*Key Words: MAOI, monoamine, oxidase, inhibitor, phenelzine, tranylcypromine, diet, tyramine, blood, pressure*

# **The Prescriber's Guide to the MAOI Diet—Thinking Through Tyramine Troubles**

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*ABSTRACT ~ This review article features comprehensive discussions on the dietary restrictions issued to patients taking a classic monoamine oxidase inhibitor (phenelzine, tranylcypromine, isocarboxazid), or high-dose (oral or transdermal) selegiline. It equips doctors with the knowledge to explain to their patients which dietary precautions are necessary, and why that is so: MAOIs alter the capacity to metabolize certain monoamines, like tyramine, which causes dose-related blood pressure elevations. Modern food production and hygiene standards have resulted in large reductions of tyramine concentrations in most foodstuffs and beverages, including many cheeses. Thus, the risk of consequential blood pressure increases is*  considerably reduced—but some caution remains warranted. The effects of other relevant *biogenic amines (histamine, dopamine), and of the amino acids L-dopa and L-tryptophan are also discussed. The tables of tyramine data usually presented in MAOI diet guides are by nature unhelpful and imprecise, because tyramine levels vary widely within foods of the same category. For this reason, it is vital that doctors understand the general principles outlined in this guide; that way, they can tailor their instructions and advice to the individual, to his/her lifestyle and situation. This is important because the pressor response is characterized by significant interpatient variability. When all factors are weighed and balanced, the conclusion is that the MAOI diet is not all that difficult. Minimizing the intake of the small number of risky foods is all that is required. Many patients may hardly need to change their diet at all.* Psychopharmacology Bulletin. *2022;52(2):73–116.* **Fincent Van den Eynde, Peter Kenneth Gillman,**<br> **Fincent Van den Eynde, Peter Kenneth Gillman,**<br> **Barry B. Blackwell**<br> **Assincer-Thereviewaritele/asture comprehensive discussions on the disturbentions**<br>
issued to patient

# **The MAOI Diet—***Partim Generalis*

# **INTRODUCTION**

Patients who are taking either a classic monoamine oxidase inhibitor (MAOI) antidepressant (phenelzine, tranylcypromine, isocarboxazid), or high-dose (oral or transdermal) selegiline, must be instructed to follow a tyramine-restricted diet;

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this is necessary because such (often highly effective) treatments cause considerable reductions in the body's capacity to metabolize various monoamines, such as tyramine—which may be present, in varying concentrations, in both foodstuffs and beverages.

This review article offers a comprehensive overview of recent food science research on dietary tyramine, and on other biogenic amines (BAs) and amino acids (AAs) that may interact significantly with MAOIs (BAs: histamine, and dopamine; AAs: levodopa and L-tryptophan). Much of the focus is on tyramine, the main vasoactive amine implicated in blood pressure disturbances in MAOI patients.

It is important that *recent* food science data are consulted, because modern-day hygiene and production standards have resulted in significantly lower tyramine levels in most (but not all) foodstuffs.<sup>1</sup> These findings have yet to filter fully through to medical publications. This review article is aimed at resolving the translational knowledge gap.

For many MAOI patients who already follow healthy eating patterns (e.g., no excessive amounts or aberrant combinations), the low-tyramine diet may involve few (if any) changes. The patient must follow the diet when MAOI treatment is initiated; the diet must be maintained for 2 weeks after MAOI cessation.

**Monoamine Oxidase Inhibitors (MAOIs)**

Monoamine oxidases (MAO) exist in two isoforms (MAO-A and MAO-B), and play a role in deaminating various (endogenous and  $\alpha$  exogenous)  $\beta$ As;<sup>2</sup> those of particular dietary relevance for the purposes of this *Prescriber's guide* are tyramine (TYR), histamine (HA), and dopamine (DA). The effects on the metabolism of the AAs levodopa (L-dopa) and L-tryptophan (TRP) are also discussed. and amino acids (AAs) that may interact significantly with MAOIs<br>
(BAs: histamine, and dopamine, AAs: levodopa and L-tryptophan).<br>
Much of the focus is on tyramine, the main vasoactive anine implicated<br>
in blood pressure

MAOIs inhibit the breakdown of various (mono)amines—the extent to which this may occur depends on the specific properties of the MAOI used.

The 'classic' (irreversible and non-selective) MAOIs currently on the market are phenelzine (PLZ), tranylcypromine (TCP), and isocarboxazid (ISO); as they inhibit both MAO-isoforms, some dietary precautions are required. The details are discussed in the subsequent sections of this article.

Other, 'non-classic' MAOIs include selegiline (in essence an irreversible, selective inhibitor of MAO-B), and moclobemide (a reversible, selective inhibitor of MAO-A).

Selegiline is typically used in the treatment of Parkinson's disease; it is selective for MAO-B at conventional doses of  $\leq 10$  mg/day, and

does not require dietary modifications.<sup>3</sup> At higher doses (typically 30–60 mg/day), selegiline also inhibits MAO-A, and becomes an effective (non-selective MAOI) antidepressant; restrictions in the intake of dietary TYR are required at such doses.<sup>4</sup> A transdermal method of delivery was then devised so as to bypass hepatic metabolism<sup>1</sup> (supplied as skin patches that deliver 6–12 mg/24 h); as a result, the lowest dose (6  $mg/24$  h) comes without dietary requirements<sup>5,6</sup>—but at higher doses, TYR restrictions do become necessary.<sup>7</sup>

Moclobemide, a selective MAO-A inhibitor, has not shown sufficiently effective in treating severe, 'treatment-resistant' depression—certainly when compared to the classic MAOIs (or to high-dose selegiline).<sup>8</sup> Specific dietary precautions are not required with moclobemide, $9$  even at high doses of 600 mg/day.<sup>10</sup>

Collectively, the dietary recommendations in this *Prescriber's guide* are intended, primarily, as a reference guide for physicians—it is important that they understand the principles of the MAOI diet, and can pass this (practical) knowledge on to their patients.

# **Biogenic Amines (BAs)**

Biogenic amines (BAs) can be either endogenous to the human body, or can be absorbed from exogenous (food) sources. This guide is aimed, exclusively, at discussing the latter variety.

BAs can be present in various concentrations in both foodstuffs (raw or processed) and beverages; they are considered anti-nutritional factors:<sup>11</sup> high BA levels are taken to be indicative of fermentation and/or of spoilage<sup>12</sup>—the latter process may be influenced by poor hygiene standards during manufacturing or storage (e.g., inadequate temperature control) of food products.13,14

Some BAs (such as TYR, HA, and tryptamine)<sup>15</sup> are produced from the enzymatic decarboxylation of AAs;<sup>16</sup> they are heat stable (i.e., they are not inactivated by cooking).17 The decarboxylating enzymes are also heat-tolerant, but comparatively less so; their action on AAs may be inhibited either by freezing (storage), $^{13}$  or by the use of hightemperature preservation methods (e.g., pasteurization)<sup>18</sup>—but these enzymes may survive cooking<sup>19</sup> (e.g., in some meats, boiling decreased HA levels, while grilling actually increased them).<sup>20</sup> Other BAs (such as DA, spermine, and spermidine) are produced by hydroxylation- and/or condensation-reactions.15 (6 mg/24 h) comes without dietary requirements<sup>5,6</sup>—but at higher doses, TYR restrictions do become necessary.<sup>7</sup><br>Moclobemide, a selective MAO–A inhibitor, has not shown sufficiently effective in retaring severe, 'retartm

While there are a variety of food-borne  $BAs<sub>1</sub><sup>21–26</sup>$  this guide will limit its discussion to those that may be of particular relevance to MAOI patients: these are TYR (first and foremost), but also HA, and DA.

# *BAs: Aspects of Detection, Control, and Toxicity*

There has been much progress in (and refinement of) measurement techniques of BAs in food<sup>27,28</sup>—that is (part of) why estimates of BA levels from older research studies are likely less accurate than those stemming from modern-day research samples. Such research is often expensive—but the various measurement methods employed (e.g., liquid or gas chromatography) are continuously finetuned,  $29$  and data are rapidly and reliably accumulating; that is why *recent* reviews of BA toxicity are so important (and may indeed supersede some older data).21,22,30–36

Aside from improved detection methods, considerable advances in food safety research have resulted in the use of various prevention and/or containment practices to reduce BA levels in foods; $37-39$  these may be aimed either/both at limiting BA formation (by limiting the growth and/or decarboxylating activity of microbes), or at increasing the decay rate of already formed BAs.13,40

Naila et al. provide an overview of such existing and emerging methods; they include temperature control (e.g., proper refrigeration at  $\langle 5^{\circ} \text{C} \rangle$ , irradiation, addition of preservatives, modified atmosphere packaging, high hydrostatic pressure, using standardized starter-cultures (which have either non-amine forming, or amine-oxidizing properties), the use of high-quality base products, etc.<sup>13</sup> experient the value and entired in the value in the value of experiment the same rapidly and rata are rapidly and related y accordinate, that are rapidly and related supersede some older BA toxicity are so important (and

TYR (vasoactive effects) and HA (scombroid poisoning) are the two BAs most commonly implicated in toxicity reactions in humans.<sup>41-43</sup> There are significant interindividual differences in bodily detoxification mechanisms (e.g., metabolization capacity of the various BAs), so that precise toxicity thresholds cannot be provided.<sup>44</sup>

# *Tyramine (TYR)*

TYR is formed from the enzymatic decarboxylation of tyrosine (its AA precursor), and may gradually accumulate in a variety of foodstuffs, certainly when hygiene and/or production standards are not up to par. This process may then be further 'aided' by improper storage. That is why proper refrigeration of foods (at  $\leq 4^{\circ}C$ ),<sup>45</sup> verified by the use of an accurate fridge thermometer, is so essential (as some domestic refrigerators fail to maintain such temperatures).<sup>46</sup>

#### **TYR Pressor Response**

Following ingestion, dietary TYR is extensively metabolized by MAO in the intestinal lumen and in the liver (high first-pass clearance);  $46-48$ the remaining TYR then enters systemic circulation, where it may be

taken up by sympathetic neurons, and is subjected to further deamination by intraneuronal MAO-A.49 It is clear that states of MAO inhibition drastically affect the amount of TYR that survives this process, whereafter it can induce the displacement of norepinephrine (and in some rare cases DA) from storage vesicles.<sup>50</sup> This results in BP increases, with a typical duration of  $1-3$  h.<sup>51</sup>

# *Symptoms*

A forceful, thumping heartbeat may be a first, tell-tale symptom of the TYR pressor response. It is accompanied by progressive BP increases (rapid onset: 30–60 min after ingestion; faster for liquids taken on an empty stomach); typically, the heart rate then slows down in response.<sup>52–55</sup> If systolic BP exceeds 180 mmHg, the rapid onset of a severe headache may be observed. Other symptoms include tightness in the chest, sweating, and pallor.

