Substance Identifiers in Regulatory Practice

Frank Switzer, PhD
US Food & Drug Administration
frank,switzer@fda.hhs.gov

The views expressed in this presentation are those of the author and do not reflect the official policy or position of the Department of Health & Human Services, US Food & Drug Administration or the US Government

Why ISO 11238 and DTS 19844?

- Substances form the essence or basis of every product
- Interactions between substances are responsible for nearly all pharmacological activity.
- Substances are a lynchpin on which to organize regulatory information but many regulatory agencies only identify/define them by names or codes
- Names and codes are not sufficient to manage substance information.
- Regulatory agencies need to be able to define substances scientifically in an unambiguous manner
- ISO 11238 provides a framework for defining all substances and related regulatory information
- DTS 19844 provides many detailed examples of which data is collected according to the standard.

Names

- Often Ambiguous
  - Different meanings in different domains
    - Lime
  - Different meanings in different jurisdictions
    - Amoxicillin

PDF's and Package Inserts

- Paper or Electronic Paper
- Information not accessible
  - Difficult to read
  - More difficult for computers to read
- Need for Structured Information

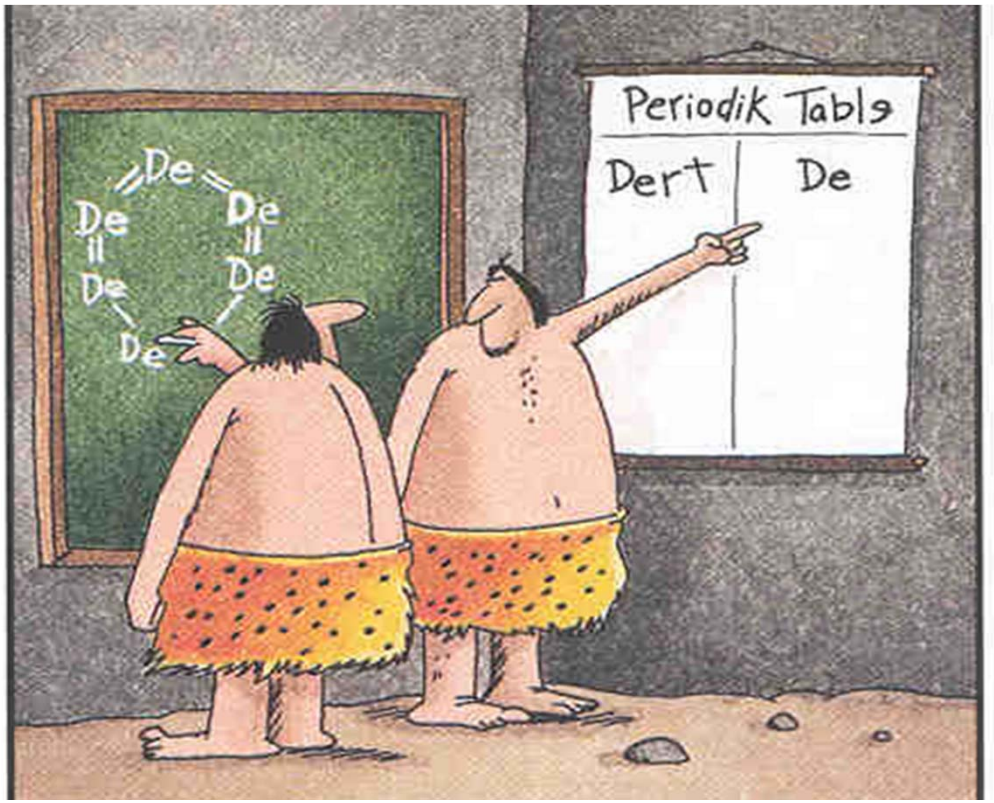
Approach to Substances

- Substances are defined based on **what they are** not how they are made or used
- Substances are defined independent of grade or level of purity

What is a Substance?

