Royal Brompton & Harefield NHS
NHS Foundation Trust

Imperial College London



BDA The Association of UK Dietitians
Food Allergy
Specialist Group

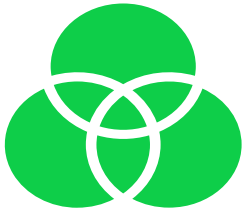
INTOLERANCE TO FOOD ADDITIVES AND NATURAL FOOD COMPONENTS

Dr Isabel Skypala

Consultant Allergy Dietitian – Royal Brompton Hospital

Senior Clinical Lecturer – Imperial College

FOOD INTOLERANCE



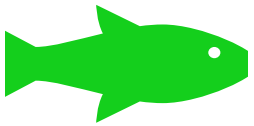
The spectrum of intolerance



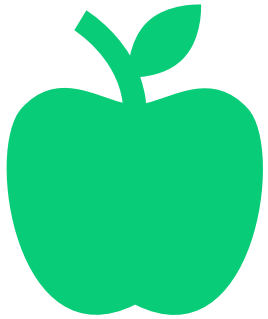
Food colourings



Food preservatives



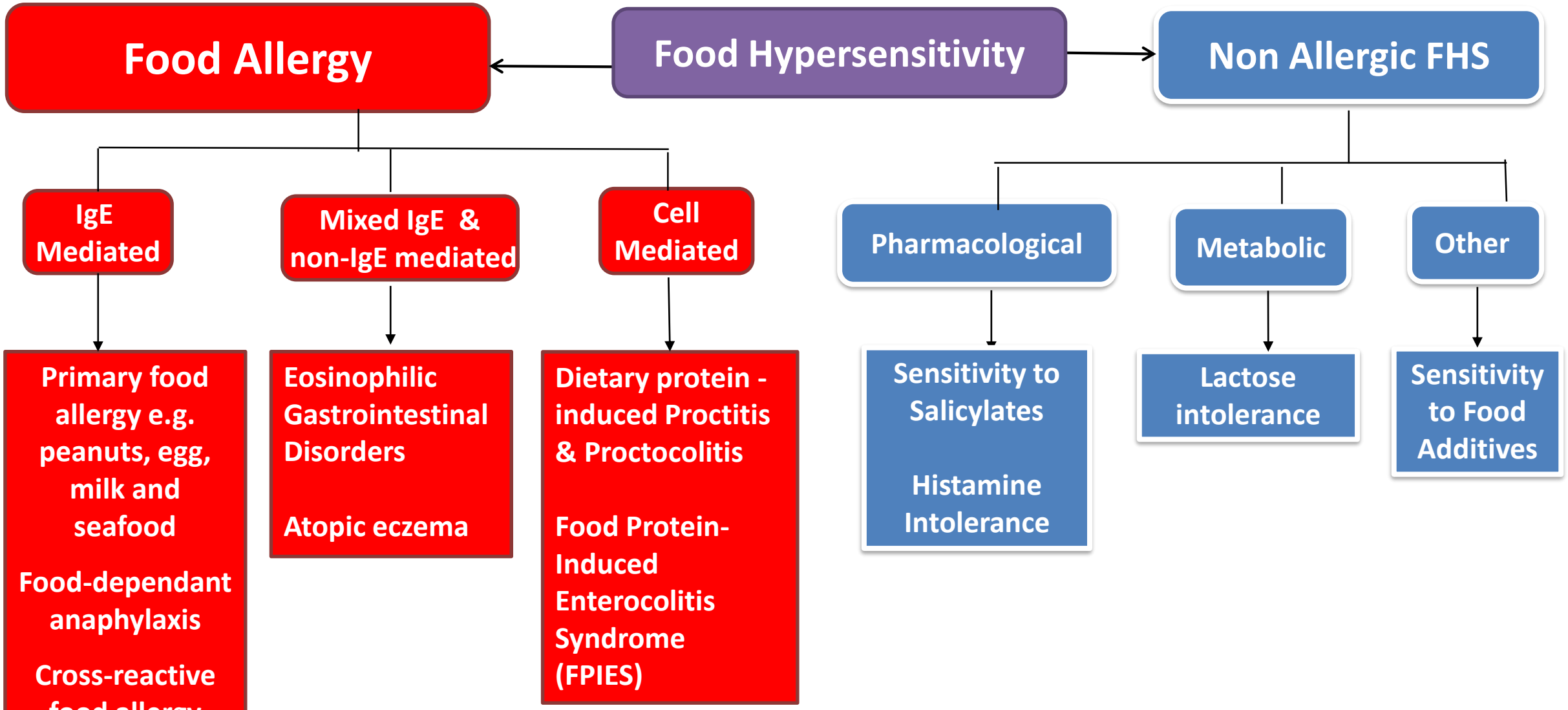
Vasoactive amines



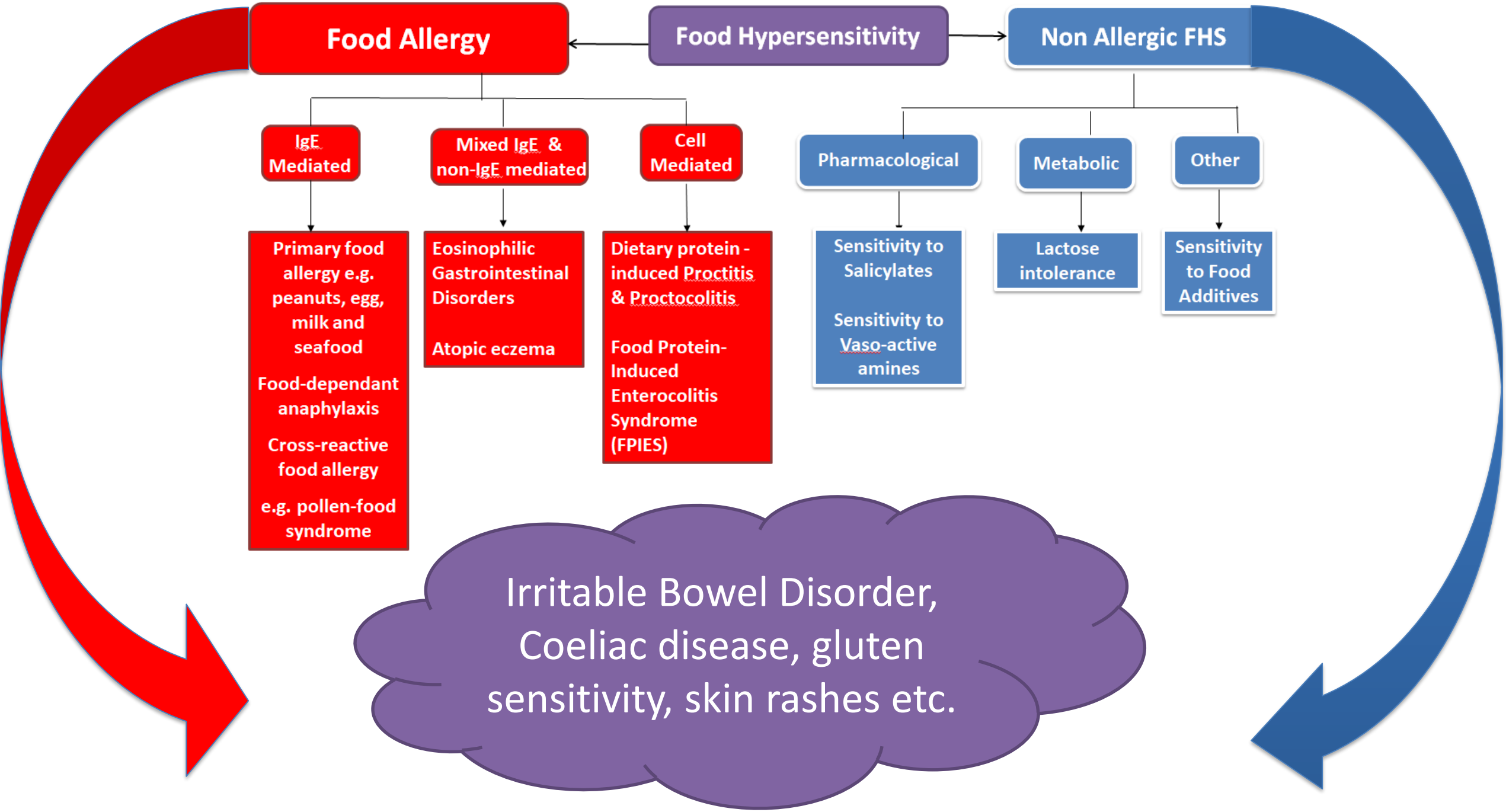
Salicylates

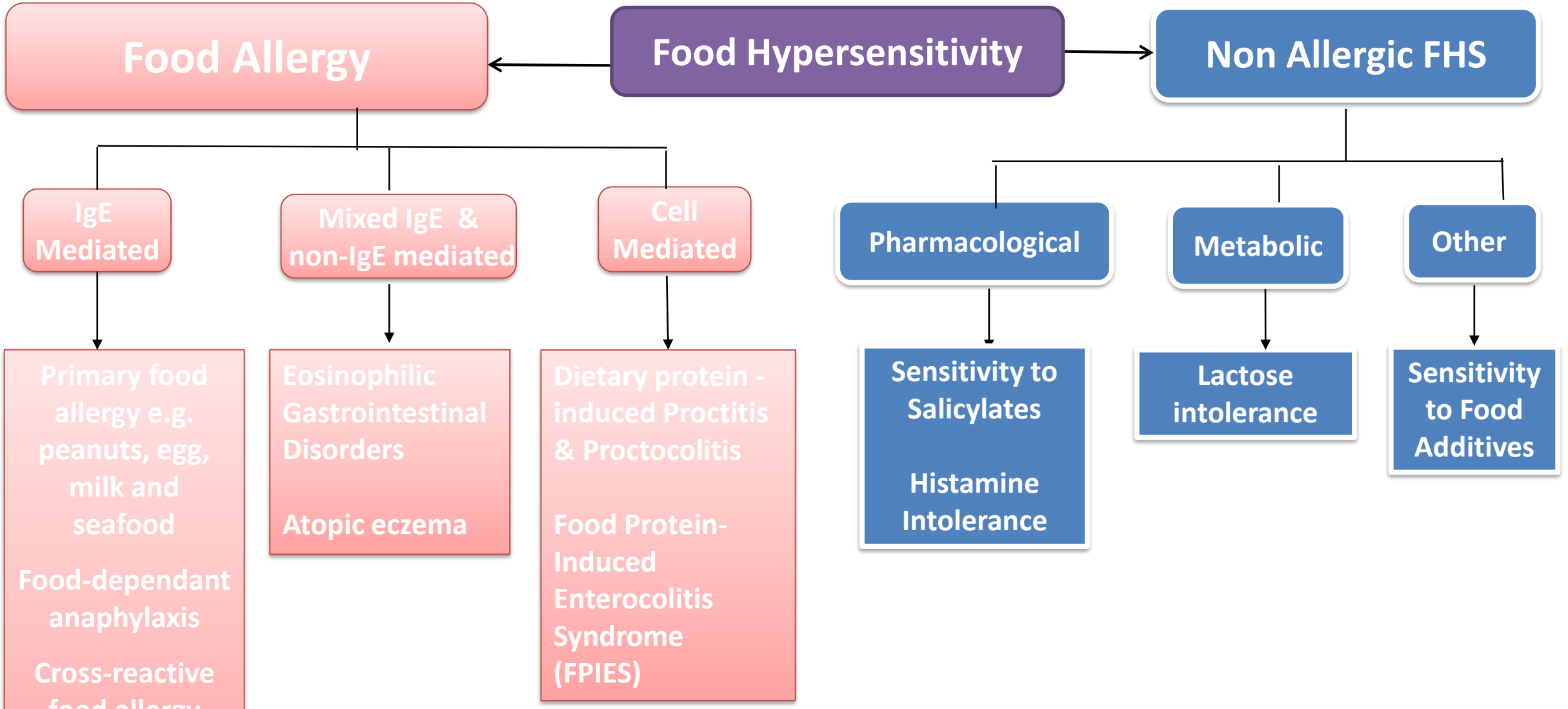


Hidden Food Allergens

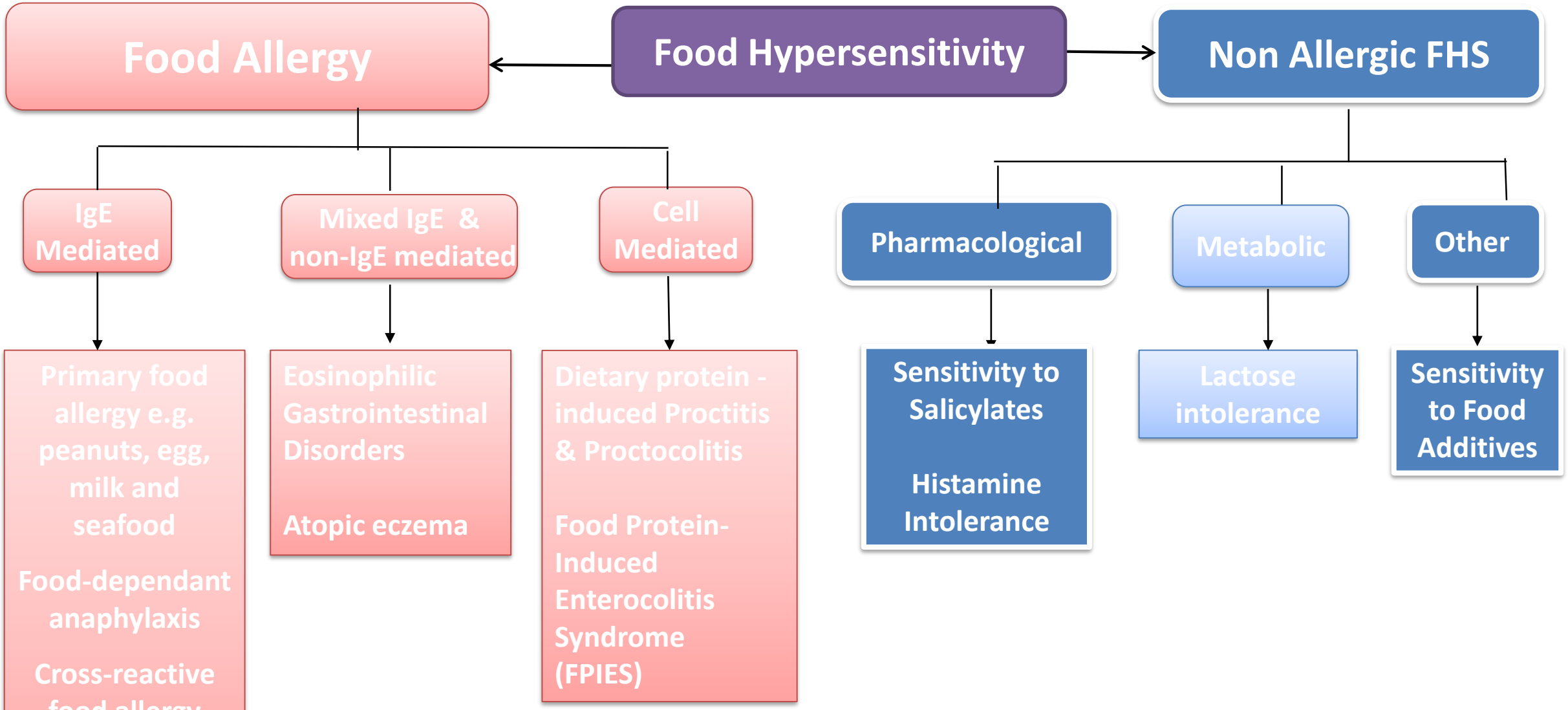


EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy (Muraro et al 2014)
Guidelines for the Diagnosis and Management of Food Allergy in the United States (Boyce et al 2010)


Food Allergy
Food Hypersensitivity
Non Allergic FHS
IgE Mediated
Mixed IgE & non-IgE mediated
Cell Mediated
Pharmacological
Metabolic
Other
Primary food allergy e.g. peanuts, egg, milk and seafood
Food-dependant anaphylaxis
Cross-reactive food allergy
e.g. pollen-food syndrome
Eosinophilic Gastrointestinal Disorders
Atopic eczema
Dietary protein - induced Proctitis & Proctocolitis
Food Protein-Induced Enterocolitis Syndrome (FPIES)
Sensitivity to Salicylates
Sensitivity to Vaso-active amines
Lactose intolerance
Sensitivity to Food Additives
Irritable Bowel Disorder, Coeliac disease, gluten sensitivity, skin rashes etc.



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FOOD INTOLERANCE

Food Additives:

- Natural and artificial colourings
- Preservatives
- Flavour enhancers

Natural Food 'Chemicals':

- Vaso-active amines
- Salicylates

No validated tests

Report multiple symptoms

Often excluding many foods

Have reduced quality of life

- Increasing incidence?
- Use of ready to eat meals, rising from 28% in 1938 to 61% in 2011 in the Canadian population (Moubarac et al 2014)

FOOD ADDITIVES

Food Colourings, Preservatives and Flavour Enhancers

ARTIFICIAL FOOD COLOURINGS

60-70% of all dyes used in food and textile manufacture