# *Treatment*

Typically, 'treatment' for cases of excessive TYR ingestion is comprised of little more than monitoring BP (for 1–4 h), as hasty and alarmist treatment of elevated BP may produce more harm than good. Conservative treatment is strongly advised;  $46$  e.g., sublingual nifedipine is contraindicated: there is a real risk of potentially severe hypotensive overshoots, possibly leading to cerebral hypoperfusion (which may result in permanent cortical blindness).<sup>56</sup> Syar<br/>rrows <br>A forceful, thumping heartbeat may be a first, tell-tale symptom<br/> $\Lambda$  forceful, thumping heartbeat may be a first, tell-tale symptom<br/>cof of the TYR pressor response. It is accompanied by progressiv

Administering a benzodiazepine has a sedative, BP-lowering effect, and is therefore recommended as a first (and typically final) intervention step.<sup>46</sup>

In rare cases, when greatly excessive TYR has been ingested, the hypertensive episode may warrant additional care; it is the emergency physician who steps in, and treats these cases (hypertensive urgency or emergency) $46,57$  with best clinical judgment, taking into consideration the limited duration of the TYR-reaction (e.g., considers infusing phentolamine, which has an elimination half-life of only 19 minutes).<sup>58</sup>

# **TYR Dose and BP**

There is significant interpatient variance in TYR pressor sensitivity (unmedicated or with  $\text{MAOI}^{59}$ —that is why empirical researchbased individualization of dietary guidelines is so important. Gillman  $(2018)^{46}$  summarized the relevant research,  $60-62$  and extrapolated therefrom the following: TYR-sensitive MAOI patients may experience a (notable but not problematic) 30 mmHg increase in systolic BP following the ingestion of 20–30 mg TYR in a meal (or of only 10 mg TYR

on an empty stomach; this is an aspect of *intra*patient variability). For many MAOI patients, reaching a systolic BP of  $\geq 180$  mmHg would require the ingestion of >40 mg TYR in a meal.

The effect of TYR on systolic BP is dose-related, but the relationship is 'non-linear': small doses of TYR in a meal will cause (virtually) no BP increase; if the TYR dose is then increased in small and equal increments, there will come a dose point—'when the amount of absorbed TYR exceeds the metabolising capacity of the  $MAO<sup>63</sup>$  which results, seemingly suddenly, in larger than (linearly) expected BP increases.<sup>64</sup>

There is some indication in early research by Blackwell et al.<sup>65</sup> that the timings of TYR ingestion and MAOI ingestion may influence the magnitude and duration of subsequent BP increases (i.e., temporal proximity of TYR and MAOI ingestion seemed to result in greater BP effects)—but confirmatory research is required.

#### **Those Who Test, Know Best**

Treatment adherence is key;<sup>66,67</sup> it improves treatment outcomes, and helps to limit both the occurrence and severity of adverse events—that is why patient compliance, or precisely the lack thereof, is a source of concern for physicians. That is also why, in the context of MAOI treatment, overly restrictive diet guidelines (or rules, even) do not work. Most publications (peer-reviewed or vulgarising) get this wrong; it appears simple and straightforward (and well-intentioned) to restrict, for reasons of safety (be they flawed or factual), the various foodstuffs and beverages that have been deemed impermissible throughout the decades of MAOI use—but this is a self-defeating strategy. Patients will learn, sooner or later, that some dietary restrictions 'are more equal than others', and that the BP effects from eating a slice of cheese may not always be as drastic as promulgated in much of the previous literature. Such an experience might lead to incorrect extrapolations, and to further dietary indiscretions—some of which may well be injurious. equal increments, there will come a dose point—when the amount of<br>absorbed TYR exceeds the metabolising capacity of the MAO<sup>683</sup>-<br>which results, seemingly suddenly, in larger than (linearly) expected<br>BP increases,<sup>44</sup><br>The

It is therefore best that proper, science-based dietary guidelines are provided, and that matters of 'diet adherence' are discussed plainly and honestly; this may greatly improve patient-physician rapport, which is an important part of successful long-term MAOI treatment.

For these reasons, cautious and mindful 'testing' is allowed; this means consumption of *low* amounts of foodstuffs, that thus contain noninjurious TYR levels (see *infra*, *'Partim Specialis'*; some foods are still contraindicated), while carefully monitoring the BP response. Safety comes first when it comes to practical application—this *Prescriber's guide* prefers, therefore, to err on the side of (excessive) caution, by sug-

gesting that any such 'testing' ought to be firmly and openly discussed between the patient and the physician. The physician can, by utilizing the precepts outlined in this guide, help to educate the patient, thereby guiding him/her along a path of safely 'testing' TYR sensitivity. It is difficult to with great certainty approximate TYR levels in a particular food; that is why portion control and BP measuring are such helpful aids for the practical parts (e.g., the 'testing') of this guide.

In closing, any testing is to be undertaken in a careful and methodical manner, with the principles provided in this guide firmly in mind.

# *Histamine (HA)*

Histamine (HA) is formed from the enzymatic decarboxylation of L-histidine, and may be present in high concentrations in proteinrich foods (e.g., meat, fish, blue or Swiss cheese)<sup>68</sup> that are improperly stored.<sup>69</sup> The consumption of HA-contaminated food may lead to one developing scombroidosis (spoiled fish of the *Scombridae* family are the prime culprits, hence the name).<sup>70</sup>

The symptoms of HA poisoning relate especially to effects on blood vessels, cell permeability and smooth muscles; they include headache, nasal secretion, bronchospasm, tachycardia, extra-systoles, hypotension (vasodilatory effect),<sup>44</sup> edema (eyelids), urticaria, pruritus, skin flushing, and asthma.71,72 Clinical presentations may closely resemble IgEmediated food allergies;73 measuring serum tryptase concentrations may help with differential diagnosis.<sup>74</sup> aids for the practical parts (e.g., the 'testing') of this guide.<br>
In clossing, any testing is to be undertaken in a carciul and methodical<br>
manner, with the principles provided in this guide firmly in mind.<br> *Histamine (* 

# **MAOIs and HA**

MAO is involved in the degradation of HA (a monoamine) $^{75}$  via enzymatic methylation (histamine-N-methyltransferase), $^{76}$  and so its metabolism in MAOI patients is altered, albeit to varying extents (based on the specific structural and pharmacological properties of the  $MAOI$ . 77

The hydrazine-derivative MAOIs<sup>78</sup> (PLZ, ISO) also inhibit diamine oxidase (DAO), and semicarbazide-sensitive amine oxidase (SSAO); both are enzymes that play a role in the degradation of HA.<sup>79</sup> The increased sensitivity to dietary HA in patients taking isoniazid, an old antitubercular drug that is also a hydrazine-derivative (with modest MAOI potency) is well established; $80$  many such reactions have been described.81–88

TCP is a propylamine<sup>89</sup> (i.e., not a hydrazine-derivative); its DAO- and SSAO-inhibiting properties are comparatively weak.<sup>77,90,91</sup>

The conclusion is that, while TCP may reduce the metabolising capacity (i.e., breakdown) of dietary  $HA$ ,  $77,92$  the hydrazine-derivative

MAOIs (PLZ, ISO) have considerably greater such effects.<sup>93</sup> Patients who take PLZ or ISO are thus at greater risk for developing symptoms from excessive HA ingestion. $94$  An additional note of caution is therefore warranted for said patients: foods that may accumulate TYR (e.g., cheeses, meat, fish), may also have elevated HA levels.

# *Dopamine (DA)*

Dopamine (DA) in the brain is an important catecholamine neuromodulator<sup>95</sup>—however, for the present discussion, it is important to distinguish between its central<sup>96</sup> and peripheral<sup>97</sup> effects, as DA does not cross the blood brain barrier in vivo (barring some limited delivery by intricate, scientifically novel means of administration).<sup>98-100</sup> Consuming DA-rich foods (e.g., large quantities of bananas)<sup>101</sup> may cause elevations in plasma DA concentrations (via the release of endogenous DA, and/or via increases in L-dopa and/or other DA-precursors or -releasers); $^{102}$  raised peripheral DA may in turn cause vasoconstriction, resulting in BP increases.<sup>103</sup> The extent to which this may be relevant for MAOI patients is unclear due to a paucity of research data. Some portion control of DA-rich foods is thus advised. Dopamine (DA)<br>
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**80** *Van den Eynde, et al.*

# **Amino Acids**

Substantial intakes of various dietary amino acids (AAs) may affect BP (long-term or immediate effects): methionine (increases homocysteine levels),104 and alanine may result in BP increases; whereas cysteine,<sup>105</sup> arginine,<sup>106</sup> histidine, and threonine may lower  $BP^{107}$  but there is a relative paucity of reliable (and independently verified) research data, so that definitive statements on the effects of AAs on BP are premature.

Interactions between dietary AAs and certain medications are complex, and may be bidirectional: absorption of AAs may be reduced by certain medications,108,109 and absorption of certain medications may be reduced by the simultaneous intake of dietary AAs.<sup>110</sup>

Any evidence indicating major implications for the MAOI diet is absent in the literature; it is likely that this may be taken to constitute evidence of absence of any serious interactions, given moderate consumption patterns.

Two AAs that are at times weaved into MAOI-related discussions (albeit not typically out of dietary concerns) are L-dopa, and TRP; they are summarily reviewed hereunder, if only to clear up potential misconceptions.

# *Levodopa (L-dopa)*

Levodopa (L-dopa) is a precursor (but not a releaser) of  $DA^{111}$ (i.e., not an indirectly acting sympathomimetic like amphetamine),  $^{112}$ meaning the BP effects in MAOI patients are likely only (moderately) potentiated; see *supra*, *'Dopamine (DA)'*, for the presumable mechanistic explanation.