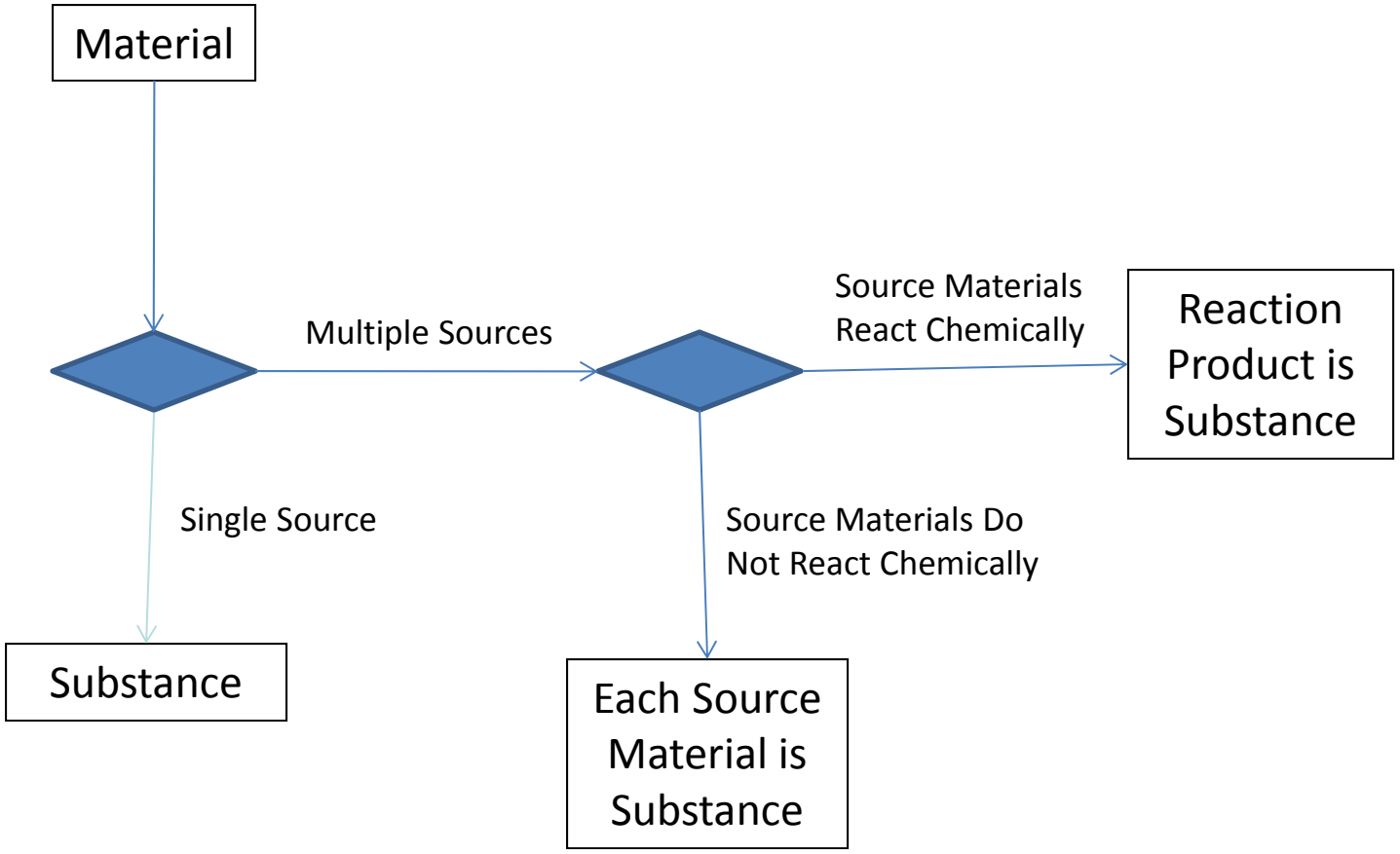
- **ARISTOTLE (Metaphysics)**...the generally recognizable substances... are the sensible substances, and sensible substances **all have matter**..., and in another sense the formula or form..., and thirdly the complex of matter and form, which alone is generated and destroyed, and is, without qualification, **capable of separate existence**

What is a Substance?



Early Chemists describe the first DIRT MOLECULE
(The Far Side by Gary Larson)

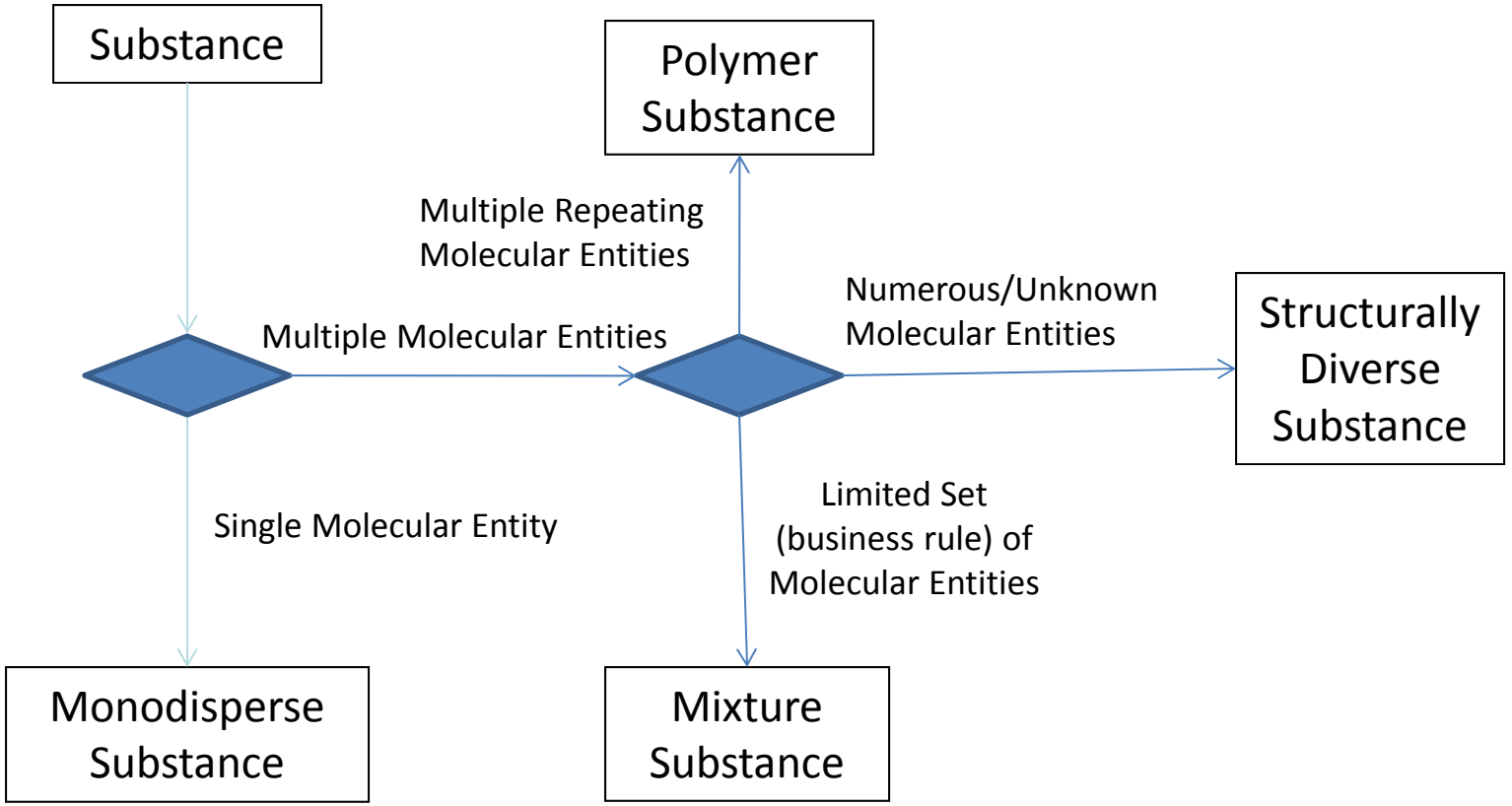
Is the Material (Ingredient) a Substance?



