## **Review Monograph**

# Monoamine oxidase inhibitors: A review concerning dietary tyramine

## Abstract

This comprehensive monograph surveys original data about dietary tyramine and **Monoamine Oxidase Inhibitors (MAOIs)**, about which there is much outdated, incorrect, and incomplete information in the medical literature and elsewhere. It has a comprehensive explanation of how tyramine builds up in different foods and beverages, as well as extensive information and references, about all foods.

Few foods now have problematically high tyramine levels, that is a result of changes in international food production methods and hygiene regulations. Cheese was the only food that, in the past, has been associated with documented fatalities resulting from acute tyramine-induced hypertension. Nowadays most cheeses are safe, and even 'matured' cheeses are usually safe in healthy-sized portions. The variability of 'pressor' sensitivity to tyramine between individuals, and the unpredictable amount of tyramine content in a few foods, requires a little knowledge and care.

Many of the drug interactions previously supposed to be serious are either nonexistent or non-serious. The few interactions between MAOIs and other drugs are now well understood and are quite straightforward to avoid and deal with. They are detailed in other commentaries.

The low degree of risk consequent upon a brief episode of acute hypertension, and the dangers of over-treating it with drugs such as nifedipine, are explained and discussed.

MAOIs have good efficacy in most forms of serious depressive illnesses, including melancholic and psychotic conditions, and are of comparable safety to most other currently used treatments, and straightforward to use, contrary to much current teaching. Previously held concerns about MAOIs are, as White said in a report to the American College of Neuropsychopharmacology 40 years ago, mostly 'mythical' and misleading: either they are of over-rated importance, or incorrect, or no longer relevant.

## Keywords

Monoamine oxidase inhibitors, hypertension, drug interactions, serotonin toxicity, decarboxylating enzymes, biogenic amines, washout intervals, tricyclic anti-depressants (TCAs), clomipramine, imipramine, tranylcypromine, phenelzine and isocarboxazid, isoniazid, narcotic analgesics, triptans, histamine, putrescine, cadaverine, tyramine, tyramine pharmacokinetics, tryptamine, 2phenylethylamine, spermine, spermidine, methylamine, trimethylamine, scombroidosis, hypertensive urgency, hypertensive emergency, sub-lingual nifedipine, subarachnoid haemorrhage, end-organ damage, anaesthesia, indirect sympathomimetic activity, adrenaline, noradrenaline, dietary tyramine, cheese reaction, L-DOPA, dopamine, chocolate, wine, beer, chianti, aged cheeses, cured meats, pepperoni, salami, sauerkraut, kimchee, soy sauce, miso, fish sauce, yeastextract spreads, health supplements, Marmite, broad bean pods, fava beans

#### Abbreviations and synonyms

adrenaline (adrenalin or epinephrine), noradrenaline (noradrenalin or norepinephrine), serotonin (5-HT), serotonin/noradrenaline re-uptake inhibitor (SRI, NRI) or serotonin/ noradrenaline transporter (5HTT or SERT/NAT or NET), monoamine oxidase inhibitors (MAOIs), serotonin toxicity (ST), Biogenic amines (BAs), tricyclic anti-depressants (TCAs), indirect sympatho-mimetic activity (ISA), 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy), reversible inhibitors of monoamine oxidase A (RIMAs).

## Introduction and background

If a man is offered a fact which goes against his instincts, he will scrutinize it closely, and unless the evidence is overwhelming, he will refuse to believe it. If, on the other hand, he is offered something which affords a reason for acting in accordance with his instincts, he will accept it even on the slenderest evidence. The origin of myths is explained in this way.

Bertrand Russell, Proposed Roads to Freedom

This monograph is intended to update, inform, and assist both medical and nonmedical readers — it is now supplemented by, not only the extensive commentaries already on the website, but also by several videos and podcasts in the links provided on my website, here: https://psychotropical.com/youtube about/

The one on tyramine is here https://youtu.be/Wbo3GJ2DvkI

This monograph is lengthy, not because the subject is complex, but because exposing the myths surrounding MAOIs involves more than mere contradiction, and because I provide extensive references. The subject of MAOIs is richly cloaked in myth: unfortunately, a mythical assertion often repeated is more firmly established in people's minds than a truth stated but once.

Standard texts cover many issues within tight space constraints. They contain abbreviated discussion and information, often by authors who are not expert in the subject; that causes confusion because such texts contradict the contents of in-depth analyses, such as this monograph.

There is now a lot of new quality data on tyramine in foods, and on how much tyramine is likely to constitute a potentially serious problem [1]. Previous opinions and advice have been based on old and sometimes inaccurate data, e.g. [2].

This monograph surveys more original data on tyramine than any paper previously published. There are more than 200 new references, mostly recent, that have never been cited in the medical literature.

An abridged version of this monograph has (2019) been published as a peer-reviewed article in the Journal of Neural Transmission [3], but that does not have the full list of references — so this version may be preferred by those who wish to have full references and details.

**Biogenic amines (BAs),** including tyramine, are heat stable: they are not inactivated by cooking. Furthermore, decarboxylating enzymes are also heat-tolerant and may survive some cooking methods, allowing continued accumulation of Bas, if cooked food is then poorly refrigerated.

Storage of foods below at  $<4^{\circ}$ C is a crucial requirement, and some domestic fridges fail to maintain temperatures of below that. An accurate thermometer must be used to check fridge temperatures.

## Some common myths

Science must begin with myths, then progress to the criticism of myths. Karl Popper

All the following statements are wrong:

- The diet is difficult
- People cannot have cheese or red wine
- Tyramine reactions are dangerous and need urgent treatment
- Patients should be given nifedipine sub-lingually

All concentrations are given as milligrams (mg) of tyramine per kilogram (kg) or litre (L). Most food labels are legally obliged to quote information as content per 100 grams (abbreviation 100 g). Other abbreviations like: G, gm, gms and grms, are used, but 'g' is generally considered the correct notation.

Those living in non-metric areas will find it helpful learn to work in metric units: it is confusing to use standard servings/standard drinks or oz./pints. Some scientific papers still use different units of measurement in the same sentence (a patient weighing 180 pounds took a dose of 150 mg of a drug). That is like saying that someone is one meter 32.9 inches tall. Such practices are ultimately dangerous to people's lives. Especially for those in the USA, see the US metric association information:

http://lamar.colostate.edu/~hillger/common.html

and see also

http://www.newscientist.com/article/mg20827840.200-uks-chief-measurerunits-unite-the-world.html

## How much tyramine produces a risk of serious hypertension?

For a majority of those who already follow healthy eating amounts and patterns the low tyramine diet involves few changes.

Although a small percentage of people may get a significant, but not serious or 'risky', blood pressure elevation with only 10 mg of tyramine, a substantial proportion of people need to have closer to 50 mg (in a meal) to get a **blood pressure (BP)** increase meeting the definition of a 'hypertensive urgency' (i.e. systolic blood pressure [SBP] >180 mm Hg). BP levels in 'hypertensive urgency' range from 180-220 mm/Hg **and rarely engender an acute risk of serious consequences** (e.g. sub-arachnoid haemorrhage).

For a detailed analysis of the evidence relating to tyramine 'dose' and blood pressure <u>see below</u>, and <u>in commentaries</u>, and Gillman [3, 4]. Nevertheless, it is prudent to keep in mind that human responses to drugs and drug interactions vary from one individual to another and that there will always be exceptions to generalisations about doses and responses: that is one reason it is wise to monitor sitting & standing BP before and during treatment. See this pdf for instructions about BP monitoring:

http://www.psychotropical.com/images/pdfdownloads/MAOI\_treatment\_BP\_so.pdf

It is easy to work out how much tyramine is in 10 or 100 grams or milliliters of any of these foods. **People should familiarize themselves with what 10 g and 100 g looks like, and what constitutes a sensible food portion.** Those who eat 1 kg beef steaks, or half a kilo of cheese etc. will need to adjust to avoid trouble (and to be healthy). Some people (those with a BMI of more than 26)

may benefit by consulting a dietician for explanations and education about how to eat healthily.

BMI (body mass index) is weight in kg divided by height in meters squared. i.e. for an average man =  $70 (\text{kg})/1.7(\text{m})^2$ ; or 70/2.89 = 24.22 Also see website information like

http://www.win.niddk.nih.gov/publications/PDFs/justenough.pdf

Healthy portion sizes of cheese are approximately what is safe tyramine-wise: i.e., 100 grams of cheese in a meal is an unhealthily large portion. A healthy portion is 25 grams. Few cheeses (even 'mature' cheeses) contain more than 25 mg of tyramine in 100 grams (25 mg in 100 g = 250 mg/kg). Thus, a 25 g portion contains only 6 mg of tyramine and that will not cause a significant blood pressure rise, even in tyramine-sensitive individuals. Many cheeses have between 1 and 5 g of salt per 100 g [5], or 10-50 g/kg. The recommended daily sodium intake has now been reduced by *some* authorities to 2 g daily (this is equivalent to 5 g of table salt). Thus, 30 g of a typical cheese provides 1 g of salt.