Azo dyes - tartrazine (E102), Quinoline yellow (E104), Sunset Yellow (E110), Carmoisine (E122), Amaranth (E123), Ponceau 4R (E124) and Allura red (E129)

Tartrazine – linked to asthma but poor evidence

Mix of sodium benzoate and food colourings including tartrazine shown to increase hyperactivity in some children

Food colourings shown to mainly be associated with spontaneous or chronic urticaria

(Juhlin et al 1972, Nettis et al 2003, Feingold 1975,McCann et al 2007, Gultekin & Doguc 2013)

Clinic Rev Allerg Immunol (2013) 45:6–29
DOI 10.1007/s12016-012-8300-8

Allergic and Immunologic Reactions to Food Additives

Fatih Gultekin · Duygu Kumbul Doguc

Table 2 Allergic reactions or symptoms caused by colourings

4-Hexylresorcinol	Contact dermatitis [17, 18]
Annatto/bixin/norbixin	Triggers chronic urticaria [20, 23, 24], severe anaphylaxis [21, 22], irritable bowel syndrome [25]
Indigotine/indigo carmine	Severe anaphylaxis [26, 27], occupational asthma [29], urticaria [30]
Cochineal/carminic acid/carmines	Occupational asthma [32, 35–37] and rhinoconjunctivitis [31, 35], urticaria [38, 39], asthma [19], anaphylaxis [19, 40–42, 45–47], contact dermatitis [43]
Ponceau 4R/Cochineal Red A	Anaphylaxis [49], triggers allergic LCV [51], triggers chronic urticaria and angiooedema [23]
Tartrazine	Triggers symptoms in asthmatic individuals [53, 57], urticaria and angiooedema [23, 50, 54, 55], triggers atopic eczema [59], atopic dermatitis [55, 60], drug eruption [61, 62], anaphylaxis [63], triggers progressive pigmented purpura [65], triggers allergic LCV [66, 67]
Allura Red AC/FD&C Red 40	Urticaria and angiooedema [23], triggers allergic LCV [68], rhinoconjunctivitis [69]
Ferrous lactate	Anaphylaxis [70]
Erythrosine	Triggers chronic urticaria and angiooedema [23], triggers chronic vasomotor rhinitis [56]
Sunset Yellow FCF	Triggers chronic urticaria and angiooedema [23, 50], triggers allergic LCV [68], aggravates orofacial granulomatosis [72]
Riboflavin-5′-fosfat	Urticaria and anaphylaxis [73]
Patent Blue V	Urticaria [74]
Carmoisine	Aggravates orofacial granulomatosis [72]
Fast Green FCF and FD&C Yellow 10	Triggers allergic LCV [68]