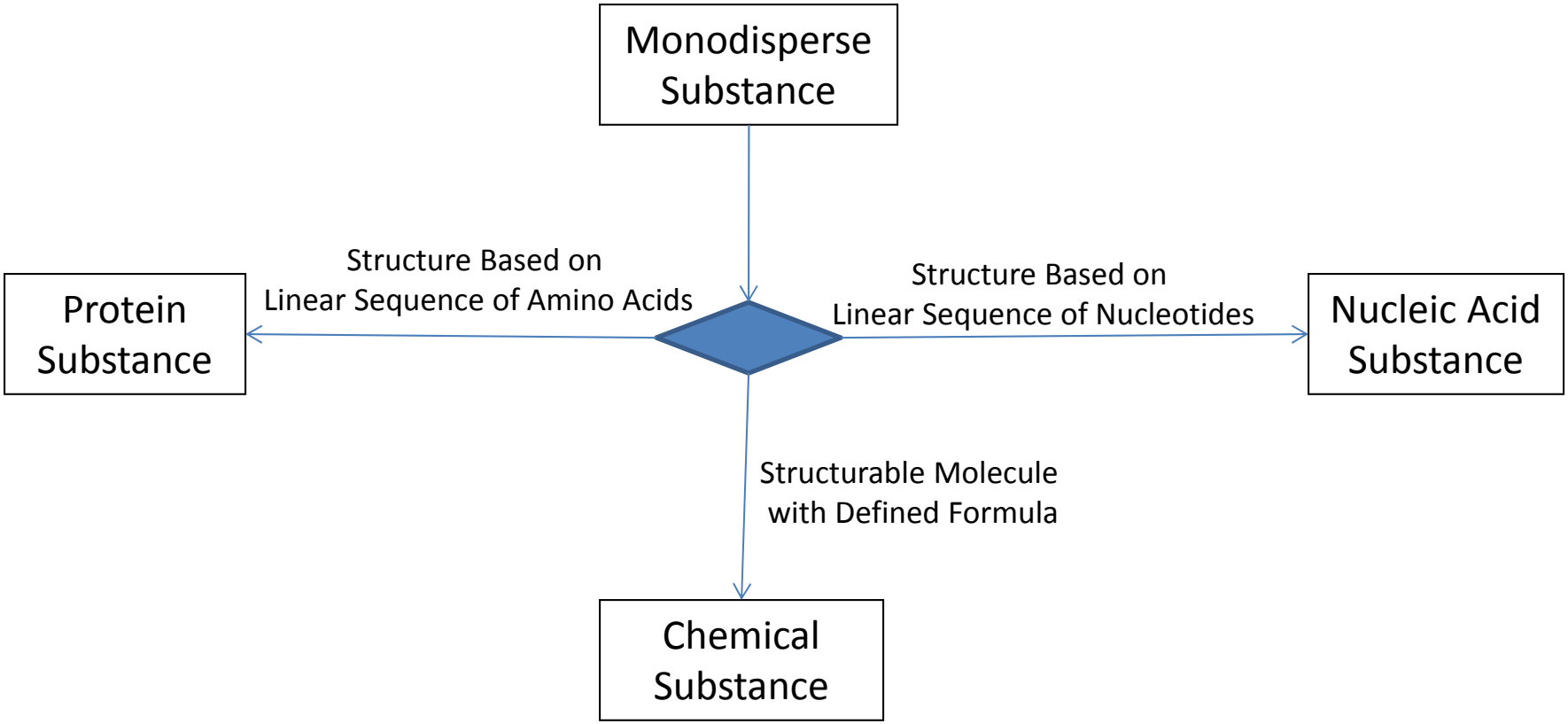
Substances

- Five groups of elements are used to describe single substances
  - Monodisperse
    - Chemicals
    - Proteins
    - Nucleic Acids
  - Polydisperse
    - Polymers (polysaccharides and synthetic polymers)
    - Structurally Diverse Substances
- Mixtures are comprised of combinations of single substances and source where relevant

Monodisperse, Polydisperse or Mixture Substance Type?