Even if excessive tyramine is ingested and BP increase occurs, grave consequences are very unlikely. With present-day lower tyramine foods, it is difficult, if not impossible, to ingest the massive quantities of tyramine that led to patient deaths in decades past.

Ingestion of excessive tyramine it will usually mean nothing more than monitoring blood pressure for a 1-4 hours. In many mild ingestions, which is all one is likely to see nowadays, BP will peak at about one hour.

Hasty and alarmist treatment of high BP by inexperienced doctors produces a risk of doing harm. Current expert opinion strongly advocates that hypertensive urgencies should be treated conservatively [3]. The safest 'out-of-hospital' intervention is a sedative dose of a benzodiazepine, see below, 'Hypertensive urgencies and emergencies due to tyramine, and the questionable relationship to subarachnoid haemorrhage', for details.

#### Monitoring blood pressure while on MAOIs

It is quite simple to monitor blood pressure with an electronic BP monitoring device (upper-arm, or wrist cuff). It is wise to school those on MAOIs to keep a blood pressure record from the beginning of treatment (including a one-week pre-treatment base-line record). The decrease in blood pressure on standing is a good indication of whether MAOIs are having a sufficient effect [3]. There is further explanation on Psychotropical.com explaining blood pressure monitoring and MAOIs.

http://www.psychotropical.com/images/pdfdownloads/MAOI treatment BP so.pdf

There are good reasons for blood pressure monitoring.

In my experience it is not possible to make logical and timely decisions about dose adjustment without properly monitoring the BP. BP drop on standing (two measurements are essential) is the best measure of the effectiveness of a given dose and essential to optimal speed of adjustment to the final effective dose, whilst avoiding problems of excessive faintness, or even falling, from postural hypotension.

Although most people will only react to larger amounts of tyramine there is wide variation in the population and a minority will experience greater BP elevation with relatively smaller doses of tyramine. Therefore, monitoring the BP will soon reveal those who are in the tyramine-sensitive group and warn of the need for extra care about diet (or <u>addition of a noradrenaline re-uptake inhibitor</u> (NRI), and <u>see below</u>).

## Introduction to dietary guide

'Dis-moi ce que tu manges, je te dirai qui tu es' (Tell me what you eat, and I will tell you what you are)

~ Anthelme Brillat-Savarin Physiologie du Goût 1825

The drugs discussed in this monograph belong to the group called Mono-Amine Oxidase Inhibitors (MAOIs). The enzyme Mono-Amine Oxidase (MAO) has two sub-types, A and B. This information is most relevant for irreversible 'non-selective' MAO-AB inhibitors (the most common are tranylcypromine, selegiline, phenelzine, and isocarboxazid), and less important for various other types of MAOI.

Persons on these drugs may be advised to keep some means of identifying the fact that they are on MAOIs readily available. Similar steps as would be taken with insulin dependent diabetes and those suffering from epilepsy are appropriate; this is in case of accidents or emergencies. This might be a medical alert bracelet, and/or information in handbag or purse or wallet, or mobile device.

All treating medical practitioners should be informed if a patient is taking MAOIs, but most of them will not know what to do and will therefore offer inappropriate advice taken from out-of-date sources. Generally, advice on MAOIs should come from specialist psycho-pharmacologists, general psychiatrists may have insufficient knowledge to optimally manage MAOIs. Most information on the Internet is significantly inaccurate, and even the information on sites of many educational institutes is out-dated and misleading [3].

The information provided here is authoritative; I have published papers in prestigious scientific journals on the pharmacology of MAOIs and **tricyclic antidepressants (TCAs)** and their interactions and I have a great deal of first-hand practical experience, see especially references: [1, 3, 4, 6-14].

#### The mechanism of tyramine formation

Tyramine formation in foods requires the availability of the amino acid precursor tyrosine and the presence of micro-organisms with amino acid decarboxylase enzyme activity. If favourable conditions for their growth and decarboxylating activity exist then tyramine, and other **biogenic amines (BA)** like histamine, cadaverine and putrescine may gradually accumulate in foods.

Tyrosine, **but little or no tyramine**, is present at up to 20 mg/kg in animal protein sources, but is generally lower in plants (see below for exceptions). That is why fresh properly cold-stored foods are always safe. Animal protein can accumulate tyramine if allowed to go 'off'. **Meat, fish etc. must be stored at a fridge temperature of less than 4°C**. Meats that have been minced are more prone to bacterial contamination if unhygienically handled and could accumulate significant tyramine quite quickly. That is why meat and fish processing must now take place at below 4°C by regulation in most countries. Few people in western society would now accept green rotten smelly meat, however, eating meat like that was a widespread practice in times gone by, and still is in some places.

Histamine, putrescine, cadaverine, tyramine, tryptamine, 2-phenylethylamine, spermine and spermidine are the most important BAs in foods [15-19]; that is why smell (putrescine – putrid) is a guide for what to avoid.

#### *Measurement of biogenic amines*

There has been much progress and refinement of measurement techniques of tyramine and biogenic amines in food [20, 21]. Older estimations of tyramine concentrations may sometimes have been less accurate, especially because the isolation of amines from complex food matrices is not simple. Usually a derivatisation procedure needs to be applied to enable analysis by methods such as liquid chromatography (LC), or gas chromatography (GC) with various detectors, including a mass spectrometer [15, 22-25]. Techniques are continuing to become better, faster, and less costly, so data are continuing to accumulate [15, 22-25]. Google scholar finds over 1000 references for 'biogenic amines food wine' between 2014 and 2015).

#### Toxicity of biogenic amines

Some BAs are toxic above a quite low concentration. The Food and Agriculture Organization of the United Nations (FAO) considers BA in foods as a potential biological hazard.

The amine most commonly implicated in toxicity in humans is histamine, which is responsible for the type of poisoning that occurs on eating spoiled fish (scombroidosis, <u>see below</u>). Recent reviews of the toxicity of amines give up-to-date information [15, 16, 26-28].

## The symptoms of a hypertensive reaction

A reaction is a progressive increase of **blood pressure BP** over 30-60 minutes (faster for liquids taken on an empty stomach) and may manifests first as a forceful thumping heartbeat. The heart rate usually becomes slower [29-32], in response to the increase in BP. If **systolic blood pressure (SBP)** goes above around 180 mm Hg quite rapid onset of severe headache is usual (although headache is not a reliable indicator of high BP). Tightness in the chest, sweating, and paleness (pallor) may occur.

The degree of increase in **BP** is proportional to the amount of tyramine ingested; however, because the relationship is 'non-linear' relatively small increases of tyramine may produce larger than expected increase in **BP**.

BP elevation starts soon after ingestion, usually around 30–60 minutes, and symptoms may occur soon after. Any symptoms, including headache, starting more than two hours after eating are less likely to be due to a hypertensive reaction because Tyr is rapidly absorbed, and the duration of the reaction is usually not more than 1-2 hours.

An SBP of 180 mmHg or more, **sustained over 3 measurements in 10 minutes** or so, performed in a calm setting with an accurate sphygmomanometer is now referred to as a 'hypertensive urgency'. If 'end organ' dysfunction is present it is called a 'hypertensive emergency'. End organ dysfunction is uncommon unless **diastolic blood pressure (DBP)** is greater than 130 mmHg.

The term 'hypertensive crisis' is considered redundant.

In hypertensive urgencies the treatment aim is to reduce BP slowly over 24-48 hrs. Since tyramine reactions are self-limiting over 2-4 hrs., even for moderately severe ones, it is clear they will rarely require intervention.

## Tyramine in foods and beverages

Myth: The diet is difficult. One cannot have cheese or red wine

## General comments on diet and tyramine

'The pleasures of the table belong to all men and to all ages, and of all natures gifts remain the last, to console us for the passing of the rest.'

~ Anthelme Brillat-Savarin

This monograph reviews tyramine concentrations as indicated by a large body of food science research. Tyramine concentrations for ordinary foods depend on storage time and storage conditions. Modern food hygiene and handling practices and regulations in developed countries mean that excess tyramine levels are unheard of in 'fresh' foods. That leaves those foods that are produced deliberately using micro-organisms, that is the subject-matter of a major part of this monograph.

Minimising or avoiding the few high tyramine foods and beverages that exist is easy and necessary whilst taking MAOIs. Only a few foods can build up the degree of excess tyramine (hundreds of mg/kg) that can greatly elevate the BP. The result of any BP reaction is in proportion to the amount of tyramine consumed i.e. **BP elevation is a dose-related effect**: that is why it is permissible to cautiously 'test' small quantities of some foods e.g., your favourite cheese. Such testing should be done cautiously because the relationship of tyramine dose to BP is non-linear — a slight increase in the amount of tyramine may give rise to a larger than expected elevation of BP.

This monograph cannot and does not deal individually with compound foods, e.g., pizza. Such foods can have many ingredients that may have widely different tyramine contents. The total tyramine content of such foods will depend on the individual ingredients; but a little common sense and calculation, from the information here, will yield an estimate of the tyramine content.