ANNATTO (E160B) - *Bixa orellana*

- Cheese, margarine, butter, smoked fish
- Case reports of severe reactions to Gouda cheese, breakfast cereal and coffee creamer precipitated by Annatto
- 15/56 patients with chronic urticaria and/or angio-oedema who excluded annato, had a positive oral challenge with annatto extract

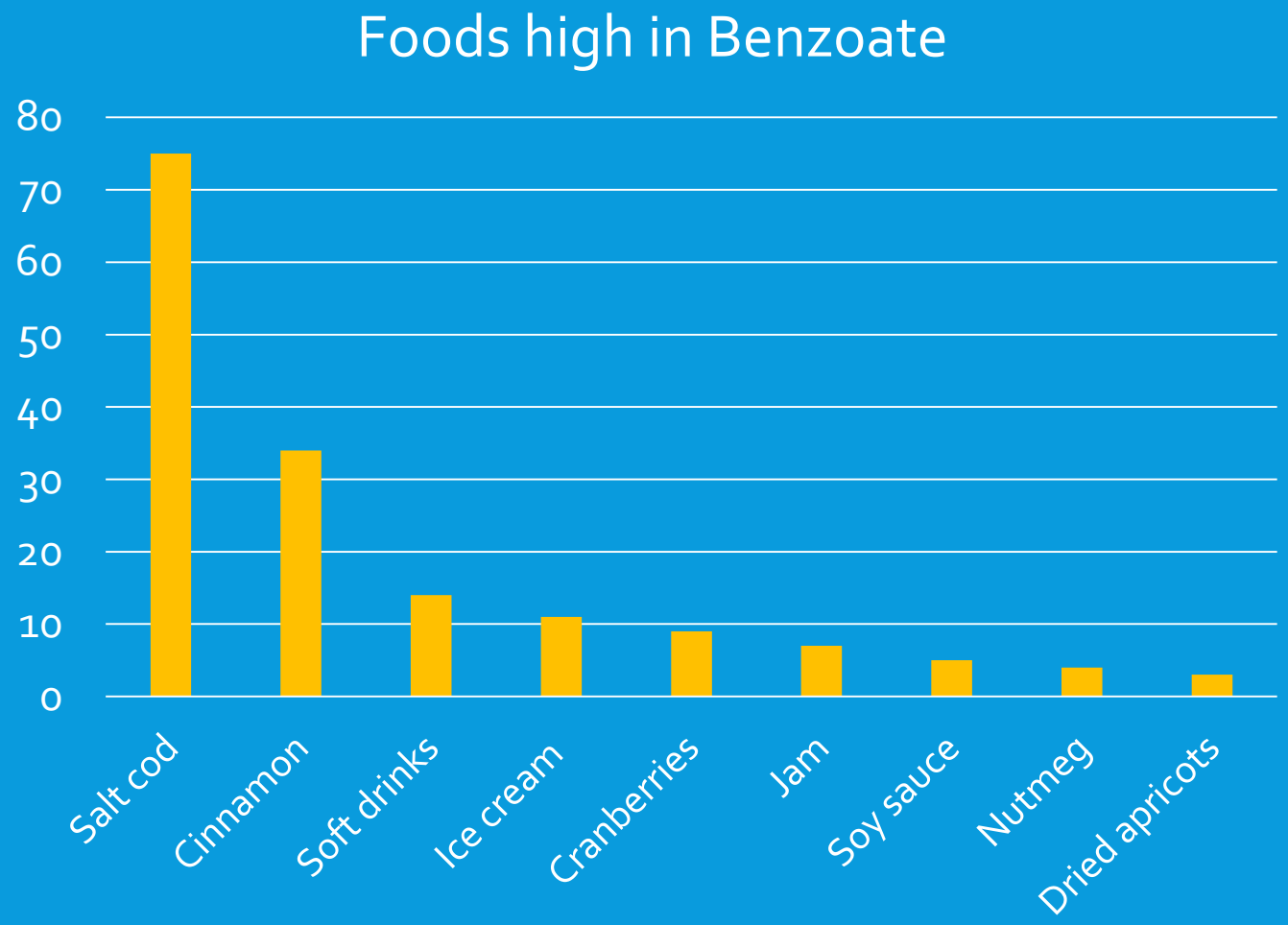
COCHINEAL (E120) OR CARMINE
Derived from *dactylopius coccus*

- May retain insect proteins -linked to urticaria and occupational asthma
- Anaphylaxis to cochineal in 1990s led to new labelling laws in USA and Europe
- 22 cases of cochineal allergy in Japanese women - foods, drinks and cosmetics triggered reactions
- Japanese law limits the use of cochineal and any used has had allergenic proteins removed so subjects were probably sensitised to European foods/cosmetics
- Major allergen, CC38K, was sequenced in 2009, and is possibly a phospholipase or related enzyme

Wüthrich et al 1997, Takeo et al 2018, Ohgiya et al 2009

BENZOATES (E210-219)

- Added to some foods to retard the growth of bacteria
- Occurs naturally in other foods e.g. cinnamon
- Parabens - esters of para-hydroxybenzoic acid – found in cosmetics and drugs



Campbell et al 2013

- Not linked to allergic dermatitis or asthma
- Perennial rhinitis - 9% of subjects reacted on DBPCFC and improved on an additive-free diet
- Urticaria - 0.7-2% of those with chronic urticaria and angiooedema are reactive to sodium benzoate
- Oro-facial granulomatosis (a rare chronic granulomatous inflammatory disease of the lips, face and mouth) - 54-78% with this condition improved on a cinnamon and benzoate-free diet

(Wuthrich 1998, Van Bever and Stevens 1989, Park et al 2008, Weber et al 1979, Tarlo et al. 1981, Pacor et al. 2004, Ortalani 1984, Nettis 2004, Di Lorenzo 2005, White 2006, Campbell 2011)

MONOSODIUM GLUTAMATE (E621)

Flavour enhancer - savoury snacks, crisps, soups, stock, gravy, rubs, coatings, ready-meals, black bean sauce, oyster sauce, tomato sauce, marmite

Natural sources - Fish Sauce, Parmesan cheese, mushrooms, spinach, soy sauce, miso, ripe tomatoes, cured meat

Intake - 0.5g (USA) - 1.6g (Korea)
-⅓ comes from added MSG

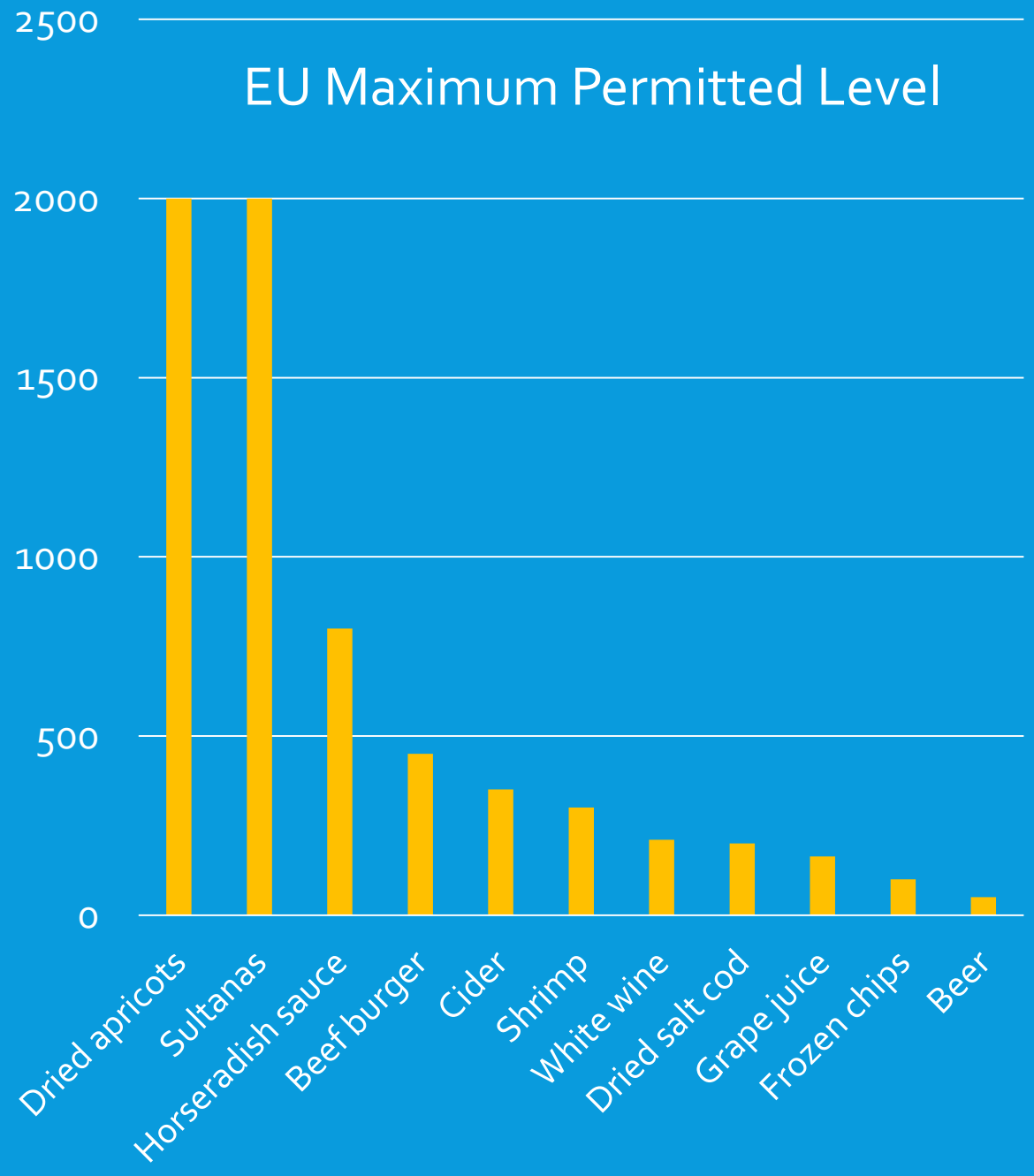
Does MSG provoke food intolerance?