Which Monodisperse Substance Type?



Guiding Principles

- **Limited Ambiguity**
  - Uniqueness
  - Identity
  - Internal Consistency
  - Completeness
- **Confidentiality**
  - Single code to track an ingredient throughout the product lifecycle

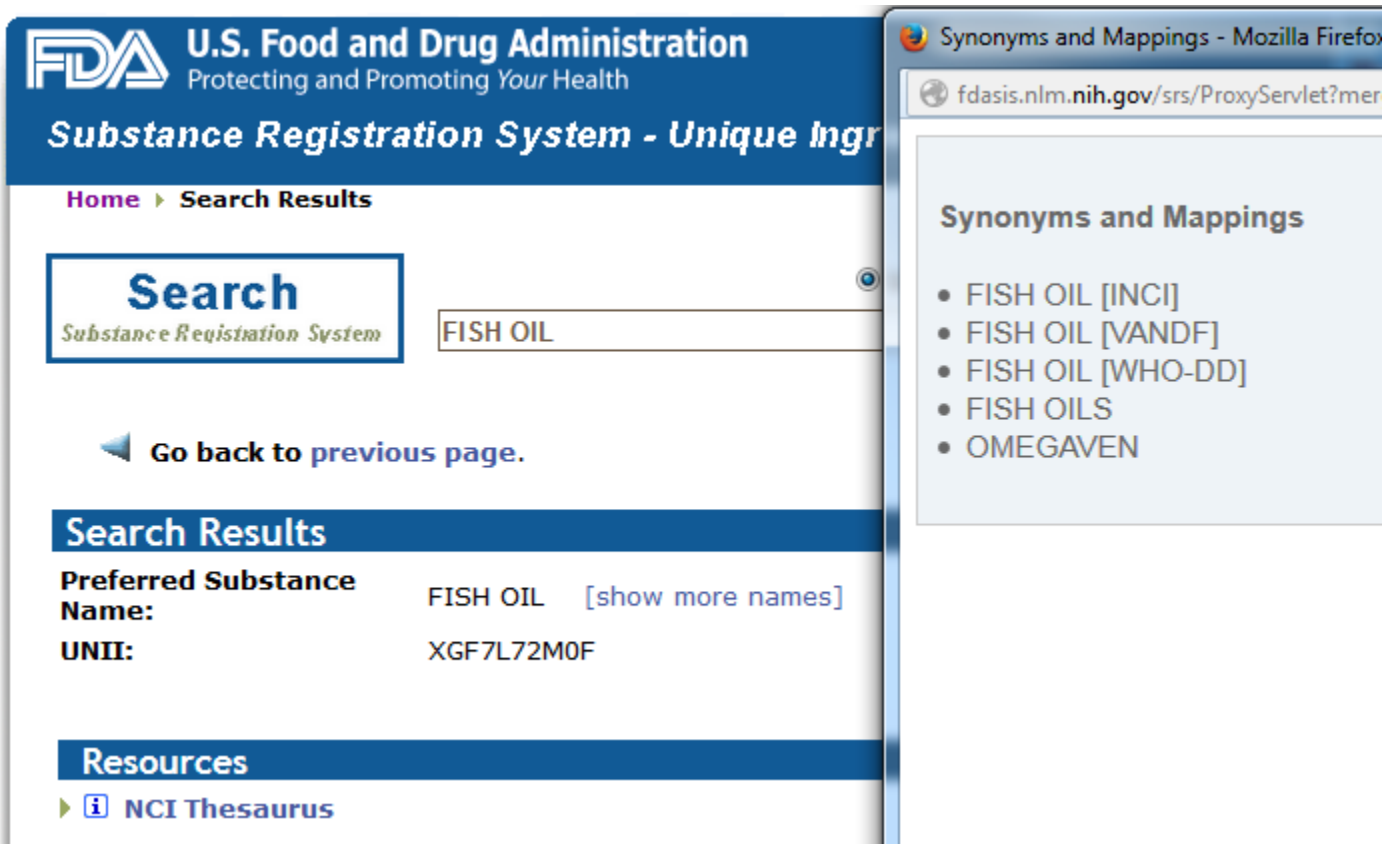
Unique Ingredient Identifier

- The UNII consists of ten alphanumeric characters.
- Non-semantic non-chronological identifier
- The first nine alphanumeric characters are randomly generated.
- The tenth alphanumeric character is determined through a mathematical algorithm, and is appended to the first nine.
- $36^9 = 10^{14}$ potential identifiers
- **Over 70k public codes**

SRS @ NLM

Created for SPL Listing

- http://fdasis.nlm.nih.gov/srs/srs.jsp



What About CAS RNs?

