e.g. 3, 11].

The role of alimentary tyramine as a foodborne hazard has been studied in particular for consumers with impaired tyramine degradation [12–14]. Risk-based tyramine limits have been proposed for several food commodities (e.g. fermented sausages [15]).

In the present study, tolerable maximum levels for tyramine in selected foodstuffs are elaborated, taking into account the consumption pattern

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in Austria. A "no observed adverse effect level" (NOAEL) is derived from placebo-controlled blind studies. Maximum tolerable levels are compared to data on tyramine contents in Austrian market samples.

Metabolism of tyramine and effects in the organism

Tyramine is an aromatic amine, which is formed in eukaryotic as well as prokaryotic cells by decarboxylation of the precursor amino acid tyrosine. By displacing noradrenaline from vesicles of adrenergic nerves, it is mimicking sympathethic activity and indirectly causing a rise in systolic blood pressure [16]. Tyramine is degraded by monoaminooxidases (MAO). The subtype MAO B, being localized in various peripheral organs (intestine, liver), degrades e.g. noradrenaline and serotonine. MAO A is localized mainly in the central nervous system and is responsible for degradation of dopamine [1, 13]. Under medication with monoamonooxidase-inhibitors (MAO-I), sulpho-conjugation is the major pathway for tyramine metabolization [17].

Besides endogenous synthesis, tyramine is synthesized by intestinal bacteria [18], and alimentary tyramine is absorbed in the intestines and, in a pH-dependent way, also in the mouth [19]. The latter way is regarded the most important for liquid foods, bypassing the intestinal and hepatic MAO enzymes.

Under conditions of reduced MAO activity or MAO-I medication, alimentary tyramine can effectuate clinical symptoms not only in laboratory animals [20], but also in humans. MAO inhibition is not only a side effect of certain antibiotics or tuberculostatic drugs, but also is the main principle of several antidepressants [1, 21]. In combination with older, non-selective MAO-I, alimentary tyramine has been reported to cause headache, hypertensive crises and even stroke ("tyramine reaction", "cheese reaction" [1, 22]). In order to treat this situation, nutritional recommendations have been elaborated [13]. These recommendations are less strict for modern MAO-I, which are reversible and more selective (antidepressants: MAO A and anti-Parkinson: MAO B), but the interaction with sympathomimetic drugs still has to be taken into account [21].

In experimental pharmacology, tyramine effects and tyramine – MAO-I interactions are evaluated by observation of the systolic blood pressure ("tyramine-pressor test"); the threshold level is set to a rise of 30 mm Hg [20, 23–25].

The onset of food-related tyramine effects is usually 1–3 h after ingestion, and thus, later than that of histamine. It includes a rise in blood pressure, nausea, increased susceptibility to noises, odours, dizziness, occasionally vomitus and diarrhoea. The effects were originally attributed to consumption of ripened cheese, thus the term "cheese syndrome" was used. Also, a relation of alimentary tyramine and migraine was suggested [26]. Generally, unless applied in highly toxic doses, alimentary or parenterally administered tyramine should not pass the blood-brain barrier [27] and thus it only affects the peripheric adrenergic system [24].

MATERIAL

Dose-response relation

A number of studies (see [1]) presented evidence that headache, migraine and rise in blood pressure are related to the consumption of certain foods, such as red wine, hard cheese or others. There are, however, some critical comments, as it was not always proven that the respective food contained high amounts of tyramine [28] or foods were tested not in a ready-to-eat condition (e.g. non-peeled bananas) [12]. It is known that migraine events are associated with changes in biogenic amine contents in the central nervous system and that the renal excretion pattern of amine metabolites is subsequently altered, but it seems that only in a limited fraction of patients suffering from migraine or tension-type headache, dietary factors, and in particular alimentary tyramine, were the causative agents [29–31].