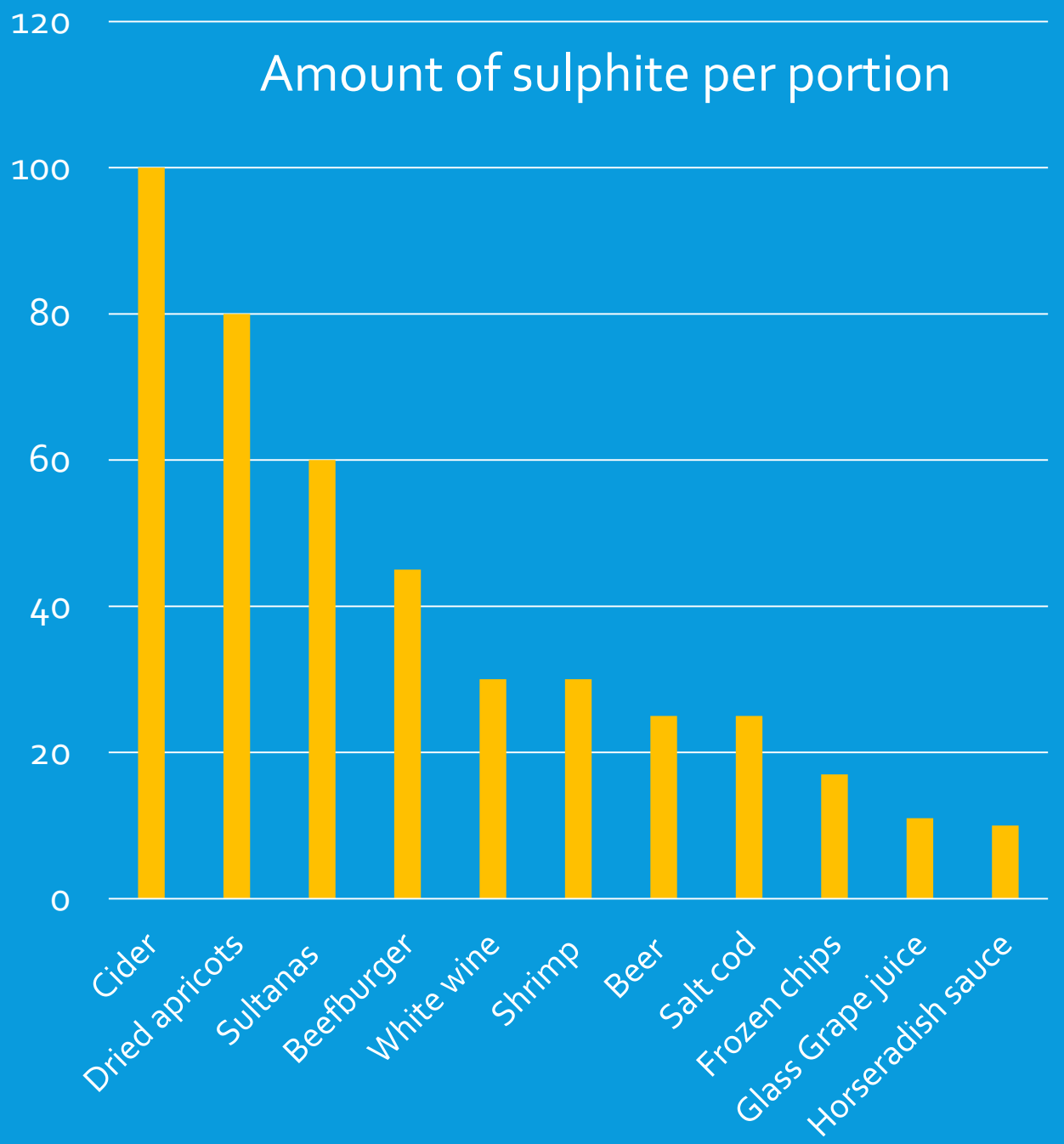
- 2/130 responded to a large dose given without food, with no responses noted when MSG was given with food (Geha et al 2000)
- Most commonly reported symptom is pressure headache, paraesthesia, neuralgic-like pain in the neck and chest.
- More research needed before establishing cause and effect between MSG and migraine (Obayashi and Nagamura 2016)

FOOD PRESERVATIVES
Sulphites E220-227

Control browning, reduce microbial spoilage, bleaching agent, control black spot in shrimps

- Acceptable Daily Intake (ADI) 0.7mg/kg: 40-60mg
- Typical daily intake 54.5mg including 20.2mg from wine (Manzi et al 1992)
- Up to 123mg/day could be consumed by adults – wine, dried fruit and salt fish (Leclercq et al 2000)

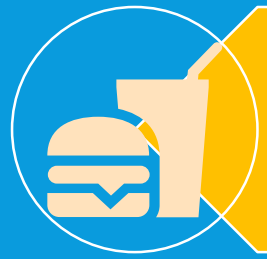

EU Maximum Permitted Level
2500
2000
1500
1000
500
0
Dried apricots
Sultanas
Horseradish sauce
Beef burger
Cider
Shrimp
White wine
Dried salt cod
Grape juice
Frozen chips
Beer


Amount of sulphite per portion
120
100
80
60
40
20
0
Cider
Dried apricots
Sultanas
Beefburger
White wine
Shrimp
Beer
Salt cod
Frozen chips
Glass Grape juice
Horseradish sauce

REASON WHY REACTIONS MIGHT NOT ALWAYS BE ON EXPOSURE TO A HIGH SULPHITE FOOD



Glass wine =30mg



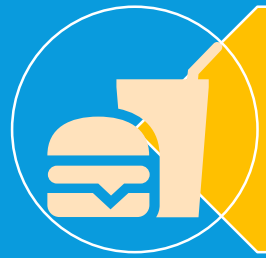
Burger and chips = 61mg



Fruit cake (sultanas) = 60mg



Glass wine =30mg +



Burger and chips = 91mg +



Fruit cake = 151mg sulphite

DOES SENSITIVITY TO SULPHITES REALLY EXIST?

250 cases of sulphite-related adverse effects in the USA in the 1980s (Yang and Purchase 1985)

Predominant symptom is bronchoconstriction but has also caused anaphylaxis (Jamieson et al 1985)

May affect up to 5% of asthmatics - range 3.9% to 8.4% if steroid-dependant (Buckley et al. 1985, Bush et al. 1986)

Sulphites are the only food additive that has to be declared - Sulphur dioxide and sulphites at concentrations of more than 10mg/kg or 10mg/litre

IS ASTHMA THE ONLY CONDITION INVOLVED?

- Sulphites can cause urticaria and angio-oedema both through topical and/or ingested sulphite (Vally et al 2009)
- In Korea 2 phenotypes of sulphite sensitivity reported:

  66% - sulphite sensitive asthma

  33% sulphite-sensitive urticaria (Ban et al 2014)
- About 4% of contact dermatitis due to occupational exposure to sodium metabisulphite, but these patients can also have systemic symptoms (Madan et al 2007, Garcia Galvin et al 2012)
- Sulphites can non-specifically activate mast cells, releasing small amounts of histamine which can cause gut symptoms and soft stools

DIAGNOSING SULPHITE SENSITIVITY

History – foods reported to provoke symptoms, time from ingestion to symptoms, presence or absence of asthma

Other tests – not validated

Oral Food Challenge – best method but not without risk

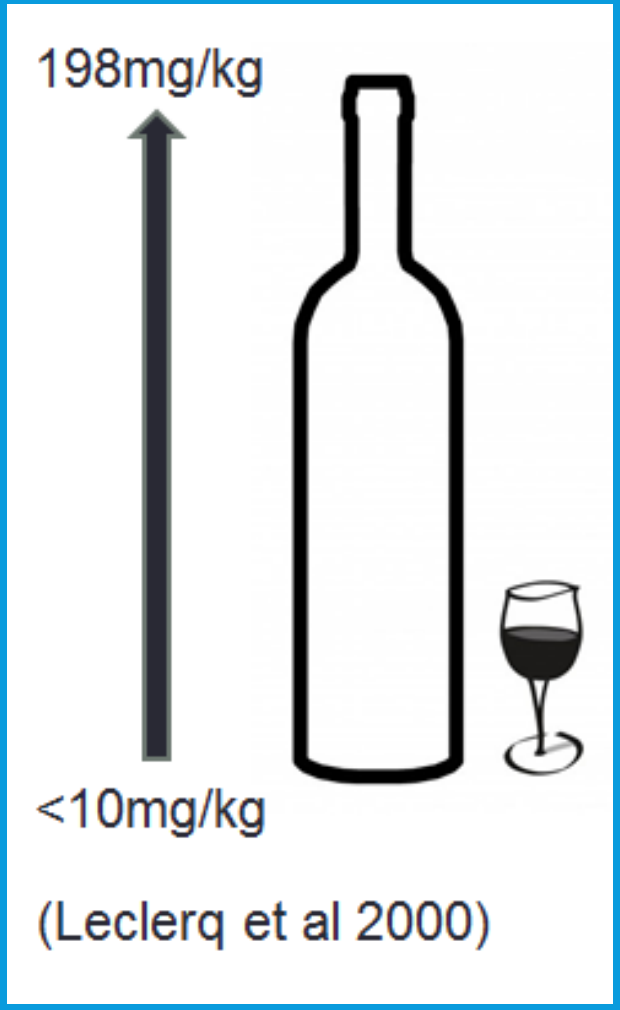
Materials

- Food - only 50% subjects with a confirmed sulphite sensitivity responded to a variety of sulphite foods – (Taylor et al 1988)
- Capsules or solutions of sodium/potassium metabisulphite (Bush et al 1986, Taylor et al 2003, Ban 2014)

Dosage

- 40mg sulphite precipitated reactions (Vally)
- Challenge dose 20mg and 50mg in capsules precipitated reactions (Skypala et al unpublished)

WINE REACTION = SULPHITE SENSITIVITY?