- 0 to many RNs for substances –**not an identity standard**
- CAS has no consistent way to capture polydispersity
- CAS RNs are copyrighted

InChI, InChIKey, SMILES, UUID (GUID)?

Data Elements and Standards for Drug Dictionaries

- ICH M5 (2003-2013, Step 2 published 2005)
  - ISO IDMP (2005-present, 5 standards published 2012, implementation guides currently being balloted)
    - Substances – implemented as GInAS
    - Medicinal Products
    - Pharmaceutical Products – clinical drugs
    - Dosage Forms, Units of Presentation and Routes of Administration
    - Units of Measure (UCUM)

Data Elements and Standards for Drug Dictionaries

- SPL and UNII developed in US through HL7 (2005-present)
- 110k+ NDC's using about 10k UNIIs
- Europe is now trying to catch up

DailyMed


NIH U.S. NATIONAL LIBRARY OF MEDICINE
ABOUT DAILYMED | CONTACT US
REPORT ADVERSE EVENTS | RECALLS
DAILYMED
I am a Healthcare Professional or from the Pharmaceutical Industry
I am a Consumer or Patient
ALL DRUGS
HUMAN DRUGS
ANIMAL DRUGS
SEARCH
Enter drug, NDC code, drug class, or Set ID
MORE WAYS TO SEARCH:
ADVANCED SEARCH
BROWSE DRUG CLASSES
LABEL ARCHIVES
TABLET/CAPSULE ID TOOL
This website contains 68147 drug listings as submitted to the Food and Drug Administration (FDA).
At the present time, this Web site does not contain a complete listing of labels for approved prescription drugs.
SHARE

DailyMed

INDICATIONS AND USAGE

AMBIEN, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. AMBIEN has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

DOSAGE AND ADMINISTRATION

- Use the lowest dose effective for the patient (2.1)
- Recommended initial dose is 5 mg for women and 5 or 10 mg for men, immediately before bedtime with at least 7–8 hours remaining before the planned time of awakening (2.1)
- Geriatric patients and patients with hepatic impairment: Recommended dose is 5 mg for men and women (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with AMBIEN (2.3)
- The effect of AMBIEN may be slowed if taken with or immediately after a meal (2.4)

DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg tablets. Tablets not scored. (3)

AMBIEN
zolpidem tartrate tablet, film coated

PRODUCT INFORMATION			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0024-5401
Route of Administration	ORAL	**DEA Schedule**	CIV

ACTIVE INGREDIENT/ACTIVE MOIETY		
Ingredient Name	**Basis of Strength**	**Strength**
zolpidem tartrate (zolpidem)	zolpidem tartrate	5 mg

INACTIVE INGREDIENTS	
Ingredient Name	**Strength**
hypromelloses Imprecise Ingredient	
lactose	
magnesium stearate	Missing Strength
cellulose, microcrystalline	
polyethylene glycols Imprecise Ingredient	
titanium dioxide	
FD&C Red No. 40 Color formulation component	
polysorbate 80	

Why Aggregate/Curate?

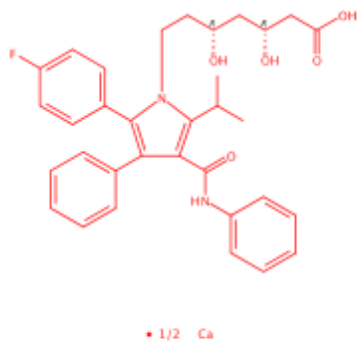
- Data sources can be incomplete/ambiguous/contradictory
- To provide a set of substance master data
- To facilitate interoperability
  - Richer data facilitates communication
  - Data must be useful both to humans and systems

What is the active ingredient in Lipitor?

1. **134523-03-8**

(Component: 134523-00-5)

~1625 ~154



Absolute stereochemistry.

C_{33} H_{35} F N_2 O_5 . $^1/_2$ Ca

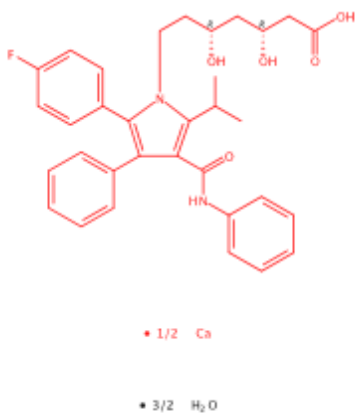
1*H*-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), (β*R*,δ*R*)-

Regulatory Information
Experimental Properties

2. **344423-98-9**

(Component: 134523-00-5)

~47 ~27



Absolute stereochemistry.