There is an analogy here between dietary L-dopa and TRP (see *infra*); it goes as follows: normal intakes of dietary TRP have not been reported to cause serious serotonin-mediated effects—and so one would expect, similarly, to find correspondingly limited effects of dietary L-dopa on BP.

# *L-tryptophan (TRP)*

L-tryptophan (TRP) is an essential AA; it is a precursor of serotonin, and plays an important role in a great number of metabolic processes.<sup>113</sup> There is a distinction to be made between (normal) dietary and (deliberately) supplemental quantities of TRP: experienced practitioners have been known to use TRP tablets/capsules as an augmenting agent with  $\text{MAOIs};^{114}$  this is an advanced treatment strategy that may result in (typically mild to modest) serotonin-mediated side-effects when comparatively high doses of TRP ( $\geq$ 2 g) are used (or if the starting dose/increase rate is too high).<sup>58</sup> By contrast, dietary TRP is not normally ingested in such high amounts, even in a TRP-rich meal (e.g., ∼400 mg TRP per 100 g of chicken breast); moreover, TRP absorption rates differ significantly if consumed alongside other AAs.<sup>115</sup> Explanator.<br>
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The conclusion is that normal, moderate consumption of TRP in meals is considered safe for MAOI patients.

# **The MAOI Diet—***Partim Specialis*

#### **Introduction**

This *Partim Specialis* of the *Prescriber's guid*e *to the MAOI diet* builds on the overarching principles set out in the *Partim Generalis.* The potentially relevant dietary interaction mechanisms have been discussed in sufficient detail in the preceding sections, and are preferably consulted in conjunction with the specialised food science data listed hereunder; read as such, this article presents a cohesive and comprehensive whole, in which 'the MAOI diet' is (finally) fully demystified.

Whilst the previously outlined considerations are thus not repeated in full, some of the most salient points are briefly restated where appropriate.

The following abbreviations are maintained:

Monoamine oxidase inhibitors (MAOIs): phenelzine (PLZ), tranylcypromine (TCP), isocarboxazid (ISO).

Biogenic amines (BAs): tyramine (TYR), histamine (HA), dopamine (DA).

Amino acids (AAs): levodopa (L-dopa), L-tryptophan (TRP). Blood pressure (BP).

The subsequent discussions on food science data will focus on TYR. The other BAs of some relevance (HA, DA), and the AA L-dopa are mentioned only when such is pertinent, i.e., in some specific food sections. TRP is not commented on, as potential interactions are not likely to be significant.

#### **Food Safety Standards and Biogenic Amines (BAs)**

Fresh, unfermented foods that are handled hygienically during production and storage (e.g., refrigerated at  $\leq 4^{\circ}C$ ) are likely to have low (or no) BA levels, and are safe to consume as part of a normal diet.

Many food production processes now make use of special startercultures that are aimed at minimizing BA accumulation.<sup>116–118</sup> Additionally, the increased (control on) hygiene and production standards worldwide<sup>119</sup> (e.g., the extensive monitoring procedures in regulations by the European Union)<sup>120</sup> have greatly contributed, and continue to do so, in reducing food-borne BA levels.21,121,122 That is why consulting *recent* food science data is so important.

# *Tyramine (TYR): A Tale of Fermented Foods and Spoiled Appetites*

TYR is the most hazardous BA for MAOI patients, and its dietary intake should be significantly reduced. TYR's formation in foodstuffs requires (a) the presence of the AA tyrosine, which is then (b) converted to TYR via microbial decarboxylation.123,124 This process may be the result of either the *deliberate* use of (some) fermentation processes, or of the *indeliberate* failure to maintain appropriate hygiene, production, and/or storage standards. Blood pressure (BP).<br>
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#### **Cheeses**

The TYR pressor response is also known, more colloquially, as the 'cheese effect'. A brief historical excursion may frame the discussion; it can explain why 'hypertensive crises' were comparatively commonplace (although still relatively rare) 'back then', and why that is no longer so. This brings us back to the olden days of psychopharmacology (1950s),

and to the 'serendipitous' discovery of the antidepressant (or 'psychic energizing')<sup>125</sup> action of iproniazid, an antitubercular drug that was also, later, found to inhibit MAO.126 This also brings us back to the seminal research by Blackwell et al. (1960s), who first described the cause–effect relationship with TYR, which was/is richly present in some cheeses, $127$  such as cheddar (TYR levels of 3500 mg/kg were found in cheddar samples by Bullock and Irvine, 1956).<sup>128</sup> It is a testament to their impressive foresight and pharmacological prowess that these publications have withstood the test of time, and remain of striking relevance even today.65,94,129–136

#### *General Overview*

Data from modern-day food science indicate that many (commercial) cheeses now have comparatively low TYR levels (e.g.,  $\langle 20 \text{ mg/kg} \rangle$ , whether they are hard, semi-hard, acid-curd style, or soft.<sup>31,33,137-140</sup> Some cheeses (e.g., matured varieties)<sup>141</sup> do still have high TYR levels (e.g., some acid-curd cheeses:  $\geq 335$  mg/kg TYR)<sup>21</sup>, with (typically) more TYR near the rind than in the core.142 Matured (typically for 3–6 months or more) and/or 'artisanal' cheeses will contain higher TYR levels than their 'commercial' counterparts.<sup>143</sup>

Mayer and Fiechter (2018) reported findings from 150 cheeses; they observed: <5 mg/kg TYR in 13 samples of extra-hard cheeses; mean TYR levels of ∼100 mg/kg in 14 samples of hard cheeses; <100 mg/kg TYR in 31 samples of blue-veined cheeses (with many <50 mg/kg TYR); mean TYR levels of ∼152 mg/kg in 14 samples of semi-hard cheeses; <7 mg/kg TYR in 12 samples of mould-ripened soft cheeses; ∼272 mg/kg TYR in 18 samples of smear-ripened cheeses; mean TYR levels of ∼157 mg/kg in 48 samples of acid-curd cheeses (with high variance: max. TYR levels of 1597 mg/kg).144 Spizzirri et al. reviewed 40 samples of hard-ripened, ripened, and unripened cheese styles: all had  $\leq 150$  mg/kg TYR.<sup>139</sup> Bullock and Irvine, 1956).<sup>128</sup> It is a testament to their impressive foresight and pharmacological provess that these publications have withstood the test of time, and general of striking relevance even today.<sup>65,54,122–</sup>

There are many different cheese styles; they are not all discussed here. The following subsections are ordered, for the most part, in accordance with the classification system presented by Almena-Aliste et al.<sup>145</sup> Some cheese styles (and indeed, some research set-ups) defy such rigorous classification, and may come in a range of textures, from 'fresh' to 'hard', depending in part on their maturation status. The following categories are thus merely indicative, and present a broad-sweep overview of TYR levels in some prominent cheese styles.

#### *Fresh Cheeses*

Fresh, non-matured (i.e., unripened/unaged) cheese styles (e.g., fresh cheese, mascarpone, ricotta, cottage cheese, bocconcini) are likely to have

low TYR levels, unless stored at unhygienic temperatures.146 Spizzirri et al. found undetectable TYR levels in 6 samples of robiola, ricotta, and mozzarella.139 Novella-Rodriguez et al. found max. TYR levels of 0.6 mg/kg in 20 such samples.147 Spizziri et al. also found TYR levels of <5 mg/kg in 3 fresh goat cheese samples, and undetectable TYR levels in a whey cheese sample (Ricotta Romana).<sup>139</sup>

#### *Soft and Semi-Soft Cheeses*

Brie and Camembert are typical examples of soft-ripened, 'bloomy rind' cheeses; these styles are made with surface moulds, are typically aged for several (e.g., 3–5) weeks before release, and are expected to have comparatively low TYR levels. Mayer et al. looked at 5 samples (from Austria, Denmark, and France), and found TYR levels of  $\leq 5$  mg/kg;<sup>33</sup> similarly, Bonczar et al.<sup>148</sup> found  $\leq$ 6 mg/kg TYR (3 samples). In some older reports (1960s), notably higher TYR levels (∼100 mg/kg) were reported;149,150 poor production and/or storage standards, or faulty assays are possible explanations. By contrast, Kosikowski (1950s) reported low/undetectable TYR levels.127 Colonna and Adda (1976) reviewed 20 samples of French Camembert, finding TYR levels of ∼100 mg/kg in many samples—but there was a wide variance (max. 1800 mg/kg TYR).151 De Vuyst et al. (1976) found TYR levels of 0–400 mg/kg in various Brie samples, with lower TYR levels (max. 20 mg/kg) in Camembert samples.<sup>152</sup> Voight et al. (1974) found TYR levels from  $0-260$  mg/kg in various Brie samples.<sup>153</sup> Soft and Semi-Soft Cheeses<br>
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Blue cheeses are made with internal moulds. Roquefort is an example of a blue-veined, sheep milk cheese; Mayer et al. examined 4 such samples, and found no TYR.<sup>33</sup> Komprda et al. tested various samples of Czech blue cheeses, establishing mean (380 mg/kg) and median (289 mg/kg) TYR levels, with a wide variance (10–875 mg/kg TYR).154 Novella-Rodriguez et al. found a wide range of TYR levels (0–1585 mg/kg) in  $20$  samples of blue cheeses.<sup>147</sup>

Smear-ripened cheeses are soft, and come in washed- and unwashedrind styles; BA levels in the unwashed varieties are significantly higher: Samková et al. examined 75 samples of various smear-ripened cheeses (aged ∼21 days); they found mean TYR levels of 1.7 mg/kg in 30 washed-rind samples, and mean TYR levels of 137 mg/kg (with a wide range of 17.5-469 mg/kg TYR) in 45 unwashed-rind samples.<sup>155</sup> Pleva et al. tested 6 samples of smear-ripened cheeses, and found TYR levels ranging from  $\sim$ 177–1200 mg/kg).<sup>156</sup>

Valsamaki et al. reviewed various Feta samples, a 'brined' (or 'pickled') cheese, finding variable TYR levels that increased with maturation (0 mg/kg TYR at day 1; 246 mg/kg TYR at day 120)<sup>157</sup>—note that, throughout the maturation process, these cheeses develop from 'soft' to 'hard'.