Special starter-cultures that have low levels of decarboxylating micro-organisms in them have been developed and are now used in many food production processes including most cheesemakers, partly because they minimise the formation of undesirable 'off' flavours [33]. They also minimise the proliferation of undesirable contaminant organisms (cf. yoghurt, below) and thereby lessen, or even prevent, tyramine formation. Worldwide, attention has focussed more on 'food hygiene' and the European Union have an extensive program of monitoring and research, e.g. see 'Controlling Biogenic Amines in Traditional Food Fermentations' [34], and under 'Salami' below.

http://cordis.europa.eu/result/rcn/86612\_en.html

Tyramine only accumulates in significant quantities when tyrosine is converted to tyramine by decarboxylase enzymes possessed by some, but not all, microorganisms (see e.g. [35]). The only foods that have enough tyramine in them to cause significant reactions are those that have been subjected to the action of these types of micro-organisms. However, modern food hygiene standards are such as to make that increasingly rare, because biogenic amines, including tyramine, are monitored as part of food quality and hygiene audits.

The European Food Safety Authority (EFSA) requires reliable data about the absence of biogenic amine production as a criterion to permit starter-cultures to be used in food manufacturing [15, 36].

#### Tyramine pharmacokinetics

A potentially significant elevation BP can only occur if a relatively large amount of tyramine is ingested. For those on MAOIs, most (around 50% of the population) will need to ingest at least 25 mg of tyramine to get a problematic elevation of BP. A small proportion of people are more sensitive to tyramine and in such subjects 10 mg may be enough to cause a measurable or symptomatic

(but not risky) BP elevation. Such data is derived from the practical experiments done by researchers like Peter Bieck, sometime ago. It is time-consuming work to do, and it has not been much expanded on since.

However, there are some data to supplement this from experiments done with tyramine alone in human subjects, not in the presence of MAOIs; this has led to a little more information about the pharmacokinetics of tyramine.

Prior to the data below only VanDenBerg and Di Stefano had produced such data [37, 38].

Valuable recent (2019) data about the variable pharmacokinetics of tyramine is contained in this paper by Rafehi et al. [39]. In a decent sized sample of **88 normal volunteers (healthy people, not taking MAOIs)** given a dose of **400 mg of tyramine** on an **empty stomach** they found that SBP increased by more than 10 mmHg in 71% of individuals. BP correlated strongly with systemic tyramine concentration, which needed to be >60 microg/l to cause significant SBP elevation and >100 microg/l to elevate DBP. In less than 10% of participants, BP increased by >40 mmHg (when tyramine >60 microg/l). Note that the equivalent amount of tyramine in a normal meal (for their 400 mg in a capsule on an empty stomach) would be 800 to 1200 mg.

The worst-case scenario estimate would be that MAOIs such as TCP increase the pressor response by 40 times, so that would mean the equivalent amount of tyramine would be 20 to 30 mg in a meal (exactly in line with the previous estimate that I had made, as above, from existing data), and for >90% of people this would give an insignificant blood pressure rise. Even in the worst-case scenario of the less than 10% of people (tyramine-sensitive), in the above sample, they would still only get a rise of around 40 mmHg, which is not risky (see below).

These data add usefully to our confidence about what constitutes a safe amount of tyramine when given in conjunction with MAOIs.

Most foods with elevated tyramine (like matured cheeses) have no more than 250 mg/kg. Therefore, quantities of up to 100 g of such a cheese (and that is a large portion-size), may be consumed without risky consequence by most people. Further discussion is in Finberg & Gillman [1, 3], and on https://psychotropical.com/maois/

The earliest work on this subject remains instructive. Barry Blackwell described the cause-effect nature of the 'cheese reaction': the original papers by Blackwell [40-49] summarize most of the basic points that are in this monograph. For those who like to know more about history Blackwell has written about it recently on the web site of the 'International Network for the History of Neuropsychopharmacology (INHN)' here:

http://www.inhn.org/controversies/barry-blackwell-adumbration-a-history-lesson.html

'The wheel is come full circle, I am here' Edmund, King Lear

Barry Blackwell has expressed his appreciation of this monograph and still feels that the chemist, Rowe, who made the key observation (his wife was taking 'Parnate'), has not had sufficient recognition. Although Barry described Rowe's role in the story in a subsequent paper, his name was not in the initial publication, and Barry told me he still regrets that. It is therefore satisfying to be able to 'close the circle' by refreshing our memories of the history of this subject in this review.

Seminal early research on the tyramine content of cheeses was done by Kosikowski, e.g. [50]. It is interesting to note that the series of papers he

authored in the 1950s have never been cited in the medical literature, except by Blackwell [45] \*\*. His efforts also have had insufficient recognition.

Blackwell noted that most cases of the 'cheese reaction' then reported (1965) implicated cheddar cheese, some of which had been assayed as having around 3,500 mg/kg of tyramine [51], which exceeds by about two orders of magnitude the values generally found in assays of similar cheeses in the current era (see refs below).

#### The absence of data about tyramine in the medical literature

The explanation for the absence of data about tyramine in the medical literature is that medical writers have only searched for papers using the medical literature databases (i.e. PubMed), as also noted, indirectly, by McCabe. Since PubMed does not include many of the food-science related research journals, where the data reside, those data have been missed.

The updated review (from 1986) [52] by McCabe was published in 2006 in the *Journal of Food Composition and Analysis*, which is not in the PubMed system [53]: that paper is the only other paper that has more recent and original data.

Recent examples of papers that do not include food science journals are [54-58], which although presented as 'updates', **do not have any recent original data about tyramine**.

One 2019 paper should also be noted [59], but it contains no significant extra data — indeed, it cites some forty-year-old data (1978) somewhat uncritically.

Most of the references in this commentary come from the food science literature, most of them will not be located by a 'PubMed' search.

Only rarely encountered foods will now have high tyramine concentrations, such as 1,000 mg/kg, or greater.

## Cheeses and dairy products

Cheese: 'Milks' leap towards immortality'

~ Clifton Fadiman

Most cheeses now have low tyramine levels (<10 mg/kg), whether they are hard, semi-hard, acid-curd or soft [23, 25, 60-63].

The report of the EFSA panel (2011) had results from 2,000 cheese samples summated from studies in nine European countries [64], and in the subsequent 10 years many more measurements have accrued.

Mayer's latest 2018 summary of findings in 150 cheeses is a good recent overview [65]. Most hard cheeses had no detectable tyramine (see table 1). Blue-veined cheese (n=31) all <100mg/kg, most <50 mg/kg; mould-ripened soft cheese (n=12) all <100mg/kg; of the smear-ripened (n=18) and acid-curd cheese(n=48) some were a little higher (see Fig 4 for details).

Only three cheeses, out of the 151 tested, would have been *possibly* problematic in a patient on MAOIs, (containing no more than 25 mg tyramine), as part of a meal having a large cheese portion-size of 50 g.

It is likely that the unusually high concentrations of 1,000–4,000 mg/kg reported occasionally in older samples 1950s) will no longer occur because food regulations have driven widespread reductions of tyramine levels, especially through the use of starter-cultures [15, 63].

Matured and 'artisanal' cheeses can sometimes develop high concentrations of tyramine (~1,000 mg/kg), although most (~95%) are surprisingly low (<300

<sup>\*</sup> derived from Google scholar 'cited by' links

mg/kg). 'Matured' usually means aged for more than 3 months (typically 6 months or more), rather than just a few weeks.

Contrary to what one might assume from the (lack of) data in the medical literature there have been thousands of tyramine estimations performed from cheeses around the world: a selection of studies with extensive and varied sampling is given here to illustrate this (the references given contain data on  $\sim$ 3,000 cheese samples).

Most (~98%) of the commercial lower priced 'processed' and 'supermarket' cheeses are low in tyramine (always <200 mg/kg, usually in the range of 0-50 mg/kg) because 'supermarket' type outlets require large quantities of produce (i.e. industrial-scale, not artisan), and low prices do not pay for long warehouse ageing (i.e. more than 3 months, which has a tendency to allow a little accumulation of tyramine).

Bunkova et al. recently reviewed the widely marketed Edam-style cheese [61]. As they point out:

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

They studied tyramine levels during maturation and storage and noted particularly that:

In all ripening/storage regimes tested, the highest content of tyramine, putrescine and cadaverine was found in the edge [rind]. On the other hand, the lowest content was detected in the cheese core

They found that tyramine levels increased in approximately linear fashion over time, being 60 mg/kg at 60 days and reaching a maximum of 120 mg/kg at 100 days in the outer layer (rind), but only 70 mg/kg in the core.

## Processed cheese

Processed cheese generally has low levels of tyramine. Ibrahim et al. analysed 45 samples of processed cheese made from a variety of types and found the mean was  $\sim 200 \text{ mg/kg}$  for cheddar styles, and 100 mg/kg for Gouda styles, however, there were a small number of samples that were higher, the maximum being 800 mg/kg. [66]. Note, these were shelf samples from Egyptian retail outlets, who knows how long they had been on the shelf? Or at what temperature?