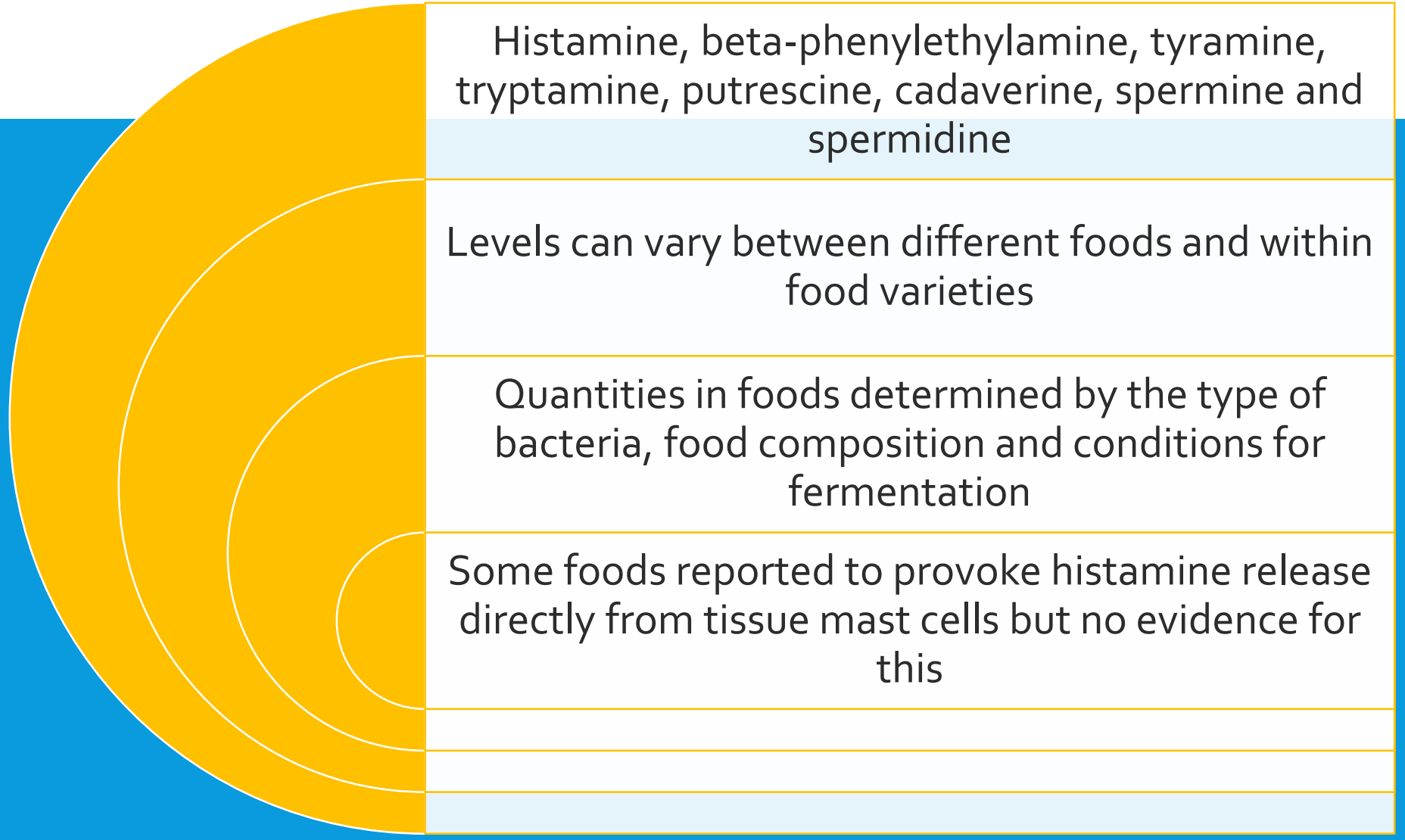
- Added to control mildew in grapes and oxidation in the wine
- Champagne bottle fermented so less added sulphite
- 43% subjects reporting reaction to white wine had positive DBPCFC to sodium metabisulphite capsules (Skypala et al unpublished)
- 122/366 adult asthmatic subjects reported reactions to alcohol but no difference in asthmatic response to high and low sulphite wine (Vally et al 2000/2007)

ALCOHOL

contains Histamine, and Acetaldehyde, a by product of alcohol metabolism, can release histamine

Alcohol	Amines mg/L	Reference
Cider	5.94-8.42	Garai et al 2006
Red/white wine	287/162	Choi et al 2007
Red/white wine	10/30	Maintz and Novak 2007
French/Italian/Spanish wine	3.63/2.19/5.02	Bodmer et al 1999

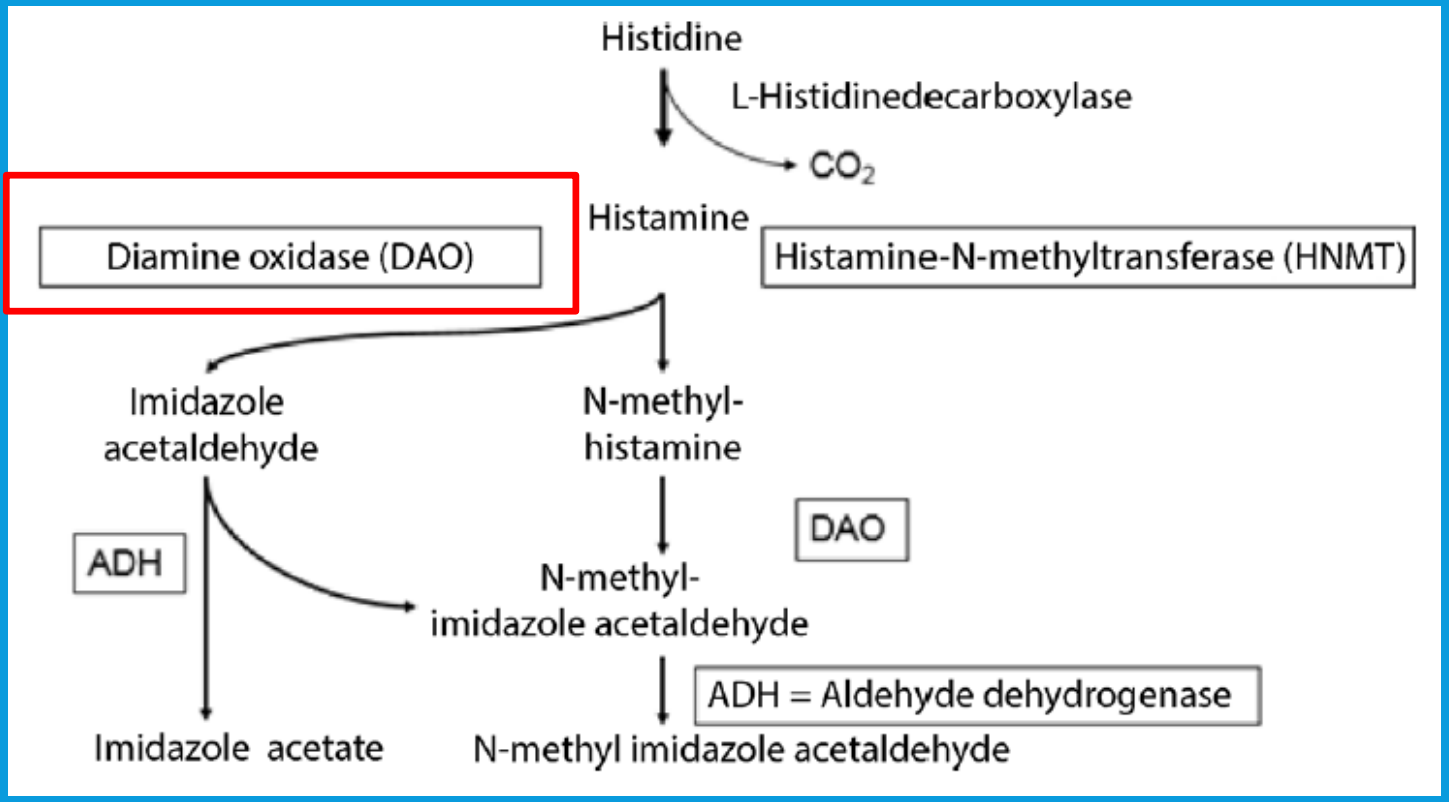
WHAT ARE VASO ACTIVE AMINES?



Bodmer et al 1999, Yang at al 2014, Maintz & Novak 2007, Vlieg-Boerstra et al 2005, Reese et al 2018