C_{33} H_{35} F N_2 O_5 . $^1/_2$ Ca . $^3/_2$ H_2 O

1*H*-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt, hydrate (2:1:3), (β*R*,δ*R*)-

Identity Problems

atorvastatin calcium

methylnaltrexone bromide

levothyroxine sodium

ferric citrate (USAN)

- Multiple established names for the same substance
- Missing links

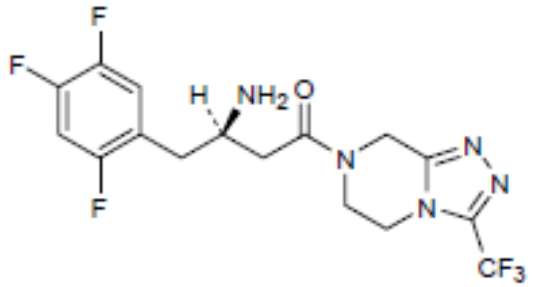
Sitagliptin (INN)

sitagliptinum
sitagliptin — (3*R*)-3-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro-5*H*-[1,2,4]=triazolo[4,3-*a*]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one
antidiabetic

sitagliptine — 7-[(3*R*)-3-amino-4-(2,4,5-trifluorophényl)butanoyl]-3-(trifluorométhyl)-5,6,7,8-tétrahydro-1,2,4-triazolo[4,3-*a*]pyrazine
antidiabétique

sitagliptina — 7-[(3*R*)-3-amino-4-(2,4,5-trifluorofenil)butanoil]-3-(trifluorometil)-5,6,7,8-tetrahidro-1,2,4-triazolo[4,3-*a*]pirazina
hipoglucemiante

$C_{16}H_{15}F_6N_5O$ 486460-32-6



INN avoids salts, solvates AND Clinical Trial codes

Sitagliptin phosphate (USAN)

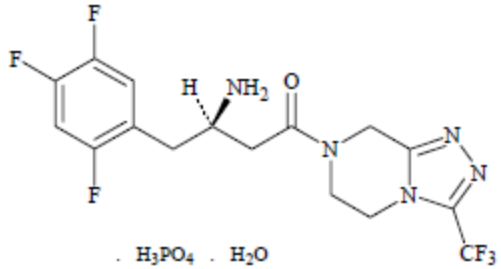
USAN	SITAGLIPTIN PHOSPHATE
PRONUNCIATION	sit a glip' tin
THERAPEUTIC CLAIM	Treatment of type 2 diabetes mellitus and related disorders

CHEMICAL NAMES

1. 1,2,4-triazolo[4,3-a]pyrazine, 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate (1:1) monohydrate

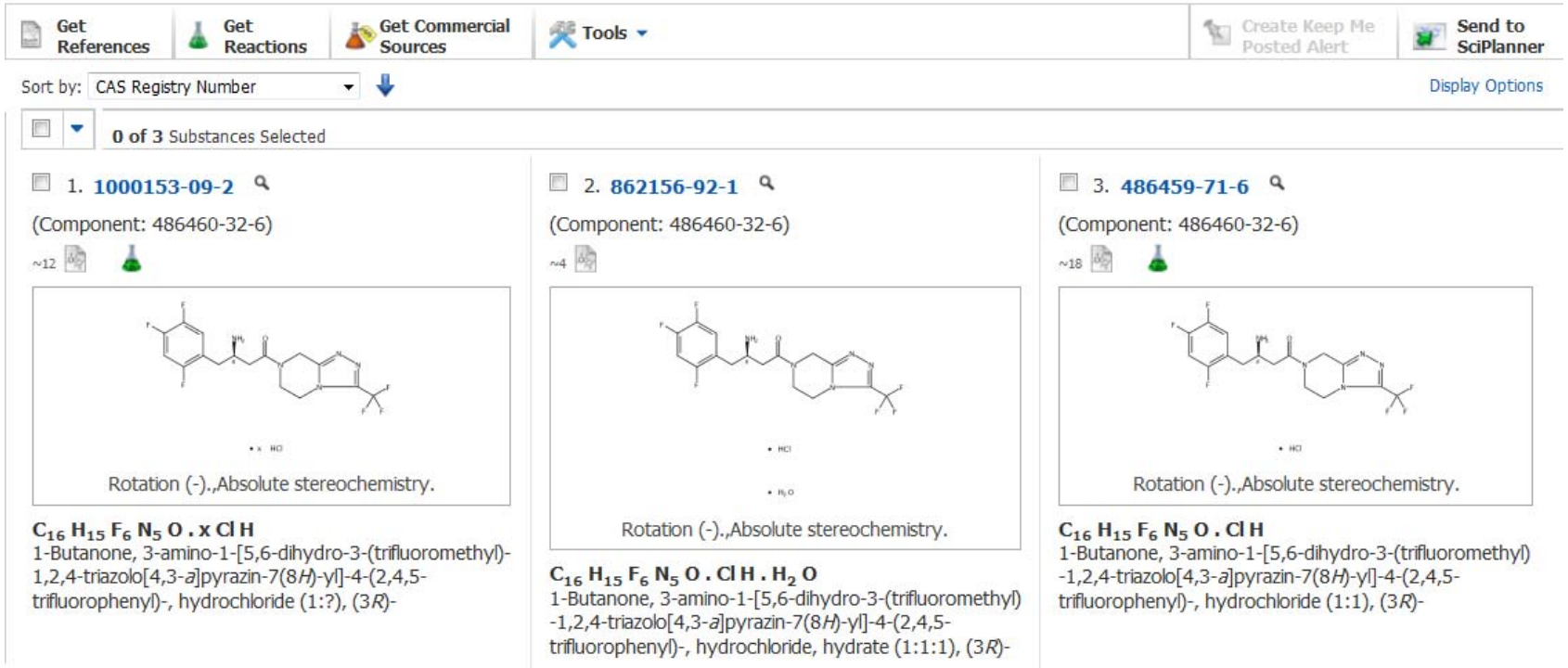
2. 7-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine monophosphate monohydrate