Pleva et al. established TYR levels for various soft, mould-ripened cheeses: 9 white-veined samples (TYR levels of 9.5–40 mg/kg), and 6 blue-veined samples (TYR levels of  $\sim$ 71–231 mg/kg).<sup>156</sup>

# *Other Cheeses*

#### **Hard Cheeses**

Spizziri et al. found that Parmigiano Reggiano samples (aged 24–30 months) had 20–150 mg/kg TYR (5 samples), and that Grano Padano samples (aged 12–22 months) had  $\langle 133 \rangle$  mg/kg TYR (5 samples).<sup>139</sup> Schirone et al. reviewed a variety of Pecorino cheeses from various regions in Italy. Some of these are 'artisan' type cheeses, and TYR levels may vary widely (more 'typical' values are 45–475 mg/kg TYR, but one sample had ∼1300 mg/kg TYR).143 Rea et al. reviewed various cheddar samples made with 6 different enterococci strains (TYR levels of <50 mg/kg after 4 weeks, and <200 mg/kg after 36 weeks).<sup>158</sup> These results align with older findings by Tarjan and Janossy  $(1978)$ ,  $^{159}$ who reported TYR levels of 70–210 mg/kg (3 samples). Variable, and sometimes lower TYR levels may be found (e.g., Bonzcar et al. found  $\leq$ 10 mg/kg TYR in some samples).<sup>148</sup> Hard Cheeses Spizzir et al. found that Parmigiano Reggiano samples (aged 24–30 Spizzir et al. founds) had 20–150 mg/kg TYR (5 samples), and that Grano Padano samples (aged 12–22 months) had <133 mg/kg TYR (5 samples).<sup>139</sup>

Komprda et al. tested various Dutch (semi-)hard cheeses: most samples had TYR levels of <50 mg/kg (max. 250 mg/kg TYR).160,161 Bunkova et al. reviewed Edam-style cheeses, noting that: '*Optimum ripening time of these products is 6–10 weeks, usually at a temperature of 10–14 °C. However, nowadays, young cheeses (2–4 weeks old) are delivered to retail by many producers for economic reasons.'*138 They found that TYR levels increased in approximately linear fashion during maturation and storage, from 60 mg/kg after 60 days, to max. 120 mg/kg after 100 days in the outer layer, or 'rind', and ∼70 mg/kg TYR closer to the core. Spizzirri et al. tested various Gruyere samples, finding TYR levels of <100 mg/kg; they also tested various Emmental samples, finding TYR levels of  $\sim$ 16mg/kg.<sup>139</sup>

Novella-Rodriguez et al. found a wide range of TYR levels when they examined 40 samples of hard-ripened cheese, of which 20 were made from raw milk (∼0–302 mg/kg TYR), and 20 were made from pasteurized milk (∼0–164 mg/kg TYR).<sup>147</sup>

Ripened goat cheese may contain variable TYR levels: Spizzirri et al. found 0–12 mg/kg TYR in 3 samples;<sup>139</sup> Novella-Rodriguez et al. established increasing TYR levels following ripening of goat cheeses (0 mg/kg at day 1, ∼25 mg/kg after 30 days, ∼55 mg/kg after 60 days, and ∼70 mg/kg after 90 days)162—but higher TYR levels may occur in some samples (e.g., Bonnetta et al. found an Italian goat cheese with 2000 mg/kg TYR).<sup>163</sup>

**85**

Fiechter et al. reviewed 47 samples of Austrian ripened acid-curd (sour milk) style cheeses, finding a wide variance of TYR levels (median TYR: 30 mg/kg; 95% quantile at 469 mg/kg TYR; max. 2000 mg/kg TYR in a sample of Ennstaler Steirerkäse with crumble texture).<sup>137</sup>

# **Processed Cheeses**

Many processed cheeses are expected to have low TYR levels: Ibrahim et al. analysed 45 samples (made from a variety of cheese types), and found mean TYR levels of ∼200 mg/kg for cheddar styles, and mean TYR levels of 100 mg/kg for Gouda styles. Some samples from Egyptian retail outlets (temperature and shelf-life unclear) had higher TYR levels  $(max. 800 mg/kg).$ <sup>164</sup>

# **Cheese Spreads**

TYR levels in cheese spreads depend on the cheese selection: whereas some commercial products may have little to no TYR, some higherquality cheese spreads (which may be made from vintage cheeses) may be high in TYR (e.g., a Parmareggio sample tested at 40 mg/kg TYR).139

# **MEAT PRODUCTS**

# *Fresh Meat Products*

While fresh and frozen meat products have low BA levels, they may accumulate in meat products that are not fresh (and are therefore subject to decomposition by micro-organisms).<sup>165–169</sup> It is essential to maintain proper storage temperatures  $(\leq 4^{\circ}C)$ : chilled meats that are stored for a limited time tend to have TYR levels  $\leq$ 10 mg/kg.<sup>165,170,171</sup> Triki et al. reviewed TYR levels of various meats (pork, lamb, turkey, chicken, beef) that were stored for  $0-10$  days at  $2^{\circ}C$ : for all meats, TYR levels were  $\leq 0.70$  mg/kg at day 0, and  $\leq 1.12$  mg/kg at day 3; TYR levels then rose precipitously by days 6 ( $\leq$ 28.5 mg/kg) and 10 ( $\leq$ 35.5 mg/kg).<sup>1/2</sup> Many processed cheeses are expected to have low TYR levels: Ibrahim<br>et al. analysed 45 samples (male from a variety of cheese types), and<br>found mean TYR levels of  $\sim$ 200 mg/kg for cheddar styles, and mean<br>TYR levels of

# **Poultry**

Various poultry meats (chicken, turkey, duck) were found, by several research groups, to have (very) low TYR levels<sup>173-177</sup> (e.g., one sample of duck had no detectable TYR).<sup>176</sup> Long storage times may result in TYR accumulations<sup>178–181</sup> (e.g., chicken stored at  $4 \pm 1^{\circ}$ C was found to have 3 mg/kg TYR after 1 day; after 20 days, TYR levels had increased to 15 mg/kg).173 Improperly stored or spoiled meats are likely to have high BA levels (e.g., a chicken sample with 222 mg/kg TYR).<sup>182</sup>

# **Beef and Pork**

Typical ('commercial-grade') beef is not usually aged, and typical TYR levels may be <10 mg/kg (e.g., Galgano et al. measured TYR levels of 7 mg/kg after 8 days of storage at 4°C).171 'Restaurant-quality' beef can have significant TYR levels when stored above 0°C: when stored at 4°C for 21 days, TYR levels of 60 mg/kg were found; after 36 days, they had increased to 120 mg/kg TYR.168 Beef that was stored at −18°C for 178 days was found to contain  $\leq$  4 mg/kg TYR.<sup>170</sup> Pork and fresh pork products are likely to have low (sometimes undetectable) TYR levels.183–185

# **Minced and Ground Meats**

Accurate TYR levels for minced and ground meats (e.g., hamburgers) cannot be provided due to the unpredictability of the preparation process: contaminant bacteria may find their way into the mix (as the mince has a large surface area), and the procured meat products may be stored sub-optimally. While one assay by Durlu-Ozkaya et al. found low TYR levels  $(<$ 3 mg/kg),<sup>186</sup> it is unclear how reproducible these findings are. It is a heartening sign that there are no case reports known to us indicating hypertension in MAOI patients following hamburger consumption—but caution and portion control remain warranted. A similar observation can be made with relation to other processed meat products of uncertain make (e.g., chicken nuggets, which have been implicated in hypertensive reactions in MAOI patients),187 for which BA levels cannot be reliably estimated. had increased to 120 mg/kg TYR.<sup>168</sup> Beef that was stored at  $-18^{\circ}\text{C}$  for 178 days was found to contain  $\leq 4$  mg/kg TYR.<sup>170</sup> Pork and fresh pork products are likely to have low (sometimes undetectable) TYR levels,

#### **Offal Meats**

Fresh offal (organ) meats are unlikely to contain significant TYR: various samples of fresh kidneys, livers, duck giblets, etc. were all found to contain low TYR levels.176,188–190 The fact that case reports of hypertensive reactions to such meats exist, $191,192$  appears to indicate, once more, the importance of proper production and storage practices<sup>193</sup> (and of avoiding unreasonably large portions).

#### **Meat Pâtés**

Providing accurate TYR levels for meat pâtés as a general category is not possible, much like is the case with minced and ground meats. The reasoning is that fresh meats have little to no TYR, but once processed (and possibly contaminated with various bacteria), the product becomes an ideal culture medium; i.e., any laxity in hygienic preparation, storage time, or temperature  $(\leq 4^{\circ}C$  is essential) will result in a

steady increase in TYR levels. Therefore, in contaminated and/or poorly stored products, TYR may rapidly accumulate (e.g., 100–500 mg/kg TYR after  $1-2$  weeks).<sup>194</sup>

# *Preserved Meat Products*

# **Dry-Cured Meats**

Dry-cured meat products (e.g., Parma ham, pastirma, jamon, prosciutto, coppa) that have been properly handled and stored may have comparatively low TYR levels<sup>195</sup> (e.g., Lorenzo et al. found TYR levels of 5–10 mg/kg in lacón, a dry-cured Spanish meat product)196—but there are numerous exceptions; e.g., Salchichón (280 mg/kg TYR), dry-cured ham (104 mg/kg TYR), $197$  and various salamis (20 commercial samples ranged from 0–355 mg/kg TYR, and 0–505 mg/kg HA).<sup>198</sup>

#### **Fermented Sausages**

*Van den Eynde, et al.*

**88**

TYR levels in fermented sausages (and similar products) depend heavily on the hygienic quality of the meat used, and on the strains of bacteria involved; those produced with frozen meat (low temperature processing) may well have  $\leq 100$  mg/kg TYR (owing also to the widespread usage of standardized starter-cultures,<sup>199</sup> which may have little/no AA decarboxylase activity—resulting in lower BA levels).200–205

Suzzi and Gardino reviewed 20 studies on fermented sausages from around Europe, and found that TYR levels were usually  $\leq 200$ mg/kg (mean values), but that some samples contained significantly more TYR  $(>600 \text{ mg/kg})$ .<sup>206</sup> Similarly, Ruiz-Cappilas and Jimenez-Colmenero identified some higher TYR samples,<sup>195</sup> and so did Bover-Cid et al.: they examined various samples of Spanish fermented sausages (Chorizo, Fuet, Sobrasada, and Salchichón), finding TYR levels of  $\leq 600$  mg/kg in some sausages, with mean values of about 200 mg/kg TYR.207 Various other samples (some artisanal, some industrial) were found to have TYR levels of  $\leq$ 270 mg/kg.<sup>206,208</sup> Papavergou et al. tested 50 samples of dry fermented sausages sold in Greece; they were found to contain mean TYR levels of 100 mg/kg, and max. TYR levels of 500 mg/kg. $^{209}$ Dry-Cured Meats<br>Dry-cured meat products (e.g., Parma ham, pastirma, jamon, prositured may that product and products  $^{195}$  (e.g., Lorenzo et al. found TYR levels<br>of 5–10 mg/kg in lacon, a dry-cured Spanish meat product)<sup></sup>