MECHANISM

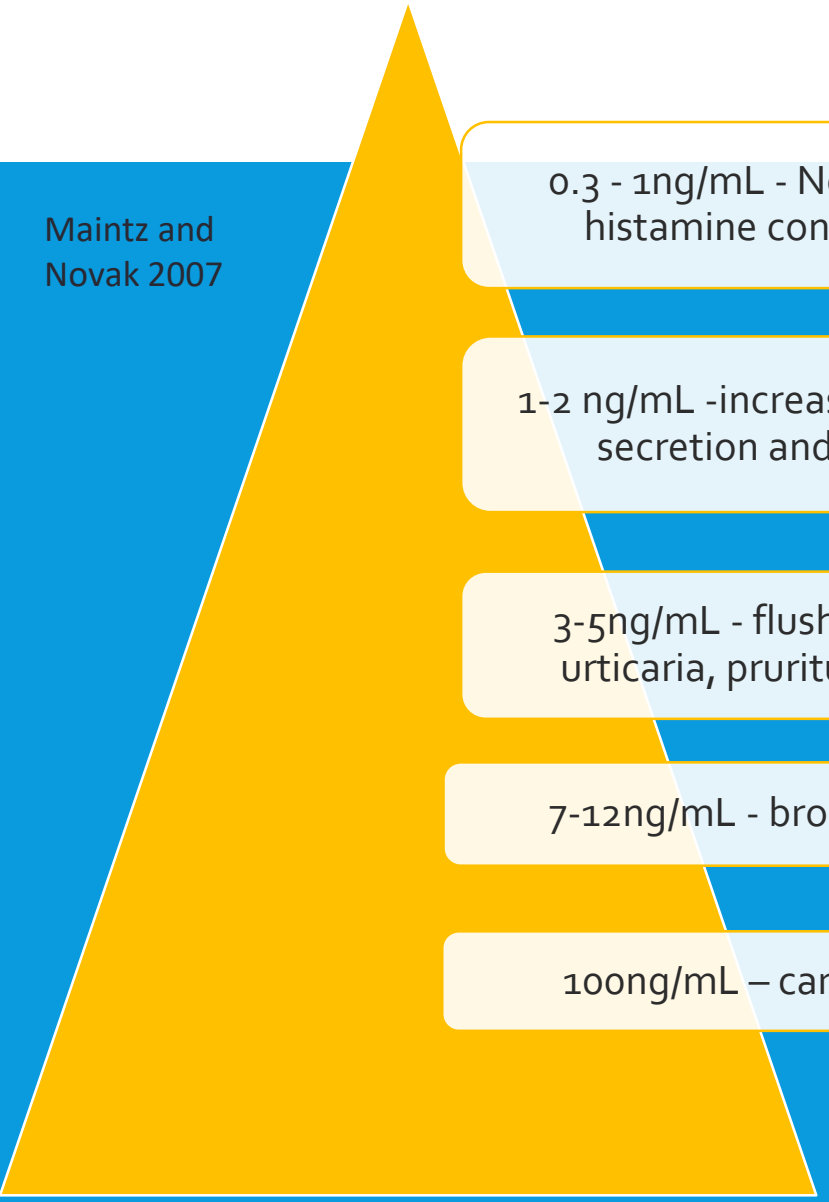
Impaired histamine catabolism due to diamine oxidase (DAO) deficiency BUT this causal link yet to be proven (Reese et al 2018)



Not known whether histamine release from mast cells and basophils or histamine produced by gut bacteria is a contributory factor

HISTAMINE REACTIONS

Maintz and Novak 2007



0.3 - 1ng/mL - Normal plasma histamine concentrations

1-2 ng/mL -increased gastric acid secretion and heart rate

3-5ng/mL - flushing, headache, urticaria, pruritus, tachycardia

7-12ng/mL - bronchospasm

100ng/mL – cardiac arrest

- Migraine and headache
- Cutaneous - erythema, pruritus, flushing, urticaria
- Gastrointestinal - nausea, vomiting, flatulence, colic, diarrhoea
- Respiratory - nasal obstruction, rhinorrhoea, asthma
- Cardiac including arrhythmia
- Fatigue

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100ng/mL – cardiac arrest

Maintz and Novak 2007

Fish

Fresh – 2.6mg/kg Canned – 3.1mg/kg

Frozen– 5.8mg/kg Dried - 104mg/kg

Yesudhason et al 2013



Sea Bass Visciano et al 2012

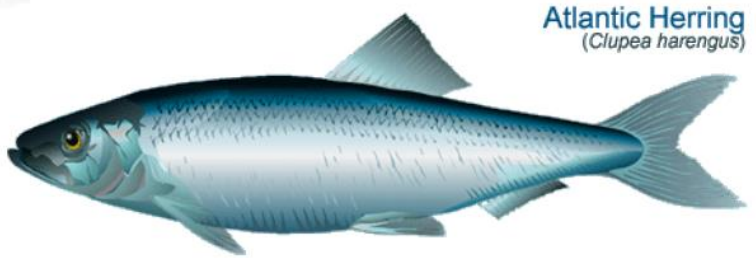
Fresh – 0.0mg/kg

16 days old – 0.0mg/kg

Herring Visciano et al 2012

Fresh – 0.0mg/kg

16 days old – 271mg/kg



Tuna -Fresh/Canned – 0.2/0.4mg/kg Visciano et al 2012

Tuna – Unspecified - 2.967mg/kg Choi 2007

Scombroid poisoning - severe pseudo-allergic reactions usually caused by toxic levels of histamine in seafood due to bacterial conversion of histidine to histamine

DOSE RESPONSE

Reactions dose dependant - 36-250mg histamine

10 healthy volunteers challenged on two consecutive days with 75mg histamine - 50% experienced immediate as well as delayed symptoms including GI symptoms

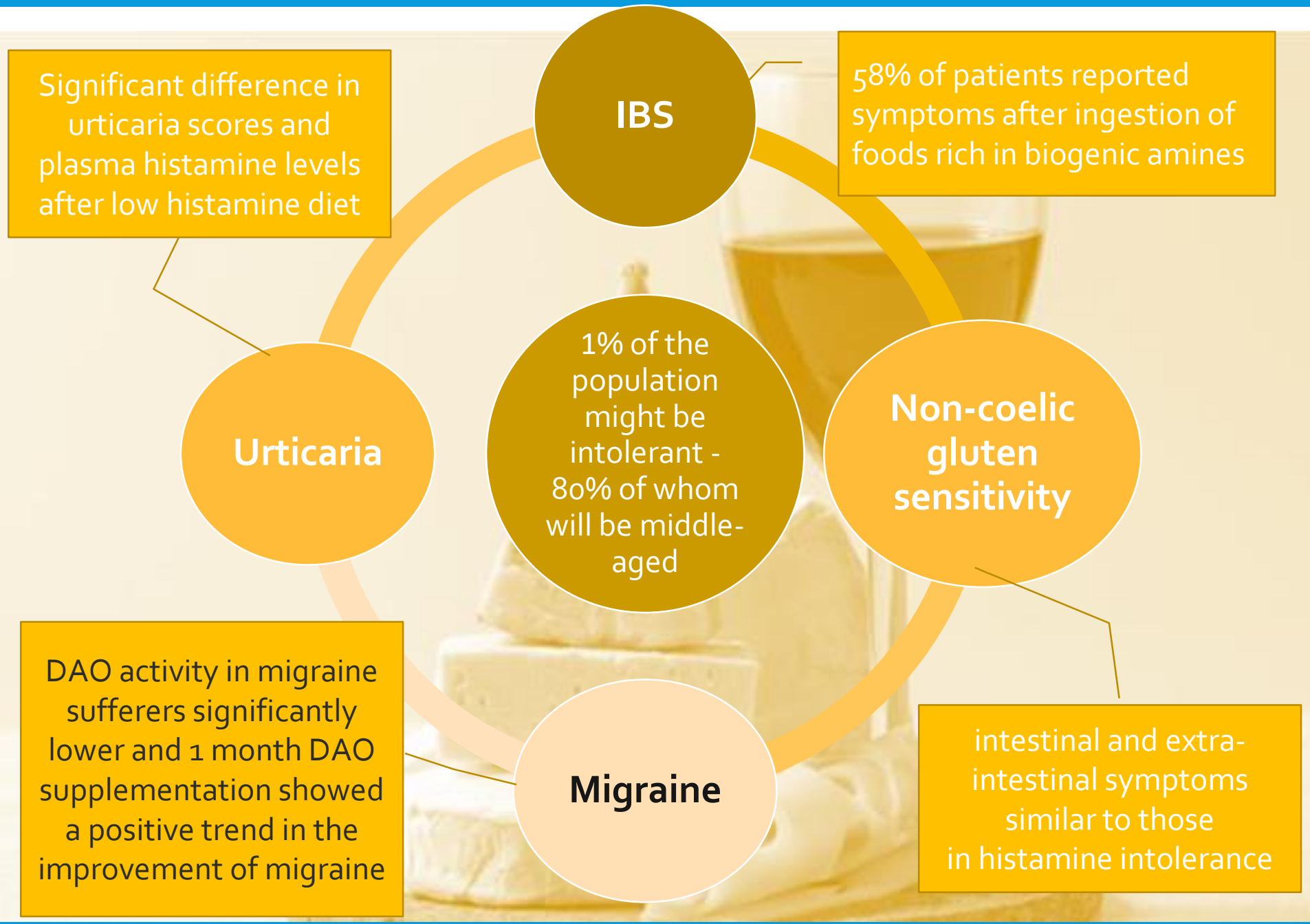
39 patients reacted to 75mg liquid histamine although single symptoms were not reproducible in placebo-controlled challenges

Reactions to amounts as low as 2.5mg have been reported

Malone et al 1986, Morrow et al 1991, Wöhrl et al 2004, Komericki et al 2011



(Missbuchler 2004 Smolinska 2013, Schnedl et al 2018, Jee Hee Son et al 2018, Izquierdo-Casas et al 2018)



(Missbuchler 2004 Smolinska 2013, Schnedl et al 2018, Jee Hee Son et al 2018, Izquierdo-Casas et al 2018)

WHAT ABOUT CHILDREN?