STRUCTURAL FORMULA



MOLECULAR FORMULA	$C_{16}H_{15}F_6N_5O \cdot H_3O_4P \cdot H_2O$
MOLECULAR WEIGHT	523.3
TRADEMARK	Unknown as yet
MANUFACTURER	Merck & Co., Inc.
CAS REGISTRY NUMBER	654671-77-9

Sitagliptin hydrochloride (no official definition)

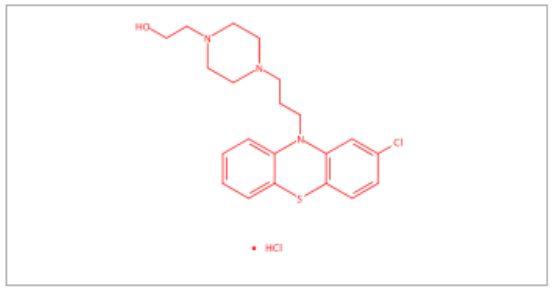


Perphenazine hydrochloride (no official definition)

7. **3111-71-5**

(Component: 58-39-9)

~9



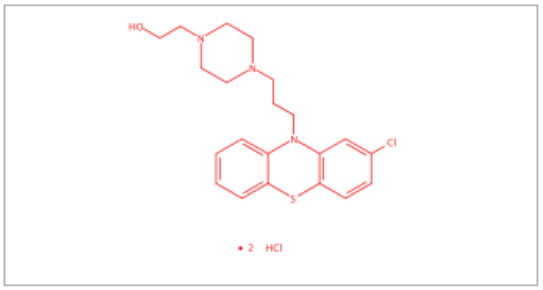
$C_{21}H_{26}ClN_3OS.ClH$

1-Piperazineethanol, 4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-, hydrochloride (1:1)

8. **2015-28-3**

(Component: 58-39-9)

~39 ~7



$C_{21}H_{26}ClN_3OS.2ClH$

1-Piperazineethanol, 4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-, hydrochloride (1:2)

Key Physical Properties

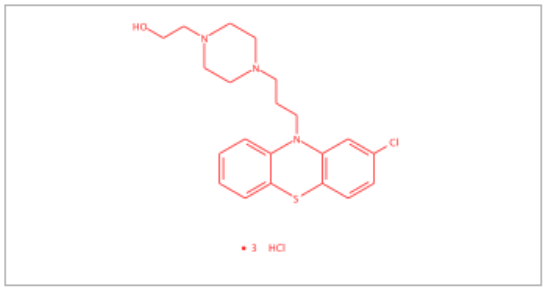
Regulatory Information

Experimental Properties

9. **130-69-8**

(Component: 58-39-9)

~7



$C_{21}H_{26}ClN_3OS.3ClH$

1-Piperazineethanol, 4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-, hydrochloride (1:3)

(Polydisperse) Polymers

Hypromellose Example

USP 33: Hypromellose is a methyl and hydroxypropyl mixed ether of cellulose. It contains, calculated on the dried basis, methoxy (–OCH3: 31.03) and hydroxypropoxy (–OC3H6OH: 75.09) groups conforming to the limits for the types of Hypromellose (hydroxypropyl methylcellulose) set forth in the accompanying table.

	Methoxy (percent)		Hydroxypropoxy (percent)	
Substitution Type	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

(Polydisperse) Polymers

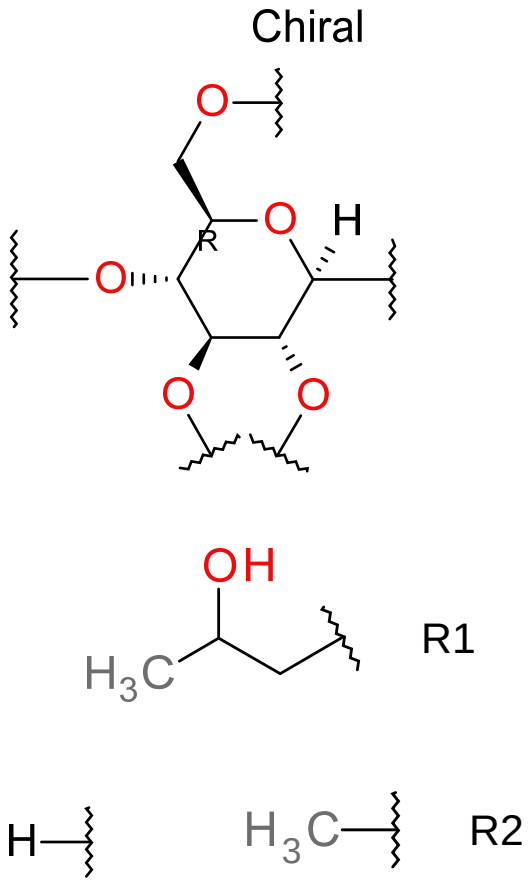
Hypromellose Example

USP 33: Labeling—Label it to indicate its substitution type and its nominal viscosity value in milli-Pascal per second (mPa·s).