> Hygiene standards continue to improve: more recent surveys tend to find lower BA levels:202,210,211 e.g., Latorre-Moratalla et al. (2012) tested fermented sausage samples, and found average TYR levels of 150 mg/kg (with max.  $\langle 200 \text{ mg/kg} \text{TYR} \rangle$ .<sup>201</sup>

# **FISH PRODUCTS**

#### *Fresh Fish*

BA levels in fish are dependent, to a substantial degree, on the freshness of the product and on the use of proper, low-temperature handling and storage methods; $^{212}$  as such, quality control and screening of imported fish produce continue to be powerful forces for improving hygiene standards worldwide.<sup>175,213</sup> Whilst all BA levels (e.g., TYR and HA) may be significantly increased if such conditions are not maintained, it is important to note that BA levels do not necessarily increase simultaneously and proportionally: fish spoilage can result in greatly elevated HA levels,  $2^{14}$  without the occurrence of correspondingly significant increases in TYR levels.215 To further illustrate: Özogul and Özogula tested TYR levels of fresh, ice-stored (∼2°C) herring, and found <5 mg/kg; whilst the specific storage conditions of these samples varied a little, HA levels could reach 400 mg/kg whilst TYR levels remained comparatively low.<sup>216</sup>

Fresh, properly handled (raw or processed) seafood products are expected to have low TYR levels:<sup>217</sup> various such samples were found to have 1–5 mg/kg TYR.<sup>218,219</sup> Whole and filleted trout that had been kept on ice for up to 18 days had TYR levels of  $\leq 7$  mg/kg.<sup>220,221</sup> Emborg et al. tested various samples of fresh (frozen) salmon, and established max. TYR levels of  $\leq$ 25 mg/kg by the end of shelf life (14–21 days), whereas TYR levels of thawed salmon had increased to just below 70 mg/kg by the end of shelf life (21-34 days).<sup>218,222</sup> Kulawik et al. found TYR levels from 10–14 mg/kg in 6 supermarket-bought ready-to-eat-sushi samples.223 The following fish samples (freshness unknown) have tested high in TYR  $(>100 \text{ mg/kg})$ : amberjack, anchovy, cod, mackerel, tuna.<sup>182</sup> of imported fish produce continue to be powerful forces for improving<br>hygien standards worldwide.<sup>175,233</sup> Whilst all BA levels (e.g., TYR and<br>HA) may be significantly increased if such conditions are not main-<br>tained, it

With respect to containing HA levels, Abajay et al. further demonstrated the importance of storage time and conditions: they tested 2 samples of market-bought yellowfin tuna; sample 1 was immediately gutted and subjected to HA level analyses for 18 h (HA levels of 3.18 mg/kg), and sample 2 was gutted 12 h after purchase and subjected to the same storage conditions (HA levels of 6289 mg/kg).<sup>224</sup>

As previously outlined—see *supra*, *'Histamine (HA)'*—the ingestion of high HA foods may cause Scombroidosis (HA poisoning);<sup>24,217,225</sup> this is a form of food-borne intoxication,  $226$  on which Visciano et al. state that the *'consumption of meals with HA concentrations of 8–40 mg can cause only slight intoxication, while values of 40–100 mg or higher than 100 mg are associated with intermediate and severe intoxication, respectively'*. 227

**89**

Many regulations in various jurisdictions are thus aimed at limiting HA levels:<sup>227,228</sup> e.g., the US Food and Drug Administration (FDA) considers fishery products that have <50 mg/kg HA to be 'decomposed', and products that have  $\leq$ 500 mg/kg HA to be a 'health hazard';<sup>226</sup> EU regulations set HA standards at 200 mg/kg for various 'fishery products from fish species associated with a high amount of histidine', and at 400 mg/kg HA for 'fishery products which have undergone enzyme maturation treatment in brine, manufactured from fish species associated with a high amount of histidine'.<sup>229</sup>

Patients who take a hydrazine-derivative MAOI (PLZ, ISO) are advised to exercise additional care with regard to HA intake; this is less of a concern for TCP patients (see *supra, 'Histamine (HA)'*).

# *Other Fish Products*

# **Cured Fish Products**

The preservation of fish products via curing (instead of canning or refrigerating) is of great cultural and historical significance, and is still widely done today; fish curing is a broad term that comprises various preservation methods: smoking, drying, marinating, pickling, salting, fermenting, as well as combination methods.230 Variable BA levels are likely to occur, and may be high in some products (e.g., fermented seafoods such as surströmming, rakfisk, and kæstur hákarl);231 an exhaustive list cannot be provided. Test results from some samples are listed hereunder. 400 mg/kg HA for 'fishery products which have undergone enzyme<br>maturation tratment in brins, manufactured from fish species associ-<br>ated with a high amount of histidine<sup>7,239</sup><br>Particular divisor the caliburation of the si

Smoked salmon (dry-salted, sliced, vacuum-packed) was found to contain no TYR after 4 weeks of storage (as sterile, cold-smoked salmon blocks); the specific storage conditions were as follows: 9 days at 4°C, and 19 days at 8°C.232 Jørgensen et al. tested various cold-smoked salmon samples, and found TYR levels of  $\langle 20 \text{ mg/kg}^{233}$ —but Köse et al. found samples that had up to 470 mg/kg TYR.<sup>234</sup>

Gravlax is made from dry-salted fish filets (salmon, mackerel, trout, herring); Wiernasz et al. tested 7 samples of salmon gravlax that had been treated with various bioprotective bacterial cultures, and found max. TYR levels of  $\leq 25$  mg/kg after 21 days of storage.<sup>235</sup> Periago et al. found TYR levels of 90 mg/kg in samples of dried and salted tuna roe.<sup>236</sup>

# **Canned Fish Products**

Veciana-Nogues et al. tested several canned tuna samples, and found TYR levels of  $\leq 10$  mg/kg for most samples;<sup>237</sup> canned, pickled herring (3 samples) had  $\leq$ 10 mg/kg TYR and  $\leq$ 3 mg/kg HA; some samples of semi-preserved anchovies contained up to 70 mg/kg TYR and

220 mg/kg HA.238 High HA levels were also found in some canned fish samples, with one sample reaching 1000 mg/kg HA.239,240

#### **Fermented Cereals**

#### *General Overview*

There are a great many fermented cereal products available worldwide. Such products can be made from various cereals (e.g., wheat, maize, barley, oat, barley, rye, rice, millet, sorghum); they include boza, idli, injera, kumru, khambir, uji, kunu, dhokla, tarhana—and many more varieties exist.<sup>241</sup> They may have significant BA levels;<sup>242</sup> e.g., Yeğin and Üren tested 11 samples of boza, and found a range of TYR levels of 13–65 mg/kg;<sup>243</sup> Özdestan and Üren tested 20 samples of tarhana, and found a range of TYR levels of 50–100 mg/kg.<sup>244</sup> Data on BA levels in many fermented cereals remain to be collected; caution is warranted.

#### *Sourdough Bread*

Sourdough bread is produced with the use of bacterial activity in the starter-culture for making the dough. BA levels are lower when standardised starter-cultures (with minimal decarboxylase activity) are used, as is now generally the case with commercial production.<sup>118</sup> However, artisan-producers may utilise cultures with greater decarboxylase activity. Therefore, their products may sometimes contain significant TYR levels (e.g., Rizzello et al. (2010) found TYR levels of ∼700 mg/kg in sourdough fermented wheat germ;<sup>245</sup> Mannino et al. (2022) tested 6 sourdough bread samples—3 of which were made in a bakery  $\left($  <0.4 mg/kg TYR), and 3 of which were home-made (wide range of 5–120 mg/kg TYR).246 Özdestan et al. tested 10 samples of kumru (a similar Turkish food) from different manufacturers, and found TYR levels  $\leq$  5 mg/kg.<sup>242</sup> There are a great many fermented cereal products available worldwide. Such products can be made from various cereals (e.g., whent, maize, barley, oat, barley, reg, millet, sorghum); they include boza, ald, i, njera, kumun

#### *Marmite and Related Products*

Marmite and related products (Bovril, Promite, Vegemite, etc.) are made from brewers' yeast extract, which may contain wheat, barley, and rye. These products are considered high in BA content: recent TYR level readings range from 322 mg/kg<sup>247</sup> to ∼650 mg/kg<sup>248</sup>—both numbers are significantly lower than Blackwell et al.'s earlier (1960s) estimate of ∼1500 mg/kg TYR; this may represent improvements in production technique, or measurement inaccuracies.<sup>94,135,136</sup> There is a relative paucity of recent data pertaining to BA level measurements in these products.