In contrast, experimental studies on healthy as well as volunteers medicated with MAO-I provide quite consistent data. Thus, for healthy fasted individuals, no health effects should be expected when 100–200 mg tyramine are administered orally, e.g. dissolved in water or in capsules [32–35]. When ingested with food, the threshold level can be expected to be twice as high [36], see Tab. 1. Consequently, NOAEL should be set to 200 mg per single administration. In contrast, individuals with reduced MAO activity may react with hypertension after ingestion of less than 5 mg tyramine [16].

In fact, severe reactions were observed with early, non-selective irreversible MAO-I, which increased tyramine sensitivity by 25–40 times [25, 35]. Tyramine sensitivity was far less (factor 2) increased when MAO B inhibitors were applied transdermally [35] or certain selective MAO B inhibitors were administered orally [37], see Tab. 2. For patients medicated with irreversible MAO-I, NOAEL should be set to 5 mg [22].

Tab. 1. Effects of orally administered tyramine on humans without MAO-I premedication.

Matrix	Amount of tyramine administered [mg]	Effect	Probands	Reference
Wine	4.6	No statistically significant effects	Healthy male and female volunteers including migraineurs	[50]
Apple juice	25	No statistically significant effects	Healthy male and female volunteers including migraineurs	[50]
In capsule	100	Migraine	Migraineurs	[26]
In capsule	100	Migraine	Migraineurs	[51]
In water	100–700	Rise of systolic blood pressure*	Not specified	[35]
In capsule, ingested with water	200	No rise of systolic blood pressure*	Healthy male volunteers	[32, 33]
Apple juice	200	No adverse effect (migraine)	Healthy male and female volunteers including migraineurs	[50]
In water	200	Tolerable; no rise of systolic blood pressure*	Healthy male volunteers	[52]
In capsule, ingested with water	200	No rise of systolic blood pressure*	Healthy male and female volunteers	[53]
In capsule	200	No rise of systolic blood pressure* ≥ 30 mm Hg	Healthy male and female volunteers	[34]
In capsule, ingested with water	244–800	Rise of systolic blood pressure*	Healthy male and female volunteers	[53]
In water	400	Rise of systolic blood pressure ≥ 20 mm Hg	Healthy male volunteers	[54]
In water	400	Rise of systolic blood pressure*	Healthy male volunteers	[52]
In capsule, ingested with water	400–600	Rise of systolic blood pressure*	Healthy male volunteers	[32, 33]
In capsule	400–600	Rise of systolic blood pressure*	Healthy male and female volunteers	[34]
In capsule, ingested with food	400–600	No rise of systolic blood pressure*	Healthy male volunteers	[33]
In capsule, ingested with water	423 ± 120	Average dose: rise of systolic blood pressure*	Healthy male and female volunteers	[55]
In capsule, ingested with water	450	“Average effective dose”: rise of systolic blood pressure*	Healthy male and female volunteers	[53]
In capsule	500	Average dose: rise of systolic blood pressure*	Healthy volunteers	[56]

* – threshold level was ≥ 30 mm Hg

Tab. 2. Effects of orally administered tyramine on humans with MAO-I premedication.

Matrix	Amount administered [mg]	MAO-I	Effect	Probands	Reference
In water	< 10	I	+30 mm Hg rise of systolic blood pressure	Healthy volunteers	[25]
In capsule, ingestion with water	50	I	No rise of systolic blood pressure*	Healthy male volunteers	[33]
In capsule, ingestion with water	≥ 100	R	Rise of systolic blood pressure*	Healthy male volunteers	[32, 33]
In capsule, ingestion with food	100–150	R	No rise of systolic blood pressure*	Healthy male volunteers	[33]
Ingestion with food	150–400	R	Rise of systolic blood pressure*	Healthy male and female volunteers	[34]

I – irreversible, R – reversible, * – threshold level was ≥ 30 mm Hg.