## Classic matured (hard, semi-hard) cheeses

#### French

Francophiles may be surprised to be reminded that there are relatively few French hard cheeses and even fewer that are available outside France, examples are: Cantal, Comté, Emmental (generally produced industrially) and Mimolette (Edam-like).

Comté AOC: Mayer: tyramine 0 mg/kg [25]. Comté is essentially the same as Swiss Gruyere, but still mostly in the hands of small producers, whereas Swiss Gruyere is almost entirely large-scale co-operatives. One would therefore predict the Swiss types would be even lower in tyramine.

Cantal: Mayer: 0 mg/kg [25], and 40 other 'hard' cheeses had negligible tyramine levels [65].

#### Italian

Parmigiano Reggiano: aged 24 and 30 months, tyramine 20 - 150 mg/kg [62], but Mayer [25] found levels < 10 mg/kg in the 6 samples he **tested**\*

Grano Padana (12 & 22 months old) all samples tyramine < 130 mg/kg. Mayer [25] found undetectable levels.

The Spizzirri paper included a wide range of cheeses (mostly Italian), Grana Padano, Pecorino, Provolone, Ripened goat cheese, Emmentaler, Taleggio, Bel Paese and more, none of which had more than 200 mg/kg of tyramine.

Italian pecorino [67]. This paper reviews tyramine levels in a wide variety of pecorino cheeses made from different significant producing regions of Italy. Some of them are 'artisan' type cheeses and there is great variation. Many have low levels in the region of 100–200 mg/kg, but one particular example, Pecorino Del Parco Di Migliarino San Rossore, exceeds 1000 mg/kg.

#### British

Cheddar: young cheddar (4 weeks) all tyramine < 50 mg/kg, at 36 weeks maturation all samples < 160 mg/kg [68], and only 6 mg/kg [69] and Mayer [25] found levels of tyramine **0 mg/kg**<sup>\*\*</sup>. Another old bit of data from Hungary [70] found values of 70-210 mg/kg (3 samples).

#### Dutch

Gouda is a widely copied cheese style which when young is semi-soft and hardens with age. Aged Dutch Gouda is called "Oude kaas (10-12 months old), Overjarige kaas (18 months old). Tyramine levels will vary with age, younger ones seem to have low levels, older ones 100-250 mg/kg [25].

Dutch-type semi-hard cheeses mostly tyramine <50 mg/kg, max 250 [72, 73].

#### Swiss

Gruyere: tyramine <100 mg/kg [62]

Emmental: tyramine 0-68 mg/kg [25] and Spizzirri [62] 16 mg/kg.

#### Other cheeses (non-hard)

Mould-ripened cheese is like brie and camembert contain virtually no tyramine because **moulds do not transform tyrosine into tyramine**, whereas some bacteria ripened cheeses tend to have more tyramine.

#### Brie and camembert styles (un-washed rind)

Normally these cheese styles (mould-ripened soft cheeses, fluffy 'cotton-wool' like surface) are only matured for 4 weeks before release, low tyramine levels are expected, and found. Tyramine concentrations are less now than in the past because of starter-cultures and better storage (see below for older results). Thus, it is no surprise to find that the latest estimations using modern assay techniques give low tyramine levels of <10 mg/kg.

Mayer et al. looked at examples from Austria, Denmark and France and found negligible tyramine levels (maximum of 5 mg/kg) in 5 different types of unwashed rind soft cheeses [25]. Likewise, Bonczar [69] found only 6 mg/kg in three samples.

<sup>\*</sup> Table 2; note the blank spaces in this table denote 'undetectable' as confirmed with Mayer (personnel communication).

<sup>&</sup>lt;sup>\*\*</sup> Note the enormous difference from the old assays, one or two orders of magnitude, < 50 mg/kg vs. the old value of around 4,000 mg/kg of tyramine [51, 71].

Some older papers have reported much higher levels which may be explained by poor production and storage and/or faulty assays; Horwitz [74, 75] found tyramine ~100 mg/kg. Other older papers found undetectable levels [50].

Colonna (1970s): Camembert (French), 20 samples, most had low levels of tyramine  $\sim 100 \text{ mg/kg}$ , but showing large variation up to a maximum of 1800 mg/kg [76].

De Vuyst: Brie; tyramine 0-400 mg/kg, camembert low, maximum 20 mg/kg [71].

Voight: Brie tyramine 0-260 mg/kg [77].

#### Washed-rind cheeses

Washed rind cheeses (Epoisses is the classic) encourage mould rather than bacteria and thus have low tyramine levels like Brie and Camembert Styles, Samkova [78] tested 30 samples and all had <2 mg/kg. Coton found 30 mg/kg [79].

#### Smear ripened

Cheeses made in this style are not intended for long storage and a bacterium, often Brevibacterium, is smeared onto the rind of the cheese. These tend to have slightly higher tyramine levels, of 45 samples tested average levels were 150 mg/kg (max 500 mg/kg).

#### **Others**

Acid-curd cheeses. Some are coagulated (curdled) using rennet, but some undergo curdling by bacterial lactic acid fermentation, and these might be expected to contain a little tyramine. See below under 'Austrian' [60].

Feta style: generally low tyramine but 'older' examples creep up a bit to 250 mg/kg at 120 days of age [80].

#### Austrian

An extensive analysis in 2013 of 47 different Austrian cheeses, particularly ripened acid-curd cheeses, is detailed in Fiechter et al. [60]. Most have low tyramine levels of <100 mg/kg, only 18/47 samples were >100 mg/kg). The median concentration for tyramine was 30 mg/kg. One sample of aged acid curd (Ennstaler Steirerkäse with crumble texture) was the highest was at nearly 2,000 mg/kg).

#### Roquefort and Roquefort styles

Because these are mould-ripened cheeses virtually no tyramine is expected, unless they have been stored for long periods of time in unhygienic conditions. **Moulds do not transform tyrosine into tyramine.** 

Roquefort and Roquefort style 'traditional' cheeses (all made with Penicillium roqueforti), these include: Fourme d'Ambert, Bleu de Bresse, Gorgonzola, Stilton, Cabrales, Gamonedo and the 'industrially-produced' types Danish Blue, Bleu d'Auvergne, Edelpilzkäse, Mycella.

Roquefort 4 samples: tyramine 0 mg/kg [25].

Czech blue cheeses, [81, 82]: the mean and median being tyramine 380 mg/kg and 289 mg/kg, respectively) and, different cheeses (vats) varied widely, from 10-875 mg/kg.

I suspect these blue cheeses had either been stored badly, or are made using a slightly different technique which allows some bacterial maturation, as well as mould.

## Non-matured cheeses, yogurt, milk

#### Cheese spreads

These occupy an in-between position in that it depends on what they are made from: some higher quality cheese spreads are made from proper vintage cheeses, a few of which may be relatively high in tyramine. As an example, 'Parmareggio' cheese spread clocked in at tyramine 40 mg/kg, not high, but significant if one was to eat a whole tub of it [62]. On the other hand, most spreads are like commercial cream cheeses and contain no tyramine.

#### Unripened cheese styles

Fresh non-matured, i.e. unripened/unaged, cheese styles, and yoghurt, are always safe because milk itself has no tyramine, e.g. curd styles, *fromage frais*, mascarpone, cream, ricotta, mozzarella, cottage cheeses, bocconcini are therefore always safe and less stored for long periods unhygienically.

Spizzirri et al. assayed multiple samples, tyramine: 0 mg/kg [62].

Unripened cheeses: 10 samples [83] tyramine <0.5 mg/kg.

Goats cheese [84], unripened 'frais' styles, usually tyramine <5 mg/kg, many 0 mg/kg [62].

Aged goats' cheeses: usually low tyramine <10 mg/kg [62], but some may be higher, e.g. 70 mg/kg [84].

#### Milk and yogurt

In France, the regulations are strict. To be called 'yoghurt' milk must be fermented by *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (no decarboxylase activity, no tyramine), via starter-cultures. Bacteria must be at least at 10,000,000 CFU/g till the end of shelf-life. That means it is virtually impossible for tyramine producing bacteria to gain a footing: therefore yoghurt has no tyramine. Novella-Rodriguez, 5 samples, no tyramine [83, 85].

Cho, Korea, Yoghurt, 8 samples, max tyramine of 4 mg/kg [86].

But, be warned, if you are holidaying in the Himalayas, watch out for Tibetan traditional fermented yak-milk which may have tyramine 900 mg/L [87].

## Fermented vegetables/cereals (Inc. sauces)

#### Fermented cereals: Background history

A little caution is appropriate regarding sourdough bread because it can accumulate tyramine to a level of several hundred mg/kg, as can other similarly prepared foodstuffs widespread in other countries (see below).