#### **91**

#### **Soups and Sauces**

#### *Soy Sauces and Soups*

Various soy-derived products (those not previously discussed), such as miso soups, and soy sauces, are expected to have elevated BA levels, <sup>249,250</sup> similar to processed soy foods (see *infra)*. Miso has been implicated in hypertensive reactions in MAOI patients<sup>251</sup>—but this case report is from 1987; modern hygiene and production standards may have contributed in reducing BA levels in many (but not all) such preparations.250,252

Yongmeia et al. examined BA levels in 40 samples of Chinese soy sauces, finding a wide range of TYR (8.5–600 mg/l) and HA levels  $(0-300 \text{ mg/l})$ .<sup>253</sup> Similar results were observed by Stute et al., who found one soy sauce sample that had  $5250 \text{ mg/l TYR}$ .<sup>254</sup> Guidi and Gloria tested TYR levels in 42 such samples: in 12 samples, TYR was <29 mg/l; in 4 samples, TYR was between 30–99 mg/l; in 25 samples, TYR was between 100–499 mg/l; in 1 sample, TYR was between  $500-799$  mg/l.<sup>249</sup> Ibe et al. reviewed TYR levels in the moromi mash used in some soy sauce preparations; they found max. TYR levels of 940 mg/l, with many samples ranging from  $10-200$  mg/l TYR.<sup>255</sup> hypertensive reactions in MAOI patients<sup>251</sup>—but this case report is from<br>1987; modern hygine and production standards may have contributed<br>in reducing BA levels in many (but not all) such preparations.<sup>260,292</sup><br>Morgmeia

Cho et al. tested various samples of miso (all  $\leq 25$  mg/l TYR) and soy sauces (all <50 mg/kg TYR).250 Byun and Mah tested 22 miso samples, and found a wide range of TYR levels (from low/virtually none to  $>70$  mg/kg); as previously discussed, this may in part be explained by varying hygiene standards.256 Kung et al. tested 40 misu samples, and found that all contained  $\leq 50$  mg/l TYR.<sup>257</sup>

#### *Fish Sauces*

Fish sauces may contain various seafoods (including anchovies) that have been allowed to ferment for extended periods; names include: budu (Malaysia), patis (Philippines), ngapi (Burma), ishiru ( Japan), yeesu (China), etc. BA levels for all these varieties cannot be listed (and may not yet be available).<sup>23,254,258</sup>

Cho et al. tested BA levels in Korean fish sauces (made from a variety of seafoods, including scallop, squid, etc.) and found average TYR levels of ∼350 mg/kg TYR, with one (anchovy-based) sample testing at 600 mg/kg TYR.<sup>250</sup> Stute et al. tested 45 samples of commercial fish sauces from the Far East: many samples had TYR levels  $\leq$  250 mg/kg; the highest TYR level found was 588 mg/kg.<sup>254</sup> Saaid et al. tested various samples of *budu* and *cincalok* (Malaysian appetizers), and found TYR levels of  $\leq 450$  mg/kg.<sup>258</sup> Naila et al. tested 28 samples of *rihaakuru*, a fish paste condiment, and found TYR levels of 0–93 mg/kg, and HA levels of  $0-5100$  mg/kg.<sup>259</sup>

Similar products, such as Worcestershires sauces, are available in many varieties from many producers; typical preparations are fermented, and may contain hydrolyzed vegetable protein, soy sauce, or anchovies.<sup>260</sup> There are no data available on TYR levels; caution (or outright avoidance)<sup>261</sup> is thus warranted.

#### *Bouillon-based Broths*

Typical bouillon cube-based broths and soups (e.g., meat or soup bases and extracts made with chicken, beef, or vegetable bouillon) are expected to have low (or no) TYR, as these products are not usually fermented.262 Populin et al. tested various broths (homemade or canned products from the market), soups (ready-to-eat soups, condensed soups, and creams), soup bases (bouillon cubes, pastes, and granulated powders), sauces, and salad dressings from the European and US markets; they found increased levels of the BA putrescine in products that contained monosodium glutamate (MSG), but TYR levels remained at  $\leq 10$  mg/kg in all samples.<sup>247</sup> Bouillon-based Broths<br>
Typical bouillon cube-based broths and soups (e.g., meat or soupled<br>
bases and extracts made with chicken, heef, or vegetable bouillon) are<br>
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**93** *Van den Eynde, et al.*

#### **Vegetables**

#### *General Overview*

Fresh vegetables typically have comparatively low BA levels; Moret et al. tested various typical vegetables (e.g., lettuce, onion, carrot), and found TYR levels of  $\leq 12$  mg/kg (only spinach, broad bean, potato, and arugula tested at 7–12 mg/kg TYR; the other samples tested at  $\leq$ 3 mg/kg TYR)<sup>263</sup>—but spoilage can cause increased BA levels (e.g., 8-fold increases in pre-packaged salad/leafy vegetable mixes after 6 days of storage).  $262$ 

Glória compiled TYR levels from various research studies; the following all tested  $\leq$ 5 mg/kg TYR: broccoli, cassava (cooked), cauliflower, collard greens, lettuce, parsley, fresh spinach.<sup>264</sup> Similarly low TYR levels were found in asparagus, carrot, chard, sweet corn,  $37$  and potato.  $265$  Higher TYR levels were found in canned hearts of palm ( $\leq 7.8$  mg/kg), spinach purée ( $\leq$ 10 mg/kg),<sup>264</sup> arugula (12 mg/kg), cabbage (18.6 mg/kg);<sup>182</sup> frozen spinach purée (mean of ∼10 mg/kg; max. of ∼32 mg/kg).<sup>266</sup> Spinach may also have high HA levels  $(27.5-100 \text{ mg/kg})$ .  $265,267$ 

Plants produce a range of amines and psycho-active alkaloids (e.g., opiates, cannabis, tannins, nicotine, atropine, hyoscine, aperients, innumerable toxins); our scientific understanding of these topics is rapidly advancing<sup>263,265,266,268</sup> (e.g., the recently emerged research on the potential effects of capsaicin and menthol on trace amine-associated

receptors and transient receptor potential channels).269,270 The particular relevance of such developments in plant science for MAOI patients is at this point unclear.

# *Legumes*

BA levels were shown to vary considerably in different germinating legume seeds, including chick peas, lupine seeds, and broad beans.<sup>262</sup> Glória<sup>264</sup> reviewed TYR levels from various research studies: fresh chickpea (3.7 mg/kg), germinated chickpea (12.1 mg/kg), fresh broad bean (6.2 mg/kg), germinated broad bean (13.6 mg/kg), fresh lupine (7.8 mg/kg), germinated lupine (12.2 mg/kg). Variable TYR levels were found in 12 samples of green beans (0–10 mg/kg), and in frozen peas  $(\leq 16.5 \text{ mg/kg})$ .<sup>37</sup> Low/undetectable TYR levels were found in various beansprout samples,<sup>264</sup> yellow/purple/white bean, peanut (7 samples), pea (9 samples) chickpea (4 samples), lentil (7 samples).<sup>37</sup> BA levels were shown to vary considerably in different germinating<br>legume seeds, including chick peas, lupins seeds, and broad beans,<sup>262</sup><br>Glória<sup>264</sup> reviewed TYR levels from various research studies: fresh<br>chickpea (3.7

Some legumes contain significant amounts of L-dopa in some tissues, at some stages of growth; they include *Vicia faba* L. varieties (fava/faba beans or broad beans),271 and *Mucuna pruriens* (cowhage or itching powder).272–278

# **Fava Beans**

Fava beans were found to contain TYR levels of ∼10 mg/kg (various samples).263 Topal and Bozoğlu measured L-Dopa levels272 in the leaves (<34 mg/kg), flowers (<97 mg/kg), and fresh pods (<53 mg/kg) of 20 different fava bean genotypes.279 Brown et al. noted the presence of significant DA levels in the pods, but not so much in the seeds.<sup>280</sup>

# **Soy Bean Products**

# *Fresh soy products*

Soy bean products tend to be rich in protein. Soy beans themselves have low/undetectable TYR levels,<sup>264</sup> but they are not eaten raw. Fresh soy products trend towards low TYR levels,<sup>281</sup> assuming proper handling and storage conditions are maintained<sup>282</sup>—such is evidenced by Yue et al. who tested 6 samples of firm (unprocessed) tofu, and found high TYR levels in 2 samples (31.5 mg/kg and 185 mg/kg), and low TYR levels ( $\leq$ 2.5 mg/kg) in the other 4 samples.<sup>283</sup> Sánchez-Pérez et al. report findings of undetectable TYR levels in 6 fresh tofu samples.<sup>37</sup>

# *Processed Soy Products*

Processed soy bean products, some of which may be fermented (e.g., natto,  $^{284,285}$  sufu),  $^{286}$  are more prone to having significant BA (TYR

and/or HA) levels (e.g., some stinky tofu samples were found by Gu et al. to have  $\leq 170$  mg/kg TYR;<sup>287</sup> some sufu samples were found by Guan et al. to have low or undetectable TYR levels, whereas some other such samples had TYR levels ranging from 10–470 mg/kg).<sup>288</sup> Kung et al. tested various Taiwanese sufu samples (12 white sufu samples, and 10 brown sufu samples; the TYR levels were recorded, respectively, at  $\leq$ 40 mg/kg, and at  $\leq$ 64 mg/kg).<sup>289</sup> Soy bean pastes (Doenjang) were analyzed (23 samples) by Shukla et al.: some had low undetectable TYR levels—but several samples contained >1000 mg/kg TYR.290 A full list of soy products (which exist in abundant varieties, both fresh and processed) cannot be provided.

#### *Fermented Vegetables*

Vegetables that are most commonly fermented include 'cabbage (sauerkraut, kimchi), cucumbers, onions, carrots, and garlic';291 TYR may accumulate to significant levels in such products.<sup>292</sup> Świder et al. tested various fermented vegetables (several samples each), and reported the following TYR levels (mg/kg):, broccoli (47–182), brussel sprout (120–204), radish (15–36), champignon (0.5–85), garlic (1–22), white cabbage (29–105), red cabbage (0–112), kimchi (1.2–99), cauliflower (0.3–136), beetroot (1–48), carrot (0–61), sunchoke  $(0-1.4)$ .<sup>292</sup> Kalac and Glória reviewed over 100 sauerkraut samples from 7 different countries; many had TYR levels of <200 mg/kg, but some samples had 400–900 mg/kg TYR.293 Kimchi, may also have significant TYR:294 Cho et al. tested various samples (max. TYR level found was 120 mg/kg).250 Kirschbaum et al. tested 5 samples of sauerkraut juice, and found TYR levels of ∼30–70 mg/l.<sup>295</sup>  $\approx$ 40 mg/kg, and at  $\approx$ 64 mg/kg)<sup>289</sup> Soy bean pastes (Doenjang) were<br>analyzed (23 samples) by Shukla et al.: some hal dow undetectable TYR<br>levels—but several samples contained >1000 mg/kg TYR<sup>290</sup> A full<br>list of soy

# **Fruits**

#### *General Overview*

Most fresh fruits have low TYR levels (e.g., undetectable TYR in apple,182 peach, pineapple, cherry, grapefruit, kiwi, lemon, green/red pepper);<sup>37</sup> Glória<sup>264</sup> reviewed BA levels of various fruits, and recorded TYR levels  $\leq 5$  mg/kg for the following samples: banana (green, ripe, overripe), fresh tomato, eggplant (whole, seed, pulp), red plum, strawberry, capers, jilo. Similarly low TYR levels were found in samples of courgette, cucumber, pumpkin.37 The following fruit samples had higher TYR levels: raspberry (12.8–92.5 mg/kg), eggplant peel (141 mg/kg), tomato paste (≤32 mg/kg), ripe banana pulp (∼50 mg/kg). Other reports found higher TYR levels in banana  $(23.5 \text{ mg/kg})$ ,  $^{182}$  mandarin

(13 samples: 0–5.8 mg/kg), tomato (0–6.4 mg/kg in 53 samples), plum (2 samples:  $1-7$  mg/kg).<sup>37</sup> García-García et al. found undetectable TYR levels in canned ripe olives; they also tested several other packed (pickled, unfermented) products: capers, caperberries, cucumbers all had TYR levels of  $\leq$ 4.5 mg/kg.<sup>296</sup>

#### *Avocados*

There is a case report of elevated BP in a TCP patient who had consumed 4 avocados (possibly ripened) and an undisclosed amount of guacamole.297 Whilst some reports estimate TYR levels in avocados to be ∼23 mg/kg,<sup>264</sup> others offer lower estimates (0.5–5.5 mg/kg TYR).<sup>37</sup> On the whole, there is a paucity of recent BA data; additionally, ripening/spoilage may cause considerable increases—moderation in consumption patterns is therefore advised.