Occurrence of tyramine in foods

The decarboxylases effectuating the formation of tyramine in foods rich in protein are mostly of bacterial origin. Both enzyme activity and abundance of free tyrosine determine tyramine formation [1]. In foods undergoing a ripening process, the increase in free amino acids provides continuous supply of the substrate for tyramine formation, as e.g. demonstrated for hard cheese [38].

Tyramine formation has been associated with bacterial contamination of foods or temperature abuse conditions, but can also occur as a side effect of generally desired ripening processes. Contents of tyramine either alone or in combination with other amines, have been proposed as indicator for freshness of red meat [4]. In hard cheese [39], sauerkraut [40], fermented sausage [3] and fishery products [41], maximum tyramine contents have been reported to be in the order of 2000 mg·kg^{-1}, 1000 mg·kg^{-1}, 500 mg·kg^{-1} and 100 mg·kg^{-1}, respectively. Some other food commodities, for which maximum tyramine contents of > 1000 mg·kg^{-1} have been reported, are consumed in low amounts, e.g. liquid seasonings [42] or yeast extracts [43].

A variety of foods on the Austrian market has been tested for tyramine in 2000–2008 by the Austrian Agency for Health and Food Safety (AGES), Tab. 3. It is assumed that due to the improvement in food hygiene and technology [12, 13], maximum contents of tyramine in foods have decreased in the past decades. In various fermented foods, e.g. sauerkraut [44] or beer [45], the use of bacterial starter cultures will result in lower tyramine contents in the finished product.

Tab. 3. Tyramine contents and concentrations reported in foods on the Austrian market tested in 2000–2008 by the food laboratories of AGES.

Food category	*n*	*n* < *LOQ*	Maximum tyramine content [mg·kg^{-1}] or concentration [mg·l^{-1}]
Cheese	11		
Hard cheese	3	0	89
Sliced cheese	1	1	< *LOQ*
Soft cheese	7	5	440
Sea fish, canned	53		
Mackerel	1	1	< *LOQ*
Anchovy	13	5	56
Sardine	11	8	13
Tuna	28	11	160
Sea fish, fresh or deep frozen	**26**		
Tuna fresh	15	5	87
Mackerel fresh	6	4	10
Ocean perch fresh	1	1	< *LOQ*
Anchovy fresh	1	1	< *LOQ*
Various species deep frozen	3	3	< *LOQ*
Sea fish products	16		
Salted herring	4	4	< *LOQ*
Liquamen	1	1	< *LOQ*
Mackerel smoked, salted	5	4	240
Anchovy paste	1	1	< *LOQ*
Young herring smoked	2	1	50
Surimi	1	1	< *LOQ*
Tuna on pizza	2	2	< *LOQ*
Freshwater fish	2		
Trout	1	0	20
Salmon	1	1	< *LOQ*
Freshwater fish, processed	2		
Trout, smoked	1	0	10
Salmon, smoked	1	0	10
Cured meats, ham	24		
Osso collo	1	0	37
Dried cured ham	23	0	430
Sausages	24		
Pasteurized sausages	8	0	93
Fermented sausages	16	4	433
Alcoholic beverages	18		
Wine, sparkling	1	0	0.2
Wine, red	8	2	6.5
Wine, white	3	3	< *LOQ*
Sturm	2	0	0.5
Beer	2	0	22.2
Punch	2	2	< *LOQ*
Other foods	2		
Novel food (Noni juice)	2	0	115.1

n – number of samples, *LOQ* – limit of quantification, it was 10 mg·kg^{-1} in solid foods and 0.1 mg·l^{-1} in liquid foods.

METHODS

Estimation of tolerable tyramine contents

Mode of calculation for maximum tolerable levels was as previously described for histamine and β-phenylethylamine [46, 47], see also the footnote to Tab. 4.

Assessment of the significance of estimated maximum toerable levels

Estimated tolerance levels were compared to maximum tyramine contents as reported in literature and to theoretical maximum tyramine contents. The latter were estimated under the assumption of a total conversion of the precursor amino acid tyrosine typically present in the food, a procedure that had been applied in previous studies to other dietary amines [46, 47].