Almost from the dawn of agricultural practice humans have learnt to increase the palatability and digestibility of legumes (see Soya) and cereals using fermentation, both with yeasts and bacteria. Yeast fermentation does not give rise to tyramine, but bacterial fermentation can do, depending on the types of bacteria and their decarboxylating activity.

The United Nations food and agriculture organisation (FAO) classify cerealrelated products 1) on the basis of raw cereal ingredients:

- a) wheat-based foods e.g. bouza, kishk
- b) rice-based foods e.g. busa
- c) maize-based foods e.g. ogi, bread, kenkey
- d) millet-based foods e.g. kunuzaki
- e) sorghum-based foods e.g. pito, ogi, bogobe, kisra, burukutu, kisra, injera

f) barley-based foods e.g. beer

2) on the basis of texture:

- a) liquid (gruel) e.g. ogi, mahewu, burukutu, pito, uji
- b) solid (dough) and dumplings e.g. kenkey, agidi
- c) dry (bread) e.g. kisra, injera

There are many dozens of local names for such preparations, for details consult culinary works, Wikipedia, google etc.

#### Sourdough bread

In the modern world the most prominent cereal-related solid-food vestige of these ancient fermentation practices is sourdough bread. This differs from normal bread because it utilises bacterial activity in the starter-culture for making the dough. As with other fermentation techniques this will not produce significant levels of tyramine if the usual modern standardised starter-cultures (with minimal decarboxylase activity) are used, as is now generally the case with commercial production [33]. However, Artisan producers may utilise cultures with greater decarboxylase activity. Therefore, their products may sometimes contain significant levels of tyramine.

Recent research indicates what would be expected by anybody who has understood the contents of this monograph. Preparations made with standardised starter-cultures are generally low in tyramine but there are some exceptions, usually home-made and locally made Artisan-type produce. Rizzello found tyramine levels of around 700 mg/kg in sourdough fermented wheat germ [88].

Özdestan has investigated various similar Turkish foods and found lowish tyramine levels [89, 90]: like kumru (ten samples of from different manufacturers in Turkey) < 5 mg/kg, shalgam (20 samples) <50 mg/kg, and tarhana (20 samples) 50-100 mg/kg.

## Marmite, Bovril, Promite, Vegemite etc.

It is likely that changes in the way these products are prepared in recent years have lowered the tyramine content; but there are not many measurements to rely on.

Marmite is made from the residual brewer's yeast and the first production facility was near the Bass beer brewery in Burton on Trent: production started in 1902. It had/has relatively significant amounts of biogenic amines  $\sim$ 320 mg/kg of tyramine [91] and 650 mg/kg of tyramine [92]. Both those are less than Blackwell's original estimate [46, 47, 49] of around 1,500 mg/kg, which may represent a change in production technique, or inaccuracies in measurement. One would need to take 30 ml to get 10 mg tyramine, which is more than is usually consumed.

Marmite-like spreads are like soy sauce and 'miso', which also involve 'fermentation' of brews containing non-animal proteins. They are usually used in lesser amounts, which can be safely eaten. A teaspoon (5 ml) of 'Marmite" would have only  $5/1000 \ge 300$  mg of tyramine, i.e. only a couple of milligrams.

#### Soya bean products

All *fermented* soya bean products like sauce and paste are prone to have significant tyramine levels.

For a list of fermented soya bean products see Wikipedia https://en.wikipedia.org/wiki/List\_of\_fermented\_soy\_products Non-fermented products like (most) tofu have no tyramine [93].

## Soy sauce, natto, miso and sufu etc.

Soy sauce is made from steamed soyabeans, roast wheat, and Koji fungus, the moromi mash may then ferment for as much as 2 years after which it is filtered and pasteurised. Soya beans have no tyramine; it is produced slowly during the fermentation reaching typical concentrations of ~150 mg per kg (litre) after many months. Miso is similar and there is a report of a reaction [94]. The story with these products is an echo of the fermented cereal picture, with beans as opposed to grains, levels may vary [95-97].

Japanese soy sauce: Maximum tyramine 940 mg/L (i.e. approx. 1 mg/ml). Most samples measured have ranged between 10-200 mg/L [98]. Maximum tyramine concentrations in the past may have been as high as 1000 mg/L, 25 ml of that would have contained 25 mg of tyramine.

Most supermarket Soy sauces have tyramine levels around 100 mg/L.

Yongmeia [99], 40 samples of Chinese soy, mostly tyramine less than 200 mg/L (20 of the 40 were <100 mg/kg). The total content for the five biogenic amines in these samples was 497 mg/L with a range from 41.7 to 1357 mg/L. The concentrations for each of the five amines were: tyramine 0-673 mg/L, histamine 0-592 mg/L, cadaverine 0-550 mg/L, spermidine 0-486 mg/L and spermine' 0-145 mg/L.

Stute [100], 23 samples soy, all low tyramine <200, except one clocked a staggering 6,000 mg/kg (dead rat in the vat? or a typo for 600?).

Miso, 5 samples tyramine  $\sim$ 20 mg/L [86], and Kung 40 samples: all <50 mg/L [101].

Other soya derived products like miso soup and sufu [86, 102] generally have similar concentrations. Miso, 5 samples tyramine <25 mg/kg [86], and soy sauce tyramine <50 mg/kg [86]. Sufu from Taiwan [103], and Miso 40 samples tyramine all <10 mg/kg [101] but some higher [104].

Natto' is another fermented soya bean preparation that sometimes achieves high tyramine levels, although <100 mg/kg is typical [97, 105].

Soyabean pastes ('Doenjang' etc.), of 23 samples most had undetectable levels, but a couple were >1,000 mg/kg [106].

#### Fermented sauces: Animal

#### Fish sauces

In classical Roman cooking fish sauce was called garum or liquamen. They are ubiquitous now, but have long been deeply rooted in Far Eastern cuisine. Seafood, often anchovy, is allowed to ferment ~140-200 days. Names: Nuoc-Mam (Vietnam), Nam-Pla (Thailand), Budu (Malaysia), or Patis (Philippines) ketjap-ikan (Indonesia), ngapi (Burma), ishiru or shottsuru (Japan), colombo-cure (India Pakistan), yeesu (China), aekjeot (Korea). For more see Wikipedia, and for recent reviews refs [17, 86, 100]. NB Cho is in Korean, but the tables of values are readable.

They will, like everything, vary a bit with producer and hygiene quality, but seem usually to be OK, 200-500 mg/kg (bearing in mind it is, like soy sauce, a condiment, if used in modest amounts (no more than  $\sim$ 20 grams) will be safe [107].

Korean fermented fish products tyramine <50 mg/kg [86], liquid fish sauce made from a variety of things, scallop, squid etc. tyramine average 350, max (anchovy) 600 mg/kg [86].

Stute [100], 45 commercial fish sauces from the Far East, most <200 mg/kg, maximum 588 mg/kg for tyramine.

Worcestershire sauce is fermented and contains anchovies (at least the original 'Lea & Perrins' version). There are many different producers of such sauces called 'Worcestershire' or 'Worcester' and there is no data on their tyramine content, but it is reasonable to assume it will be variable and like other fish sauces, probably lower. If used in condiment quantities, it is unlikely to add a significant tyramine load to a meal.

## Meat and fish products

Fresh and frozen meat and meat products are safe, but if they are not fresh, i.e. if they have been subject to decomposition by micro-organisms, then they could be risky. Fresh liver has no tyramine [108], but if stored badly or past its 'use by' date when purchased, and then kept in a domestic fridge that is not cold enough, may become risky [109, 110]. The Hedberg paper [109] is a great illustration of good observation and investigation.

Ordinary commercial beef is not usually aged, and concentrations of tyramine are likely to be <10 mg/kg. Galgano, 7 mg/kg after 8 days at +4°C [111].

Similarly, liver patés (and similar meat or fish pastes) are safe if freshly made and properly refrigerated (i.e. *below* 4°C), especially because such foods are consumed normally in small portions. No specific modern data is available yet, but the lessons enumerated herein tell us what is likely. Liver [112] has no tyramine, but once processed and contaminated with bugs it is an ideal culture medium, any laxity in hygienic preparation, storage time and temperature will result in a steady increase in tyramine. Concentrations of tyramine 100-500 mg/kg are likely in contaminated and badly stored product after a week or two.

## Meat, fresh

#### General

Fresh meats contain no significant amounts of tyramine, for a review of amines in meat (and vegetables) see especially Kalac [113-115]. Also, for discussion see [116-118].

Stored *chilled* meats are safe (i.e. <10 mg/kg) [111, 114, 119]. Beef: stored at – 18°C for 178 days, tyramine max tyramine <4 mg/kg [119, 120].

#### Poultry

Chicken: refrigerated for 20 days at a temperature of  $+4^{\pm}1^{\circ}$ C in a domestic refrigerator. Tyramine level at one day, 3 mg/kg, 20 days, 15 mg/kg [121-124]. Moreira found well stored product <5 mg/kg.

Poultry: insignificant levels [125-129].

Duck: tyramine 0 [128].