#### *Bananas*

*Van den Eynde, et al.*

**96**

Borges et al. reported in their extensive and recent study (2019) of many banana-varieties (including plantains), that various BAs, including TYR, HA, DA, spermidine, and spermine all decreased during the ripening process in most genotypes.<sup>298</sup> They noted, additionally, that TYR levels in the pulp were remarkably consistent across different genotypes (∼100 mg/kg, dry weight); they observed a wider variance of TYR levels in the peel (100–300 mg/kg, dry weight).

The first report relating banana consumption to DA-ergic effects stems from 1958.299 Large amounts of banana can increase plasma DA concentrations.<sup>300</sup> As with other plants, BA levels will vary widely, depending on the stage of growth, on which part of the plant is measured, on maturation and ripeness status, etc. BA levels may be higher in the skin than in the pulp.101,301–304 Borges et al. tested various banana samples, and found in the pulp: DA levels of 300– 400 mg/kg, and L-dopa levels of 50–70 mg/kg (dry weight); and in the peel: DA levels of  $\leq 6200$  mg/kg, and L-dopa levels of  $\leq 70$ mg/kg (dry weight).298 Older data largely concurs: findings include DA levels of  $\leq 400$  mg/kg in the pulp, and  $\leq 1500$  mg/kg in the skin.265,301,305 Aronados There is a case report of elevated BP in a TCP patient who had consumed 4 arous<br>does (nossibly ripened) and an undisclosed anomator of guaramole 2<sup>397</sup> Whilst some reports estimate TYR levels in a<br>wocados to be ~

# *Peppers*

Kang et al. reported on TYR levels in blended, freeze-dried (-80°C) bell pepper (∼300 mg/kg, dry weight) and green hot peppers (∼145 mg/kg, dry weight).<sup>268</sup>

# *Fermented Fruits*

Świder et al. reported the following TYR levels in fermented fruits (several samples): cucumber: 28–87 mg/kg, pumpkin: 20–112 mg/kg, tomato:  $0.5-24$  mg/kg, pepper:  $15-23$  mg/kg, and olive:  $1.7-4$  mg/kg.<sup>292</sup> Fermented, minced peppers were found to contain TYR levels of  $\leq$ 2.5 mg/kg after 10–12 weeks of storage.<sup>306</sup> Tofalo et al. found no TYR in 7 varieties of fermented table olives.<sup>307</sup>

# *Varia*

There remain foods (fruit-based, in this case) that may bring about unexpected effects, e.g., a patient reported to *PsychoTropical Research* that she noticed significant BP increases after consuming (undisclosed amounts of) quince paste—a plausible explanatory mechanism may be that this food product acts as an inhibitor of DA reuptake.<sup>308</sup>

# **OTHER FOODS**

# *Dairy Products (other than cheese)*

Fresh milk was found to have undetectable TYR levels.<sup>309</sup> This does not hold true for fermented milk products, such as kefir, which may have variable TYR levels  $(0-13 \text{ mg}/1 \text{ in } 10 \text{ samples})$ .<sup>310</sup> Some fermented milk products (buttermilk, most yoghurts) are expected to have low BA levels, whereas some others (e.g., kumis) have comparatively high total BA levels (15.3 mg/l).<sup>140</sup> Novella-Rodriguez et al. detected no TYR in 5 yoghurt samples;146 Cho et al. tested 8 Korean yoghurt samples, and found max. 4 mg/kg TYR).250 Yılmaz and Gökmen tested 7 samples made with different bacterial starter cultures, and found TYR levels ranging from ∼0–31.5 mg/kg.<sup>311</sup> More exotic products may have higher TYR levels (e.g., yoghurt made from fermented yak-milk tested at 900 mg/kg TYR). 312 <sup>252</sup>. Imply ag atter 10<sup>-1</sup>/2 weeks of storage. Totato et at. found in<br>
TYR in 7 varieties of fermented table olives,<sup>307</sup><br>
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There remain foods (fruit-based, in this case) that may bring about<br>
timespected effects,

# *Condiments*

Kalač et al. tested 24 samples of ketchup, and found mean TYR levels of 33.6 mg/kg, and max. TYR levels of 149 mg/kg.266 Sánchez-Pérez et al. found undetectable TYR levels in 3 ketchup samples.<sup>37</sup>

#### *Mushrooms*

Jabłońska-Ryś et al. tested various (un)processed mushrooms species, and found high TYR levels  $(\leq 3000 \text{ mg/kg})$  in several dried or pickled

samples of bolete and jelly ear mushrooms, and undetectable TYR levels in 6 common raw mushrooms—but significant variability in BA levels may be expected in different mushroom species.<sup>313</sup>

# *Nuts*

Undetectable TYR levels were found in almond, pine nut, pistachio,  $^{182}$ chestnut, sunflower seed; additionally, 9 samples of hazelnut were tested  $(0-2.6 \text{ mg/kg TYR})$ .<sup>37</sup>

#### *Chocolate*

Restuccia et al. reported BA levels of 48 cocoa-based products (white/ milk/dark chocolate, cocoa powder, chocolate spread/syrup, etc.); none of the samples had TYR levels  $\geq 35$  mg/kg, with many being  $\leq$ 10 mg/kg.<sup>314</sup> Other studies found lower TYR levels ( $\leq$ 3 mg/kg) in various samples of dark/milk/white/85% cocoa chocolate.<sup>265,315–318</sup>

# *Compound Foods (e.g., pizza)*

TYR levels in compound foods can vary significantly (i.e., it depends on what you put on it). Shulman and Walker (1999) concluded that most pizzas from *'large chain commercial outlets'* (which tend to use either non-matured, or commercial processed cheese) are safe.<sup>261</sup> Sensible caution remains appropriate: some gourmet pizzas may use cheeses higher in TYR. Also, salami toppings may add to total TYR content. Undetectable TYR levels were found in almond, pine nut, pistachio, <sup>182</sup><br>chestnut, unflower seed; additionally, 9 samples of hazelnut were tested<br>(0–2.6 mg/kg TYR).<sup>37</sup><br>*Chocolate*<br>Restuccia et al. reported BA levels of 4

#### *Varia*

Many plant-derived substances (alkaloids), e.g., various herbs and/ or beverages, like coffee and tea, may contain compounds that act, in a sense, as 'drugs' (e.g., stimulants such as caffeine, 2-phenylethylamine, methylamine, trimethylamine).<sup>319</sup> These substances affect everyone, but may have an exaggerated effect in MAOI patients; There is a case report of coffee-induced hypertension (unrelated to TYR) in a TCP patient.<sup>320</sup> Such products should be consumed either in moderation, or should be avoided if they precipitate symptoms such as tremor, anxiety, jitteriness, palpitations, tachycardia, agitation, or poor sleep.

The ingestion of 400–1600 mg of monosodium glutamate (MSG) was found by Balon et al. not to elicit BP increases in TCP patients.<sup>321</sup>

# **98**

# *Health and Sport Supplements*

Substances which are allegedly efficacious in improving health and/or sports performance should be approached with some wariness: they may contain various (sometimes illegal) additives,<sup>322</sup> some of which are potentially injurious, and some others quite useless. The commonest adulterants are serotonin reuptake inhibitors, like sibutramine (risk of serotonin toxicity), steroids, stimulants, and sildenafil (Viagra). Producers should list the ingredients—if they do not (clearly and reliably) provide such information, their supplement should not be used. If the ingredients are listed, one can follow the precepts outlined in this guide to assess whether the product is safe; caution remains warranted (e.g., low starting dose). monest attaceants are sectomen requireds mimotos, the solutatime<br>
(risk of serotonin toxicity), steroids, stimulants, and sildenafll (Viagra).<br>
Producers should list the ingredients—if they do not (clearly and reliably) p

#### **Alcoholic Beverages**

Many alcoholic beverages may be safely consumed in moderation.<sup>248</sup> That is because modern, hygienic production processes have, for the most part, resulted in significantly reduced BA levels—but this does not hold universally true: e.g., some home-made ('boutique', or 'artisan') wines and beers may have high BA levels still.