- Observational, retrospective study of 16 children diagnosed with histamine intolerance by measuring plasma diamine oxidase levels and symptom clearance on initiating a low histamine diet
- Treatment was based on a diet low in histamine-containing food (Rosell-Camps et al 2013)

Allowed food	Water, coffee, tea Potatoes, rice, pasta, cereals Yoghurt and unaged cheese (milk should be avoided though) Vegetables: Lettuce, cauliflower, broccoli, chicory, corn salad, cucumber, carrot, garlic, pumpkin, cardoon, pepper, mushroom, radish, rhubarb, asparagus, courgette, onion Fruits: Apple, pear, peach, plum, cherry, melon, blueberry Herbs and spices Vegetable oil, vinegar, olives Meat, poultry, fish, raw sausages Fresh whitefish: Hake, cod, angler Cold meat: Boiled ham (extra quality)
Food to be avoided	Alcoholic beverages Oily fish, either processed (tuna, sardine, mackerel) or semi-processed (anchovy, herring) Shellfish Cured meat: Chorizo, saucisson, salami, fuet, sobrassada Aged cheese: Manchego, mahón, parmigiano, gouda, emmental, gruyère, roquefort, camembert, cheddar, grated cheese Fermented food: Choucroute, soy derivatives Chocolate, vanilla Fruits: Citrus, kiwi, nuts and dried fruit, strawberry, pineapple, papaya Vegetables: Spinach, tomato (fresh or sauce), eggplant Eggs

DIAGNOSIS

DAO Levels

- Patients with typical symptoms had highly reduced serum DAO activity compared to controls BUT
- DAO found in various tissues, but not in relevant quantities in the serum

SPT with Histamine

- Wheal size of a histamine SPT greater than 3mm, 50 minutes after test
- BUT doubt cast upon this method as not validated

- Determination of histamine and methylhistamine in urine BUT
- Methylhistamine levels affected by protein content of foods and histamine is a metabolite of intestinal bacteria, so found in stools

Mušič et al 2013, Manzotti et al 2016, Schwelberger et al 2013)

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Urine/Stool Analysis

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(Comas-Basté et al 2017

Determination of DAO levels or histamine in serum/ plasma or stools not recommended (Reese et al 2018)

guidelines

Allergo J Int (2017) 26:72–79
DOI 10.1007/s40629-017-0011-5

CrossMark

German guideline for the management of adverse reactions to ingested histamine

Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Association of Allergologists (AeDA), and the Swiss Society for Allergology and Immunology (SGAI)

Imke Reese · Barbara Ballmer-Weber · Kirsten Beyer · Thomas Fuchs · Jörg Kleine-Tebbe · Ludger Klimek · Ute Lepp · Bodo Niggemann · Joachim Saloga · Christiane Schäfer · Thomas Werfel · Torsten Zuberbier · Margitta Worm

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Diagnosis -2 or more typical symptoms of histamine intolerance occur and improvement following a low histamine diet leads to resolution of symptoms with or without concomitant use of antihistamines

3 step dietary adjustment – diet and symptom diary +/- pragmatic use of H1/H2 receptor blockers

Phase	Aim	Recommendation	Duration
Phase 1: avoidance	To reduce symptoms to the greatest possible extent	– Mixed diet with emphasis on vegetables and reduced biogenic amine intake, in particular histamine intake – Nutrient optimization – Changes in meal composition – Principles of a balanced diet	10–14 Days
Phase 2: test phase	To expand the choice of food while taking individual risk factors (stress, menstruation, medication use, etc.) into account	– Targeted re-introduction of suspected foods while taking the patient's individual dietary preferences into consideration – Determination of individual histamine tolerance	Up to 6 weeks
Phase 3: long-term diet	Continuous, balanced supply of nutrients High quality of life	– Individual nutritional recommendations guided by the individual histamine tolerance, taking exogenous risk factors into consideration	–

Improvement - challenge with histamine 0.5mg/kg, 0.75mg/kg and 1.0mg/kg

(Raithal et al 2005, Reese et al 2018)

Skypala et al. Clin Transl Allergy (2015) 5:34
DOI 10.1186/s13601-015-0078-3

Clinical and Translational Allergy

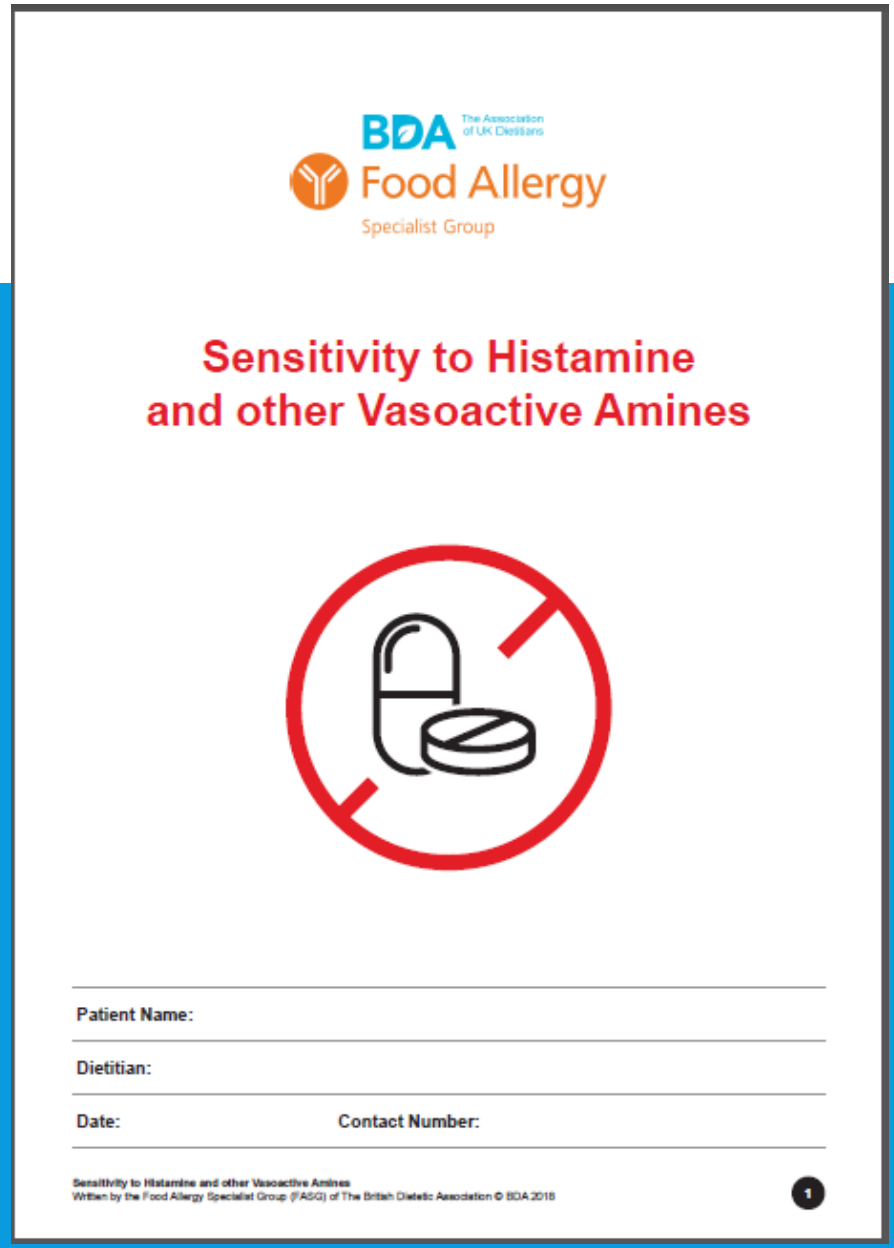
REVIEW Open Access

Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence

Isabel J. Skypala[1*], M. Williams[2], L. Reeves[3], R. Meyer[4] and C. Venter[5]

It is not possible to produce an accurate list of foods high in vasoactive amines as levels will vary within the same type of food and methods of measurement used may be different between studies.

The best way currently to diagnose a hypersensitivity to vasoactive amines is to avoid these foods for 2-4 weeks



BDA The Association of UK Dietitians
Food Allergy
Specialist Group

Sensitivity to Histamine and other Vasoactive Amines

Patient Name:

Dietitian:

Date: Contact Number:

WHICH FOODS TO AVOID?

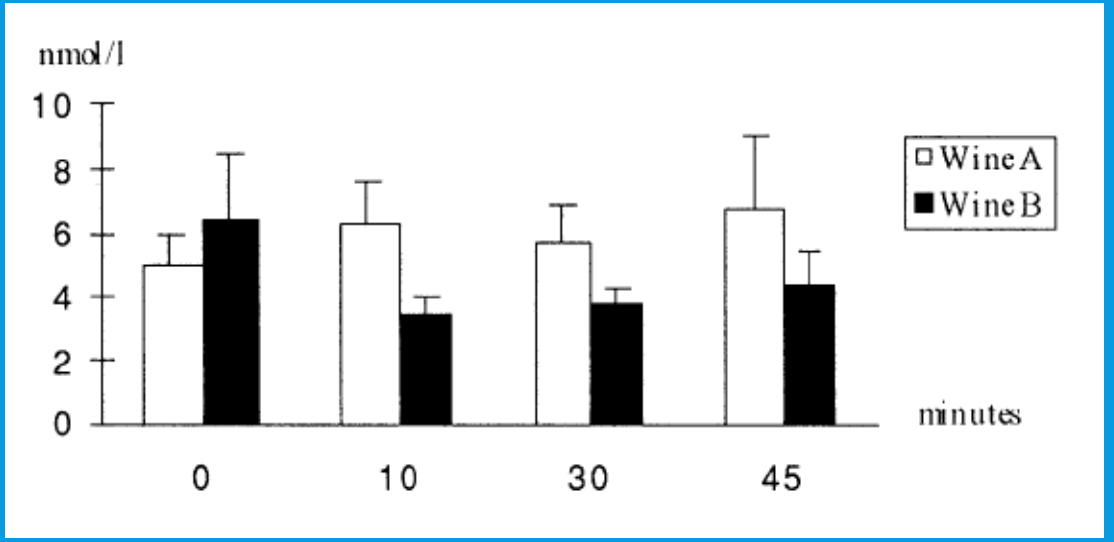
Gouda	Camembert	Emmental
Histamine 900mg/kg	Histamine 1000mg/kg	Histamine 2500mg/kg
Tyramine 900mg/kg	Tyramine 4000mg/kg	Tyramine 700mg/kg

Maintz and Novak 2007

WINE

Biogenic Amines	Wine A (mg/L)	Wine B (mg/L)
Histamine	0.4	13.8
Tyramine	2.4	9.0
Putrescine	12.1	61.0
Methylamine	0.1	0.6
Ethylamine	1.1	3.1
Phenyethylamine	0.6	0.9
Isoamylamine	0.5	1.8
Cadaverine	0.5	0.6

(Kanny et al 2001)



15/16 adults symptoms after DBPCFC with Wine A and 14/16 subjects after Wine B

Plasma histamine levels higher after wine A than wine B ($p<0.05$)

	FOODS TO AVOID
Meat	Fresh pork, cured meat e.g. ham, salami, pepperoni, bacon, sausages, aged steak, offal
Fish	Tuna, sardine, anchovy, mackerel, salmon, caviar, herring, processed fish products, Prawns, crab, lobster, squid
Cheese and Eggs	Blue cheese (e.g. Stilton, Roquefort), Parmesan, Brie, Camembert, Emmental, Gouda, Cheddar cheese and other hard cheeses (any type whether mild or strong) fresh and hard sheep's and goat's cheese Eggs
Fruit	Bananas, tinned figs, grapefruit, tangerines, oranges, limes, lemons, pineapple, grapes and strawberries
Vegetables	Aubergine, spinach, avocados, broad beans, pickled cabbage (sauerkraut), tomatoes and tomato products
Other	Miso, tempeh, soya sauce, tofu, fish sauce Tree nuts, Peanuts, Chocolate
Drinks	Coffee, cocoa / hot chocolate, Green tea, White, rosé and red wine, Champagne, Beer, cider Fresh fruit juices, tomato juice, smoothies made from above fruits

Although few plant foods contain histamine, most plant foods contain putrescene and some spermidine so plant-origin foods should be consumed when they are very fresh to reduce biogenic amine intake (Sanchez-Perez et al 2018)

WHAT ABOUT MEDICATION?