Tab. 4. Estimation of maximum tolerable contents of tyramine in various foods, based on a "no observed adverse effect level" (NOAEL) of 200 mg.

	Median consumption A	High consumption B
NOAEL per meal	200 mg	200 mg
Cheese		
Consumption per day	60 g	200 g
Max. tolerable content	3 330 mg·kg^{-1}*	1 000 mg·kg^{-1}
Fermented sausages		
Consumption per day	50 g	100 g
Max. tolerable content	4 000 mg·kg^{-1}	2 000 mg·kg^{-1}
Fish / fishery products		
Consumption per day	150 g	210 g
Max. tolerable content	1 330 mg·kg^{-1}	950 mg·kg^{-1}
Sauerkraut		
Consumption per day	150 g	250 g
Max. tolerable content	1 330 mg·kg^{-1}	800 mg·kg^{-1}

A - female user (60 kg) median, B – female user 95% percentile, based on Austrian food consumption data as used by [47, 48].
Values of maximum tolerable content were rounded.
* – calculated as 200 mg tyramine per portion of 60 g, which is equivalent to a tyramine content of 3 330 mg·kg^{-1}.

Classification of foods and their "tyramine" risk by diagrams

The intake of tyramine via foods can easily be estimated by diagrams. A template is given in Fig. 1, where serving size is plotted against tyramine concentration. NOAEL as well as expected or "typical" ranges for tyramine concentrations can be inserted in such a diagram, thus allowing a quick orientation if certain food commodity in general or a particular food item with known tyramine content is likely to pose a health hazard for healthy as well as MAO-inhibited consumers.

RESULTS AND DISCUSSION

Underlying assumptions and limitations of this study

The maximum tolerable levels elaborated in the present study are based on Austrian consumption data and are thus not necessarily applicable to other countries or susceptible consumers (i.e. those with impaired MAO capacity). Due to a lack of data, interactions with other dietary amines were not considered. NOAEL of 200 mg tyramine can be derived from published data in two ways:

1. The lowest published NOAEL for tyramine, when ingested without foods, is 100 mg [35], but when ingested simultaneously with foods, tyramine sensitivity is reduced at least by a factor of 2 [36].
2. The majority of studies reports NOAEL for tyramine, when administered with water or in a capsule, of ≥ 200 mg (Tab. 1); and the reduced sensitivity when ingested simultaneously with foods is not considered.

Thus, NOAEL of 200 mg is a conservative value compared to the lowest observed adverse effect level (LOAEL) of 600 mg recently established by the BIOHAZ Panel of the European Food Safety Authority [14]. A threshold level of the same order of magnitude as used in our study, but per day instead of per single ingestion, has also been used

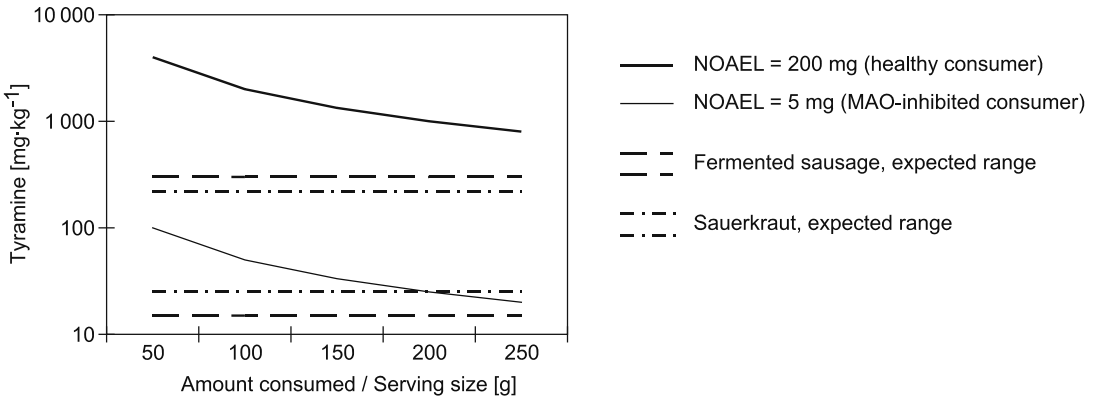

Fig. 1. Example of a graphical display of portion sizes and "typical" tyramine contents in fermented sausages and sauerkraut, and their relation to NOAEL for healthy as well as MAO-inhibited consumers.