Note that the alcohol content of a drink does not correlate with the potential for BA formation (e.g., depending on the production process, non-alcoholic beers may also have high BA levels; this is the case for spontaneously fermented non-alcoholic beers, in which TYR levels of 31.5 mg/l have been found).  $323$ 

An important reminder: TYR in liquids, certainly when taken on an empty stomach, will be much more rapidly absorbed,  $60,63$  so that additional caution is warranted.53,324

#### *Wines*

Most wine is safe to drink in moderation. Total BA content in wines depends on several factors (including the winemaking method used, e.g., typically more BAs in red wines than in white wines—this is due, likely, to the typically greater role of malolactic fermentation in producing red wines); $325$  various BAs may be formed during several distinct 'vinification stages', e.g., during malolactic fermentation (lactic acid bacteria), during alcoholic fermentation (yeast metabolism), or during the botrytization process undergone by some wines (made from 'noble rot'—i.e., fungi-infested grapes).326 Other factors include: climate and soil type,  $327,328$  length of exposure to yeast lees, and the level of bacteria variety and activity (microflora complexity increases as pH does).<sup>329</sup>

Moreno-Arribas and Polo tested various aged wines (all  $\leq 5$  mg/l TYR).330 Mafra et al. tested 30 different wines, including aged and fortified wines (Port and Madeira), finding TYR levels  $\leq 5$  mg/l.<sup>331</sup> Jayarajah et al. found similar TYR levels ( $\leq 3$  mg/l) in various USA wines.<sup>325</sup> Gómez-Alonso et al. tested 18 red wines and 14 white wines; all had  $\leq 5.5$  mg/l TYR.<sup>332</sup> Rioja crianza red wines were found to have, on average, TYR levels of 5.78 mg/l.326 Ginterová et al. found TYR levels of 1.5–2.5 mg/l in 7 Czech red wine samples.333 Marcobal et al. tested 61 different Spanish wines, including aged Rioja Gran Reserva wines; they found TYR levels ranging from 0–11.32 mg/l, with only 34 of 61 wines having detectable TYR.334 Henríquez-Aedo et al. tested 60 samples of Chilean reserve varietal wines, and found TYR levels  $\leq 6.5$  mg/l.<sup>335</sup> Hannah et al. reported on TYR levels in 12 white wines  $(\leq 6.6 \text{ mg/l})$ , 10 red wines  $(\leq 3.8 \text{ mg/l})$ , and 12 chiantis  $(\leq 4.7 \text{ mg/l})$ .<sup>336</sup> on average, TYR levels of 5.78 mg/l,<sup>326</sup> Cinterová et al. found TYR levels of 1.5–2.5 mg/l,<sup>317</sup> Mzech red wine samples.<sup>333</sup> Marcobal et al. tested 61 different Spanish wines, including aged Rioja Gran Reservations, the

Jayarajah et al. tested various wines and sakes: all were  $\leq 4$  mg/l TYR, but HA levels were higher in some samples:  $\leq 50$  mg/l.<sup>325</sup> Konakovsky et al. tested 100 high-quality Austrian red wines: TYR levels ranged from 1.07–10.7 mg/l (median: 3.52 mg/l); HA levels ranged from 0.52–27 mg/l (median: 7.20 mg/l).337 Other researchers tested 300 wine samples for TYR levels (all  $\leq 5$  mg/l),<sup>338,339</sup> and 200 wine samples for HA levels  $(1.2 \text{ mg/l on average})$ .  $340$ 

Some wines have higher TYR levels, e.g., some Spanish red wines  $(\leq 19 \text{ mg/l})$ .<sup>326</sup> Hlabangana et al. tested 9 red wines (young, Crianza, Reserva), and found a wide range of TYR levels: 9–64 mg/l.<sup>341</sup> Arrieta and Prats-Moya tested TYR levels in 7 young wines (all  $\leq 10$  mg/l), 3 Crianza wines (4.8–11 mg/l), and 4 Fondillón wines (6.8–18.5 mg/l).  $342$ Preti et al. tested 60 Italian wine samples, and found 8 with TYR levels  $>10 \text{ mg}/1.343$ 

#### *Vinegars*

Variable TYR levels have been reported in vinegars, e.g., 15.7 mg/l in both Aceto Balsamico and Sherry vinegar, but 416 mg/l in a rice-based vinegar made with salt (and undetectable TYR in a rice-vinegar made with sucrose).<sup>295</sup>

#### *Beers*

#### **General Overview**

Over the past decades, BA levels have been significantly reduced in many commercial beers, owing largely to improvements in production and hygiene standards (leading to fewer and less impactful contaminations

during the fermentation process)—but there are exceptions, 344 e.g., spontaneously fermented beers;<sup>345</sup> craft beers (from microbreweries) $346$  that are produced without a filtration or pasteurisation process; $347$ some bottled beers that have been insufficiently pasteurised, allowing for TYR and HA formation (from lactic acid bacteria activity); etc.<sup>348</sup>

BA levels can vary widely within beers of the same fermentation category: TYR levels from ∼1–37 mg/l have been reported in top-fermented beers (e.g., Kriek, Weissbier, Ale); TYR levels from ∼0.5–47 mg/l have been reported in bottom-fermented beers (Pils, Dortmunder, Lager).<sup>323</sup> Loret et al. tested 220 top-fermented beers (some of which underwent additional bottle fermentation), and found 21 samples with HA or TYR levels  $>10 \text{ mg}/1.345$ 

Kalac et al. tested 195 samples of bottled or canned beers, 'purchased from commercial outlets in Germany, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Spain, France, Great Britain, Greece, The Netherlands, Ireland, Italy, Portugal, Switzerland, and the former Yugoslavia'; many had TYR levels in the range of 2–8 mg/l (mean of 7 mg/l TYR)—but several samples had more TYR  $(\leq 70 \text{ mg/l})$ .<sup>348–350</sup> Anli et al. tested 17 Turkish domestic beers and 13 imported beers; all had TYR levels <2 mg/l.<sup>351</sup> Kirschbaum et al. found undetectable TYR levels in 6 beer samples, and 17.5 mg/l TYR in *Lambic* beer.295 Bunka et al. reviewed 114 beer samples from 28 Czech breweries; they found TYR levels of <10 mg/l in 51 samples, 10–50 mg/l in 21 samples, and ∼100 mg/l in 5 samples.352 Pradenas et al. tested over 300 beer samples on the Chilean market, and found that 99% of them had TYR levels of  $\leq$  2 mg/l (max. 6 mg/l TYR).<sup>353</sup> gory: TYR levels from  $\sim$ 1–37 mg/l have been reported in top-fermented beers, (Kriek, Weisshör, Ale); TYR levels from  $\sim$ 0.5–47 mg/l have been reported in bottom-fermented beers (Pils, Dortmunder, Lager).<sup>323</sup> Lote t et

Tang et al. tested 18 beers (all brewed in China; some under European license); they found TYR levels of 3–5 mg/l in most samples (max. 7 mg/l TYR).354 Cortacero-Ramirez et al. found TYR levels of <9 mg/l in various Spanish beers.355 Izquierdo-Pulido et al. found mean TYR levels of 5 mg/l in 17 beer samples, and mean TYR levels of 7 mg/l in 55 other samples (max. 47 mg/l TYR); various European beers (48 samples) had  $\leq 6$  mg/l TYR; 195 beer samples from various European countries were found to have a wide range of BAs: mean TYR levels were established at 6.5 mg/l, with a high max. of 67.5 mg/l TYR.<sup>356–358</sup> A substantial TYR range was also found in Brazilian beers  $(0.3-37 \text{ mg}/1 \text{TYR})$ .<sup>326</sup>

#### **Draught Beers**

BA levels, including TYR and HA, are expected to be higher in beers on tap (draught beers); this may be due to bacterial contamination of the dispense lines, the taps and/or the spouts.359 Tailor et al. reviewed 98 beer samples of 79 different brands (49 bottled or canned beers; 49 beers on tap), and concluded:

*'All of the bottled beers analysed had safe tyramine concentrations (*•*10 mg/liter; range, 0 to 3.16 mg/liter) and, thus, do not require restriction in patients receiving MAOIs. Therefore, the consumption of canned or bottled beer, including dealcoholized beer, in moderation (fewer than four bottles or cans; 1.5 litres within a 4–hour period) appears to be safe and does not require restriction in patients receiving MAOIs. Only 4 of 98 beer samples studied were found to have a dangerous (*>*10 mg/liter) tyramine concentration, one of which was the index beer. The tyramine concentration in these four beers ranged from 26.34 to 112.91 mg/liter. All four of these beers were tap beers produced by bottom fermentation (lagers) and brewed by a secondary fermentation process.' … 'Therefore, to err on the side of caution, it is recommended that patients on irreversible MAOIs avoid beers on tap.'*<sup>360</sup>

#### **Spontaneously Fermented Beers**

Loret et al. tested BA levels in 42 spontaneously fermented beer samples (e.g., Lambic), and found mean TYR levels of 28 mg/l, and max. TYR levels of  $>60$  mg/l.<sup>345</sup> Belgian Lambic beer is an old-style, spontaneously fermented beer; it is allowed to spontaneously ferment with wild airborne yeasts in well-ventilated attic roofs (accumulating enteric, as well as lactic and acid bacteria), where it is then aged for 1–3 years.345,361 High BA levels are to be expected in such beers, e.g., TYR levels of ∼68 mg/l have been found in Lambic and Gueuze style beers.<sup>323</sup> ples situalized wore found to bave a dangerous (>10 mg/liter) tyramine con-<br>entration, one of which was the index here. The tyramine concentration in<br>these four beers ranged from 26.34 to 112.91 mg/liter. All four of thes

# **Traveling and Tyramine**

Some holiday destinations will require heightened awareness of food hygiene issues e.g., Rabie et al. found TYR levels of 2000 mg/kg in some cheeses and fermented sausages;<sup>362</sup> then there is fermented Yak milk,<sup>312</sup> and the Icelandic Hákarl (fermented shark meat), etc. MAOI patients must be advised to avoid suspect foodstuffs.

# **Conclusion**

Much of the above content is necessitated in order to update and contextualise previously promulgated misinformation. Almost all foods that may occasionally accumulate high TYR levels, like soy sauce and cheese, are highly flavoured foods that are normally used only in small quantities—precisely because high levels of some BAs are the cause of disagreeable smells and flavours associated with putridity (putrescine). Thus, many people find over-mature cheese and meat unpleasant.

Comparatively few cheeses have TYR levels above 500 mg/kg meaning that a healthy-sized portion of such a cheese (25 g) is safe for

most MAOI patients. The same holds true for many soy sauces when used in typical condiment quantities (∼10 ml).

Because BAs are also relevant for other health reasons (e.g., migraineurs), we suggest the time has come for all the fermented and matured foods itemized in this review to be required to state their TYR content as part of food labelling regulations.  $\clubsuit$ 

# **Author Contributions**

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VVdE is an external research consultant for, and receives or has received consulting fees from: PsychoTropical Research, NeuraWell Therapeutics, Aristo Pharma GmbH. He has stock options in NeuraWell Therapeutics.

PKG has equity interests in, and is on the advisory board of NeuraWell Therapeutics, the company that has the patent for a modified form of tranylcypromine.

BBB has nothing to disclose.

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**103**

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