Diamine Oxidase capsules

- Intake of Diamine oxidase capsules compared to placebo -significant reduction of total symptom scores
- 20/54 had a reduction in symptoms and a significant increase in serum DAO activity values ($P < 0.0001$) when adopted histamine-free diet
- 13/14 symptomatic subjects had mean DAO 7.04U/mL compared to 39.50U/mL in healthy controls, felt better when supplemented with DAO

Recent Evidence

- Diamine oxidase supplementation improves symptoms in patients with histamine intolerance
- A Histamine-Free Diet Is Helpful for Treatment of Adult Patients with Chronic Spontaneous Urticaria
- Diamine oxidase (DAO) supplement reduces headache in episodic migraine patients with DAO deficiency

(Komericki et al 2011, Mušič et al 2013, Manzotti et al 2016, Reese et al 2018, Schnedl et al 2019, Jee Hee Son et al 2018, Izquierdo-Casas 2019)

WHAT ABOUT ANTI HISTAMINES?

- No double-blind placebo-controlled studies on the efficacy of H1 and H2 receptor blockers
- Could work in treatment of individual symptoms: H1 blockers – flushing, itch, H2 blockers – nausea, gastrointestinal symptoms
- Treat patients with suspected adverse reactions to ingested histamine with H1/H2 receptor blockers for a trial period and review symptom control

(Reese et al 2018)

SALICYLATES

Willow Bark and salicin

- White willow has a pain relieving effect
- 1828 – effect due to salicin, which is converted into salicylic acid during digestion
- 1853 – salicin extracted, oxidised and hydrolysed to make salicylic acid
- Difficulties with the digestion of salicylic acid let to its acetylation

Aspirin

- 1899 - acetyl salicylic acid was commercially launched and called aspirin
- Aspirin inhibits isoform 1 of the enzyme cyclo-oxygenase (COX-1)
- COX-1 together with COX-2 enables the conversion of arachidonic acid to cyclic prostenoids which are further processed into prostaglandins
- COX-2 is inhibited by Ibuprofen

ASPIRIN HYPERSENSITIVITY

Prevalence 0.6% to 2.5%

Increases to 4.3-11% in asthmatics

Aspirin-sensitive asthmatics may also have nasal polyps - Samter's triad (Samter and Beers 1967)

Can salicylate in plant foods also provoke a reaction?

- A nonspecific antigen-induced pseudo-allergic hypersensitivity reaction to salicylic acid, affects 2-7% of those with food allergy and IBS (Raithel et al 2005)
- 2.6mg of salicylate reported to elicit a 15% decrease in FEV1 in sensitive asthmatics (Corder and Buckley 1995)
- 2.5% of Europeans may have salicylate sensitivity (Baenkler 2008)
- **BUT - no published studies demonstrating efficacy of salicylate avoidance in gut disease or asthma (Dahlén et al1994, Gibson 2011, Barrett and Gibson 2012)**

WHICH FOODS CONTAIN SALICYLATE?

- Salicylates are found in a wide variety of plant foods
- Average intake 10-200 mg/day (Swain et al1985) OR 0-5mg (Venema et al 1996)
- One aspirin tablet contains 200-500mg of acetyl salicylate
- First data published by Anne Swain in 1985 but UK and European studies have published very differing figures (Swain et al 1985, Venema et al 1996, Scotter et al 2007, Wood et al 2011)

Food	Portion size	Salicylic acid mg/kg Scotter/Swain
Lemon	20g	3.2 / 0.18
Currants	25g	<0.01 / 5.8
Tomato ketchup	12g	0.3 / 2.48
Dried Oregano	3g	26.0 / 66.0
Mixed Herbs	3g	22.3 / 55.6
Curry powder	3g	15.2 / 218.0
Coffee	1 mug	6.8 / 0.84
Tea	1 mug	1.06 / 5.57

DIETARY INTERVENTION

Establish tolerance to aspirin and NSAIDS and review current diet and likely levels of salicylate

4 week trial of the avoidance of high salicylate foods and advice on cumulative effects of medium salicylate foods

Remember salicylates may protect against certain cancers, especially colorectal cancer, so make sure you do not leave people on a low salicylate diet indefinitely (Raithel et al 2005)

Fruits	**Granny Smith apples, cherries, strawberries, currants, raisins, kiwi, Gala melon, peaches and nectarines, raspberries**
Vegetables, nuts, seeds, savoury snacks	Asparagus, sweet corn, raw tomatoes, tomato puree
Condiments & miscellaneous	Ginger, mixed herbs, mustard, oregano, curry powder, black pepper, cardamom pods, cinnamon, cumin, fenugreek, mint, nutmeg, paprika, rosemary, thyme, turmeric, liquorice, peppermint, Worcestershire sauce, honey, tomato ketchup
Drinks	Coffee, pineapple juice, cider, Benedictine liqueur, lemon tea, black tea, apple juice, cranberry juice, orange juice, tomato juice, fizzy drinks, Drambui liqueur, wine, rum

Mitchell and Skypala 2013, Skypala et al 2015

ARE SOME FOODS HIGH RISK?

Food	Amine	Glutamate	Salicylate	Sulphite	Benzoate
Cheese	✓	✓			
Wine	✓		✓	✓	
Soy	✓	✓			✓
Tomatoes	✓	✓	✓		✓
Spinach	✓	✓			✓

MULTIPLE FOOD ADDITIVE REMOVAL IN CHRONIC SPONTANEOUS URTICARIA– IS IT EFFECTIVE?

- ☐ 140 subjects went on a 3 week pseudoallergen-free diet
- ☐ Eliminated all processed food, artificial substances, food additives, dyes, antibiotics, preservatives, phenols, foods naturally rich in aromatic compounds, alcohol, spices and herbs, sweets, eggs, seafood, most fruits and vegetables
- ☐ 20 (14%) strong responders and 19 (19%) partial responders

Mageri et al Allergy 2010

- 100 patients challenged to 11 additives including tartrazine, potassium metabisulfite, monosodium glutamate, aspartame, sodium benzoate, methyl paraben, butylated hydroxy anisole, butylated hydroxy toluene, sodium nitrate, sodium nitrite
- 2/100 had a positive urticarial response on single-blind challenge not reproducible on DBPCFC
- Sensitivity to any of the 11 food and drug additives occurs in fewer than 1% of patients

Rajan et al 2014

DIFFERENTIAL DIAGNOSIS

- Gut symptoms - Giardiasis, Helicobacter Pylori, Irritable Bowel Syndrome, inflammatory bowel disorders, coeliac disease, carbohydrate malabsorption
- Flushing - Neuroendocrine tumours
- Itching and rash – non-specific pruritis, chronic spontaneous urticaria +/- angioedema
- Swelling - Angioedema –ACE inhibitors, HAE or acquired C1-esterase deficiency
- Systemic symptoms and a high level of tryptase - Mastocytosis characterised by excessive mast cells in one or more tissues,
- Throat tightness/obstruction - Laryngospasm/Vocal Cord Dysfunction
- **Food Allergy**

DIFFERENTIAL DIAGNOSIS

- History +++++++
- Immune system:
- **Allergy (IgE)** +/- IgG, IgM, IgA (infection, autoimmunity)
- Inflammatory markers (ESR, CRP)
- Complement C3, C4, C1 Esterase inhibitor, C1 Esterase functional
- Gut symptoms:
- Tissue Transglutaminase – Coeliac disease
- Hydrogen breath tests
- Stool cultures to exclude infections (Helicobacter Pylori, Giardiasis), and assess intestinal inflammation (calprotectin)
- Other - Liver and kidney function
- Nutritional status – iron, vitamin D, Folate, B12

Do not rule out an allergy to a hidden allergen

HIDDEN ALLERGENS
Celery
Mustard
Fenugreek
Lupin
Buckwheat
Psyllium
Mycoprotein

Do not rule out an allergy to a hidden allergen

HIDDEN ALLERGENS
Cochineal
Cereal mites
Anisakis
Alpha Gal

Moneret-Vautrin DA (2001) Epidemiology of food allergies and relative prevalence of trophallergens. Cahiers de Nutrition et de Dietetique 36:247–252

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TAKE HOME MESSAGES



- ✓Artificial food colourings are an unlikely cause of food allergy but natural food colourings can cause allergic reactions as evidenced by positive tests and oral challenge
- ✓Sulphites can provoke cutaneous, gastrointestinal and respiratory symptoms, especially in those with asthma
- ✓A diet excluding sources of natural and added benzoate could reduce symptoms in those with oro-facial granulomatosis
- ✓Foods high in vaso-active amines such as histamine may provoke symptoms in sensitive individuals and excessive levels will cause scombroid poisoning
- ✓There have been no rigorous studies examining the effects of a low salicylate diet and the reported levels of salicylates in foods varies between studies
- ✓Do not exclude IgE-mediated food allergy as a cause of symptoms – look for hidden allergens




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