Fermented sausage – the range of "typical" tyramine contents (range of mean values reported in the review of Suzzi and Gardini [3]). Sauerkraut – horizontal lines mark the area of "typical" tyramine contents (range of mean values as reported by Kalac et al. [40]).

in an exposure assessment for fermented sausages [15].

Estimated maximum tolerable levels and their relation to tyramine concentration actually reported for foods

Assuming NOAEL of 200 mg tyramine, and an "average food consumption" (Tab. 4), maximum tolerable levels of tyramine in cheese, fermented sausage, fish/fishery products and sauerkraut would amount to 3330 $mg \cdot kg^{-1}$, 4000 $mg \cdot kg^{-1}$, 1330 $mg \cdot kg^{-1}$ and 1330 $mg \cdot kg^{-1}$, respectively. For a "high consumption" scenario, maximum tolerable levels are 1000 $mg \cdot kg^{-1}$, 2000 $mg \cdot kg^{-1}$, 950 $mg \cdot kg^{-1}$ and 800 $mg \cdot kg^{-1}$, respectively (Tab. 4).

Cheese, fermented sausage and fish contain sufficiently high amounts of tyrosine to allow formation of tyramine in contents exceeding 5000 $mg \cdot kg^{-1}$ [48]. Maximum tyramine levels actually reported in literature are, however, substantially lower, and only for cheese, samples exceeding the proposed tolerance levels have been reported. Likewise, surveys on market samples in Austria (2000–2008) report maximum contents of 440 $mg \cdot kg^{-1}$, 240 $mg \cdot kg^{-1}$ and 430 $mg \cdot kg^{-1}$ for cheese, fish and fermented meats, respectively. Fig. 1 demonstrates that, for fermented sausage and sauerkraut, the consumption of 50–250 g portions with "typical" tyramine contents (here defined as the range of means reported in various studies) will not result in an intake of 200 mg tyramine, but that NOAEL of 5 mg (applicable for susceptible consumers) may be exceeded even in small-sized portions.

In Austria, the intake of tyramine per meal and even per day is usually well below the NOAEL of 200 mg. For example, it has been calculated that typical Austrian meat dishes contain 2–25 mg tyramine [49], and the alimentary tyramine intake per day would be 89 mg assuming a high consumption – high content scenario [14].

CONCLUSIONS

For indivuals with no increased susceptibility to tyramine, it is justifiable to suggest a NOAEL of 200 mg tyramine per meal. For "high consumption" scenarios (based on Austrian data), maximum tolerable levels of tyramine in cheese, fermented sausage, fish/fishery products and sauerkraut would be 1000 $mg \cdot kg^{-1}$, 2000 $mg \cdot kg^{-1}$, 950 $mg \cdot kg^{-1}$ and 800 $mg \cdot kg^{-1}$, respectively. Literature data indicate that, for the four food categories under study, these proposed levels may be exceeded in hard cheeses.

Under medication with MAO inhibitors, susceptibility to tyramine can increase markedly. From literature data, a "safe-side" NOAEL of 5 mg per meal can be derived, mainly based on studies with non-reversible, non-selective MAO-I. Although for "modern" MAO-I, a higher NOAEL would be justifiable, possible interactions with other drugs have to be considered. NOAEL of 5 mg may easily be exceeded even under "normal" nutrition patterns, which requires some degree of consumer awareness.

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