#### Minced and ground beef

Minced and ground beef and 'hamburgers' are potentially problematic because any contaminant bacteria are mixed into a medium (mince) with a large surface area, which may then be sub-optimally stored. It is therefore reassuring to find assays have found negligible levels of tyramine <3 mg/kg [130]. It might also be observed that, in North America alone, they consume millions of burgers per year and there are no reports of tyramine reactions associated with burgers.

#### Beef

Beef (stored above 0°C) can have significant tyramine concentrations: stored at +4°C for 21 days, 60 mg/kg, and after 36 days at +4°C 120 mg/kg [117]. Such meat is usually only available in the restaurant trade (at a high price!) but could contribute to excessive tyramine intake as part of a gournet meal. However, there are no reports of reactions with beef in 50 years (cf. liver, a couple of reports of reactions in 50 years).

#### Pork

Pork and fresh pork products, not surprisingly, have no tyramine [126-128].

#### Offal

Fresh offal contains no tyramine. Kidneys, liver, duck giblets etc [112, 126, 128, 131, 132], all had no tyramine.

#### Sausages, pâté, meat pastes

These have minimal tyramine unless poorly prepared or stored [133-135].

#### Meats, preserved

#### Dry-cured meats

As with all *dry cured* meat products (as opposed to fermented ones) only low concentrations of tyramine are expected, Lorenzo found <5 mg/kg [136], which agrees with [137]. 'Parma ham', pastirma, jamon, prosciutto, coppa etc. will be safe.

#### Fermented sausages

Concentrations of tyramine depend, as would be predicted, on the hygienic quality of the meat used and the strains of bacteria involved. Those produced with frozen meat (low temperature processing) usually have maximum concentrations of about 100 mg/kg. The improved starter-cultures, now widely used, show a lack of, or much diminished, amino acid decarboxylase activity which results in lower concentrations of BAs [35, 138-142].

In their 2003 paper, 'Biogenic amines in dry fermented sausages: a review' Suzzi reviewed 20 studies from around Europe [143] and found tyramine was usually below 200 mg/kg, few samples were higher [137]. Suzzi 'In the several reports concerning the Spanish dry fermented sausages Chorizo, Fuet, Sobrasada and Salsichon, tyramine was generally detected at the higher concentration (exceeding 600 mg/kg in some sausages with mean values of about 200 mg/kg).'

In Spanish fermented sausages Chorizo, Fuet, Sobrasada and Salsichon tyramine was detected at up to 600 mg/kg in some sausages, with mean values of about 200 mg/kg [144].

French sausages, both artisanal and industrial, had tyramine maxima of 270 mg/kg [143, 145].

Papavergou [146]: 50 samples of dry fermented sausages sold in Greece, mean 100, max 500 mg/kg.

Hygiene and low temperature processing continue to improve steadily, more recent surveys find generally lower concentrations [140, 147, 148].

Latorre-Moratalla et al. is a good recent review: they found an average of 150 mg/kg, max <200 mg/kg. The study received financial support from the European community project: 'Assessment and improvement of safety of traditional dry sausages from producers to consumers' (QLK1 CT-2002-02240, Website:

<u>www.clermont.inra.fr/tradisausage/</u>). It is a good example of the efforts being made to monitor and improve hygiene standards.

## Preparations of stock cubes, powders, bouillon, etc.

These are not prepared by fermentation but are flavoured extracts and reductions, therefore they are most unlikely to be high in tyramine. Populin tested 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 [91]. They found none exceeded tyramine 10 mg/kg.

### Fish

#### Fresh fish

Levels of both tyramine and histamine may be increased in poorly refrigerated produce. However, with fish spoilage it is notable that histamine can be greatly elevated without significant elevation of tyramine [149]. Many regulations limit histamine, to between 50 (USA) and 200 mg/kg (EU). Histamine itself causes Scombroidosis [18, 150], see below. Freshness and low-temperature handling is everything, and quality control and screening of imported produce continues to be a powerful force for improving hygiene and handling world-wide [127, 151].

A recent review confirmed low tyramine levels in properly handled raw and processed seafood [150].

Fresh fish usually has 2-5 mg/kg tyramine [152]. Whole and filleted trout kept on ice for up to 18 days, max at 18 days was 7 mg/kg [153, 154]. Frozen fish 1 mg/kg [155].

Herring, fresh, stored on ice (i.e.  $\sim 2^{\circ}$ C) <5 mg/kg [156, 157]. Storage conditions varied a little, but histamine reached 400 mg/kg whilst tyramine was low. After reaching a maximum of 100 mg/kg after seven days, tyramine then decreased on storage to 15 mg/kg at 15 days.

Chilled fresh and frozen or thawed salmon [152, 158] had a max of 40 mg/kg at end of shelf life.

Concerning histamine in fish, see [159].

#### Cured fish

Diverse types of fish (especially salmon) are 'cooked' using food acids (see also 'pickling'). The most widely known dish using this technique is Gravlax, gravad lax (and various other spellings and derivations) which originated in the Scandinavian countries and has been adopted in America, especially in Jewish culture where the name has transmuted to 'lox'. The data elsewhere in this monograph allow confidence that fresh hygienically prepared fish done in this manner would be expected to be completely safe. However, as with vegetables, deliberately fermented, or matured, product may develop significant tyramine concentrations.

#### Smoked fish

Smoked salmon [160] dry-salted, traditional smoking, sliced, vacuum-packed stored nine days at 4°C and 19 at 8°C contained no tyramine.

Cold smoked salmon tyramine <20 mg/kg [161].

#### Dried Fish

Dried salted Tuna roe, tyramine was 90 mg/kg [162].

#### Canned fish

Some canned samples reach tyramine 10 mg/kg, but that seems rare [163]. Max 70 mg/kg [164]. Histamine (some were > FDA limit of 50 mg/kg), one was 1,000 mg/kg of **histamine**\*, see [165, 166].

#### Pickled fish

Pickled herring does not involve a fermentation process and such products are safe providing they are hygienically prepared from fresh fish. Modern food auditing processes controlling the hygiene of processing plants, and low temperature processing, suggests that commercially available supplies are likely to be of decent quality and therefore safe. As with vegetables (cf. sauekraut), product that has undergone a fermentation process is different, and can contain significant concentrations of tyramine, like the Strömming (herring) in Baltic countries, which is fermented. The Norwegians have their rakfisk (fermented fish), and the Swedish fermented herrings (Surströmming), Icelanders fermented shark (Hákarl or kæstur hákarl), and perhaps on the Kamchatka peninsula they fester something similar, perhaps an unmentionable part of a brown bear buried in a peat bog for months. There are no available tyramine data on these. But if you have read this far without learning already that they are obviously to be avoided then...

#### Fish sauces

See 'Fermented Sauces' above.

Malaysian budu and cincalok

Malaysian local appetisers 'budu' and 'cincalok' [107] tyramine up to 450 mg/kg.

#### Pizza

It depends what you put on it. It should be clear from the data in this monograph that most commercial pizzas are highly likely to be safe, as found by Shulman [167]. This is because they are most unlikely to use anything other than commercial processed cheese (usually stored ready grated and frozen), or non-matured cheese types (e.g. mozzarella, which has no tyramine). Also, any salami type products on them are likely to be in small quantities, and of the type that is low in tyramine. Pizza chains/franchises may change their cheese blend to stay abreast of cheese fashions, but for cost reasons are unlikely to use large proportions of matured cheese that might have a higher tyramine content.

Gourmet pizzas may contain mature salami and cheese with higher tyramine concentrations, but the quantities are likely to be small, the total tyramine load is unlikely to be problematic. The data herein should allow a reasonable estimation of the total amount of tyramine. Sensible caution is therefore appropriate with some "gourmet" pizzas and with large servings of some "commercial" pizzas.

## Vegetables and fruits

Vegetables generally have total BA concentrations of only a few mg/kg and tyramine levels of about 0.2 mg/kg with a maximum of 1 mg/kg [168], but can these increase a little with spoilage (see below re avocados). As stated in 'Key facts' in normal sized portions these things are safe.

Plants do produce an extraordinary range of amines and psycho-active alkaloids, many are part of the ancient battle whereby plants manipulate the behaviour of animals and enhance their own survival (e.g. think of opiates, cannabis, tannins, nicotine, atropine, hyoscine, aperients & innumerable toxins). Many of these

<sup>\*</sup> That level of histamine would likely precipitate 'scombroidosis' in someone on phenelzine.

compounds are more common in a greater variety of plants than a casual reading of the literature would lead one to suppose. Their concentration varies greatly depending on many factors like plant variety, tissue type, stage of growth and attack by other organism etc.

Useful reviews are [168-171], it has recently emerged that some of these compounds affect TAA receptors and TRP channels, e.g. capsaicin, menthol [172, 173].

#### Avocado and banana and other oddities

There is one credible report of high BP after consumption of about six avocados, probably over-ripe [174]. There are no recent data on Tyr levels. The fact that there have been no further reports in more than thirty years indicates it is difficult to ingest risky amounts via fruits.

A recent (2019) more extensive study of bananas, of various genotypes, including 'plantain', showed the amines tyramine, histamine, dopamine, serotonin, spermidine and spermine all **decreased** during the ripening in most genotypes [175]. Levels of tyramine in the pulp were remarkably consistent across different genotypes (100 mg/kg, dry weight), appr approximately 10 mg/kg fresh banana, but varied more in the peel (max 100-300 mg/kg, dry weight). Levels of dopamine and L-Dopa were (d/wt.) DA 30 and L-Dopa 5 in pulp, and in peel DA typically 100 and max 6,000, and L-Dopa 50 (d/wt.).

This study must be considered as the most definitive data currently available concerning bananas, and the older data cited in previous versions of this monograph, below, now takes a backseat.

Older data: dopamine, up to 400 mg/kg in the pulp, about 1,500 mg/kg in the skin [176], but little tyramine [171, 177].

The first report of dopamine was in 1958 [178]. Large amounts of banana (20 per day) may increase plasma dopamine concentrations [179]. This may be via release of endogenous DA, and or via L-DOPA or other precursors or releasers. Although **DA cannot cross the blood brain barrier** (or only to a limited extent [180]), plasma DA may be elevated, and raised peripheral DA may raise BP by vaso-constriction. As with other plants, concentrations will vary greatly according to variety, part of plant, stage of growth, maturation, and ripeness. Concentrations may be higher in the skin (1,000 mg/kg) than the pulp, depending on ripeness [176], at only 2 mg/kg [181] and see [182-184].

Banana might possibly inhibit the adsorption of medicinal L-DOPA [185, 186]. It is unlikely that bananas in usual quantities would have any significant effect [Added 7/2021: however, a scientist in South America contacted me to say he was taking TCP in high dose. He reported that he definitely got BP elevation when he consumed half a dozen overripe bananas, he repeated the experiment several times using less ripe and overripe bananas whilst monitoring his BP and got consistent and reliable results. He got substantial but not dangerous elevation of blood pressure, to a BP of 180 mm/Hg.

Paprika and green pepper appear to have higher tyramine contents 286 and 141.5 mg/kg of dry weight, respectively [169].

There is always something new. Ever heard of 'fermented minced pepper'? Evidently it is enjoying rising popularity in China! It may have slightly elevated tyramine levels [187], do not eat a whole jar.

In summary, it would seem normal servings of fresh vegetables, fruits etc. are unlikely to have any serious adverse effects via histamine, tyramine, or L-dopa (that includes broad-beans, aka fava beans, and related species).

Nevertheless, interactions are sometimes noticeable and there is much yet to learn about the psycho-active contents of plant derived foods. One interesting

recent reaction [personal communication] involved a reliably documented alteration of BP associated with consumption of quince paste, for which there would appear to be a possible explanation, since it has been claimed to contain a constituent that acts as a dopamine re-uptake inhibitor [188]. This finding needs to be replicated, especially because the probity of much Chinese research is doubtful [189].

#### Spinach

Tyramine in spinach [190] was <5 mg/kg, but histamine can be higher  $\sim$ 50-100 mg/kg.

#### Fava/faba beans

Fava beans (*Vicia Faba*, aka broad beans) have tyramine at about 10 mg/kg [168], & L-DOPA, but at low concentrations, which is probably not sufficient to have any effect in normal portions. See 'L-DOPA'.

#### L-DOPA

Dopamine (DA) is present in many plants and plays a role in repelling pathogens. It is the precursor of the quinones that cause browning when they polymerise into melanin (e.g. bananas, avocados). Some legumes contain significant amounts of L-DOPA in some tissues, at some stages of growth, including *Vicia faba* L. varieties (aka fava beans, broad beans) and *Mucuna pruriens* (Cowhage, itching powder) [191-196]. Varieties of these plants are being genetically engineered to try to find a suitable dietary source for L-DOPA because it may be better than pharmaceutical L-DOPA (better absorption, more stable plasma concentrations). Various preparations are being sold on the internet. A search for 'mucuna aphrodisiac' or 'mucuna parkinson' returns many thousands of hits.

Maximum concentrations of 10-20 mg/g (dry weight) have been found in *Vicia faba* [191], equivalent to a wet weight concentration of approximately 100 mg/kg. However, the edible beans are lower.

Since L-DOPA is a dopamine precursor, not a releaser, i.e. not an indirectly acting sympathomimetic like amphetamine is, it is likely to have an effect more analogous to L-tryptophan with MAOIs (i.e. moderate potentiation only). L-tryptophan does not cause serious problems with serotonin toxicity, and nor would one expect L-DOPA to do so with BP.

Despite the warnings on interactions with medicinal L-DOPA — early papers were [197-199], the evidence for serious hypertension (see below for discussion) with L-DOPA and MAOIs seems inconclusive.

Such amounts of L-DOPA may potentiate or precipitate moderate BP increases, but, in my opinion, it is unlikely that a seriously risky BP elevation would result.

## Pickling and preserving

Preservation, mostly of vegetables, using the acidic properties of natural acids, mostly acetic and lactic acid, is widespread and usually involves no fermentation, just the addition of vinegar (acetic acid), as in typical pickled onions. However, other pickled preparations involve a bacterial lactic acid fermentation process, such as sauerkraut and kimchi, see below. It is these fermentation processes which can give rise to small amounts of tyramine. Naturally occurring fermentation, without the use of starter-cultures (see above) tends to produce more contaminant biogenic amines, including tyramine.

#### Olives, capers, caper berries

Preparation of olives may involve bacterial lactic acid fermentation, tyramine levels in olives, and capers are low [200, 201].

#### Sauerkraut

Sauerkraut is made by lacto-fermentation, as are kimchi & traditional pickled cucumbers. These keep for several months, unrefrigerated.

Sauerkraut: review [113], more than 100 samples from 7 countries, almost all tyramine <200 mg/kg, but a couple from Czech Rep. were 400-900 mg/kg.

Tyramine concentration was 50 mg/kg in one canned sauerkraut, other samples <12 mg/kg.

Korean 'kimchi' cabbage average tyramine 50 mg/kg, max 120 mg/kg [86].

Lavizzari [170, 171]: Spinach tyramine 2 mg/kg. Histamine concentrations were 100 mg/kg.

Kosson [202] found insignificant levels of tyramine.

#### Chocolate

Chocolate sometimes does involve a short fermentation stage. Somewhat variable concentrations of amines have been reported, mostly low, and inconsequential — unless *large* quantities are consumed (i.e. more than 100 grams).

A few recent papers have added data on dozens of samples of cacao powder, chocolate (white, milk, dark) and syrup, see especially [203, 204], none of which exceeded 35 mg/kg, most being <10 mg/kg.

These other results are in the same range: Pastore found 2 mg/kg for tyramine [205]; Lavizzari [171] found concentrations of tyramine of 0.3 mg/kg; Baker [206], powdered cacoa: tyramine 3 mg/kg, chocolate <1 mg/kg & Granvogl [207-210].

#### Health and sport supplements

Such substances can contain various 'illegal' additives, some potentially injurious, and most of them useless. The commonest adulterants are SRIs (like sibutramine — danger of ST), steroids, stimulants, and sildenafil (Viagra). They should list the main ingredients, if they do not, then they should not be used. If they do, then do not use them if they contain tyramine at levels that would be injurious, i.e. more than 5–10 mg per portion or 'dose' [211].

Yeast extracts and tablets do not contain significant TYR [52, 53, 92]: This is because they result from yeast fermentation, not bacterial fermentation. This is the reason why marmite and similar substances **do contain significant tyramine** because the methods of production involve maturation with non-yeast organisms.

## Other non-serious interactions

Many plant-derived substances (alkaloids), e.g. 'herbs' and 'foods' like coffee, and tea contain various compounds that act as 'drugs', stimulants like caffeine, 2-phenylethylamine, methylamine, trimethylamine (see Strolin Benedetti & Tipton [212]). These affect everyone but may have an exaggerated effect in those taking various sorts of antidepressant drugs, including MAOIs; they should be taken in moderation and avoided if they precipitate symptoms such as tremor, anxiety, jitteriness, palpitations, tachycardia, agitation, or poor sleep.

#### Some tyramine champions

One soy sauce clocked in at 6,000 mg/kg [100], does one smell a rat there, or a measurement error?

An old cheddar cheese measurement from the 1950s 3,700 mg/kg [51].

An Italian goat cheese at ~ 2,000 mg/kg [213]

And, there is a French cheese called 'crotte du diable' (translates as 'Devil's turds'), and various rotten-fish brews (best consumed on isolated Scandinavian mountain tops), that one presumes would be contestants, but I was unable to find any data. Would any lab technician be brave enough to endure them?

For an introduction to some other strong-smelling foods see Andrew Zimmern:

http://www.openjourney.com/article/18-stinky-foods-around-the-world-41.html

#### Holidays

Some holiday destinations will require heightened awareness of food hygiene issues, in "Biogenic amine contents in selected Egyptian fermented foods as determined by ion-exchange chromatography" Rabie found levels of 2,000 mg/kg in cheese and fermented sausage [214], then there is fermented Yak milk [87], and Icelandic fish-dish called Hákarl (fermented shark meat).

## Wine, spirits and beer

A meal without wine is like a day without sunshine. Anthelme Brillat-Savarin

Wine in healthy quantities is always safe, a few beers do have substantially elevated tyramine, especially open fermented Lambic style beers. Spirits and liqueurs are safe.

Wine and beer in moderation (two drinks in 2 hours) are safe (as far as tyramine is concerned), but home-made wines or 'artisan' (non-pasteurised) beers may be risky. Modern hygienic production methods for beer have made tyramine concentrations >10 mg/L rare (there is now extensive regulation and documentation of this, see below for details). Home-made wines or beers may sometimes be risky. Bottled beer is safe if pasteurised; a little caution is warranted with 'live' beers which may be available from 'boutique' producers. They can be distinguished by the sediment (of dead yeast) and they are cloudy if shaken.

Modern commercial wines do not contain significant tyramine.

Tyramine in liquids taken on an empty stomach should be regarded as a special case, because tyramine will be absorbed much more rapidly [37, 215], amounts of tyramine of one third of the figures given above may evoke a reaction. One small (330 ml) glass of some 'live' beers could, in *rare* instances, have about 10 mg of tyramine; this is sufficient to cause a reaction in a minority of people, when taken on an empty stomach, e.g. see [30, 216].

#### Wines

Here with a loaf of bread beneath the bough, A flask of wine, a book of verse – and thou

~ Omar Khayyam

Wine can rarely contain significant concentrations of tyramine (>10 mg/L).

Recent major reviews have covered many hundreds of different wines of all types: almost all have had tyramine levels of less than <5 mg/L [217-226].

Aged wines, all tyramine <5 mg/L [227].

Thirty different wines, including aged fortified wines (Port and Madeira), max tyramine 5 mg/L [228]. Wines 200 samples, histamine average 1.2 mg/L [229] and 300 samples max tyramine <5 mg/L [230, 231].

USA wines, max tyramine 3 mg/L [221].

Marcobal, 61 different Spanish wines including aged Rioja Gran Reserva wines [232]: Tyramine range 0-11.32 mg/L, Average  $1.40 \pm 2.35$  mg/L. Only 34 of 61 wines had *detectable* tyramine.

However, Preti et al. found 8 of 60 (personnel communication) Italian wines tested recently had tyramine levels >10 mg/L [233], none of these were chiantis!

The repetition of the notion that Chianti, uniquely amongst wines, contains significant concentrations of tyramine [74], illustrates, it seems, how easy it is to be careless about the relevance and reliability of sources of information. The chianti error was countered long ago [234]. The most likely explanation for these anomalies is that in the past many of these wines were made by farmers with little knowledge of wine or fermentation techniques. Hygiene practices were poor; it is only in the last 20 years that Italian winemaking has reached a modern standard, in most places.

#### Vinegars

Ordinary vinegars have low tyramine, but: Chinese rice wine vinegar (old) 400 mg/L, Sherry vinegar 15 mg/L, Italian Balsamic ~15 mg/L [235].

#### Beers

An overwhelming majority are low tyramine and safe, but if your favourite tipple is a 'micro-brewery', open fermented or 'live' or something exotic like Belgian lambic, watch it! Test it out carefully before swigging too much!

Standards, and awareness of brewing hygiene issues, have increased since some of the older results, **but caution is still warranted**: it would seem likely that most, but not all, standard commercial and modern beers world-wide will be safe (<10 mg/L) in moderation; some low volume 'artisan' and 'boutique' ones are a little more likely to be risky. Beers made using natural yeasts (spontaneous fermentation) rather than starter-cultures, are more likely to have contaminants and therefore high tyramine. This is an observation echoed throughout this monograph with all types of 'fermentation', whether with cereals or sausages. Some examples are high enough to be risky, especially if beer is drunk on a more-or-less empty stomach, when it will be absorbed more rapidly.

It is established that the presence of tyramine is indicative of bacterial contamination and less than ideal hygiene practice.

A review by Kalac [236-238], "195 samples of bottled or canned beers were 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". They found a vast majority were low (2-8 mg/L, mean 7), but a few are up to 30-50 mg/L, with a maximum of 70 mg/L.

Bunka more recently reviewed 114 samples of beer from 28 breweries in the Czech Republic which were "monitored at their purchase and at the end of their best-before period" [239]. Tyramine was <10mg/L in 51 samples, between 10 and 50mg/L in 21 samples and 100 mg/L in 5 samples.

Pradenas et al. in Chile assayed over 100 samples and found 99% of 316 beer samples were no more than 2 mg/L, one was 6 mg/L [240].

Tang [241]:18 beers all brewed in China, some European under licence, values mostly tyramine 3-5 (max 7) mg/L.

Spanish beer: tyramine <2 mg/L [242]; 17 samples mean tyramine 5 mg/kg; 55 samples mean 7 mg/L, max 47 mg/L. Europe 48 samples max 6 mg/L [243, 244].

16 European countries, 195 samples, mean tyramine 6.5 mg/L max 67.5 mg/L [245].

17 domestic Turkish and 13 imported beers [246], all were tyramine <2 mg/L.

Ken Shulman's group [247] looked at a total of **98 beer samples** (79 different brands of beer) in 1994:

'All of the bottled beers analysed had safe tyramine concentrations (< or = 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'.

## This was an influential paper; subsequent knowledge suggests a slight modification of their conclusions.

Belgian beers especially can have high tyramine. Loret et al. [248], considered a large number of these Belgian beers: the types covered four different brewing processes; low or bottom fermentation (LF, 18 samples), top fermentation (TF, 36 samples), top fermentation followed by a secondary fermentation in bottle (TF+ BSF, 184 samples), and spontaneous fermentation (SF, 42 samples).

They found 21 samples out of 220 that exceeded 10 mg/L of either histamine or tyramine, these 21 had a mean tyramine of 28 mg/L, and the maximum was nearly 70 mg/L. They developed a "Beer biogenic amine index" (BAI) that would allow assessment of the quality of the production process. Since the work was financed in part by the Belgian Brewer Confederation, we may assume they are trying to improve things because of EC regulations and a recommended limit of tyramine 10 mg/L.

Belgian Lambic beer is an old style (see Wikipedia for information) allowed to spontaneously ferment with wild airborne yeasts and then aged for 1-3 years, breweries locate their open fermenters in well-ventilated attic roofs. The general category is spontaneously fermented beers (SF beers) which are obviously likely to have more tyramine (because they have more 'contaminant' organisms).

One more recent assay of SF Belgian beer found only 20 mg/L of tyramine, which may reflect improved standards [248]. Gueuze is an aged unflavoured Lambic style. This is a good illustration of why dirty farmhouse styles of anything are more likely to have contaminant strains that have decarboxylase activity, and thus potential for tyramine production, especially if a rat/sparrow/cockroach falls into the open fermenter.

## MAOIs and scombroidosis (histamine fish poisoning)

The anti-tuberculosis drug isoniazid (INH) is closely related structurally and pharmacologically to phenelzine, but not related to tranylcypromine. INH is capable of inhibiting other amine oxidase enzymes, including the one largely responsible for breaking down histamine. That results in increased sensitivity to any histamine ingested in food by patients on INH and many histamine reactions have been described [249-256]. The potency of phenelzine (but not TCP) for these effects is probably like isoniazid, and the blood and tissue concentrations reached in the system are also probably similar. However, there have been no reports of definite histamine reactions involving phenelzine: nevertheless, it is probable that phenelzine does increase people's sensitivity to histamine. The seminal early work by Blackwell and Marley is still worth reading, and indeed, they presciently predicted sensitivity to histamine as discussed in this MS — they were indeed ahead of their time [46].

Bearing in mind that foods that accumulate tyramine, like cheeses, may also have elevated histamine concentrations, this may be of relevance to patients taking phenelzine.

Symptoms of histamine poisoning are lowered BP, headache, palpitations, skin flushing, nausea, vomiting, and pruritus (itching).

The symptoms of histamine poisoning relate especially to effects on blood vessels, cell permeability and smooth muscles, and include headache, nasal secretion, bronchospasm, tachycardia, extra-systoles, hypotension, edema (eyelids), urticaria, pruritus, flushing and asthma [257, 258]. Serum tryptase concentrations may help to distinguish allergic symptoms from scombroidosis [259].

It is inevitable that some instances of BA poisoning will exhibit mixed symptoms of both histamine and tyramine effects, especially in people taking hydrazine drugs like carbidopa, isoniazid and phenelzine, and as above, Blackwell and Marley discussed this, but it does not seem that anyone has read, or at least remembered, what they wrote — maybe we might stop a moment and raise our glasses for a toast in their memory.

Marley went on to write more seminal papers on MAOIs that are important visa-vis ST [260-265], those were also 'over-looked' by most writers: so, raise your glass again.

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