Hypromellose is the INN and BAN

CAS *9004-65-3*

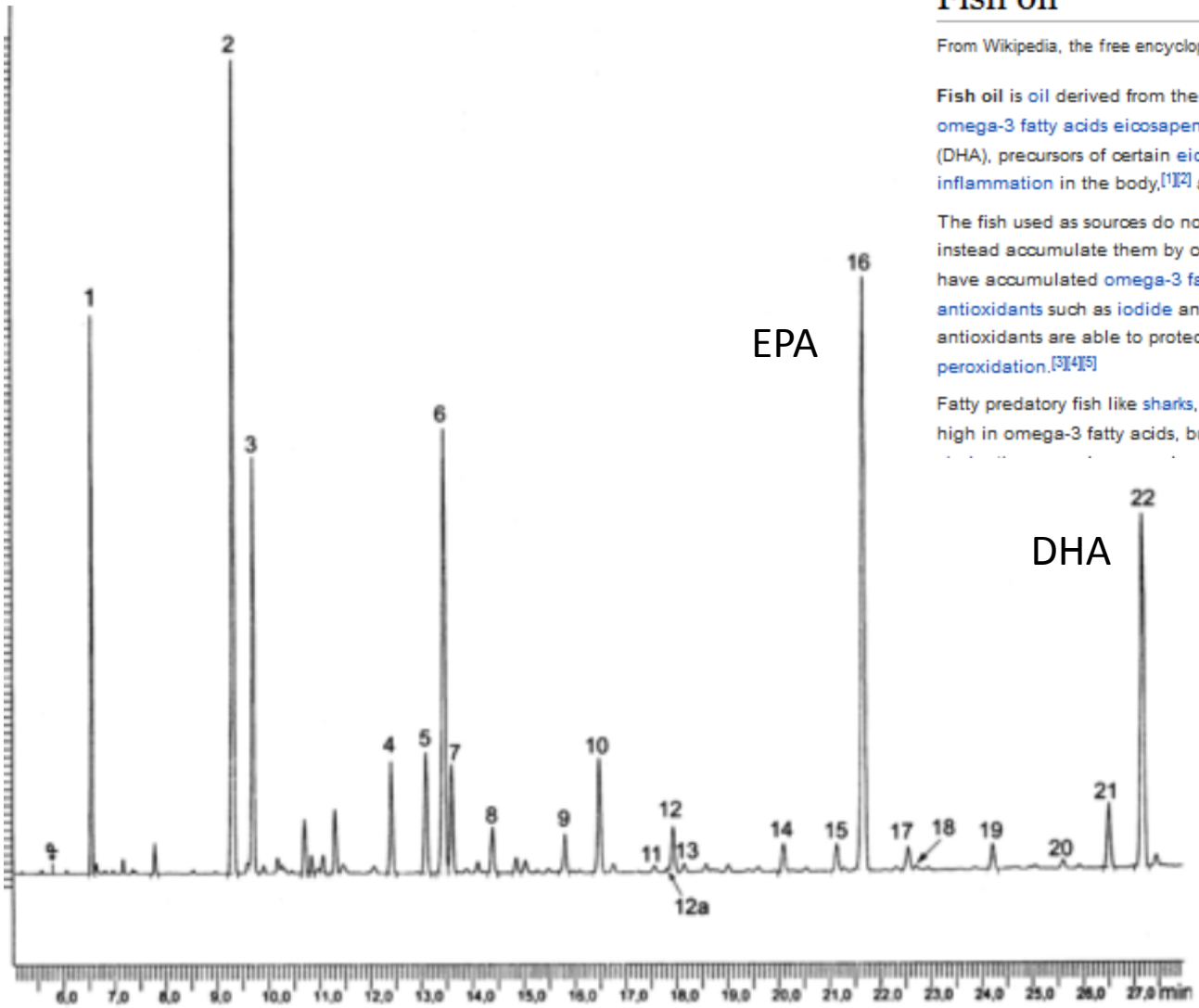
Hypromellose



<POLYMER_TYPE>HOMOPOLYMER
<NUMBER_OF_SRU>1
<ORIENTATION_OF_POLYMERIZATION>HEAD-TAIL
<R_ID>R1
<LIMIT_TYPE>WEIGHT
<AVERAGE>10
<LOW_LIMIT>7
<HIGH_LIMIT>12
<R_ID>R2
<LIMIT_TYPE>WEIGHT
<AVERAGE>29
<LOW_LIMIT>28
<HIGH_LIMIT>30
<TYPE_MW>NUMBER
<MW_AVERAGE>8000
<LOW_LIMIT_MW/>
<HIGH_LIMIT_MW/>
<PHYSICAL_PROPERTY_TYPE>VISCOSITY
<AVERAGE>3
<LOW_LIMIT>2.4
<HIGH_LIMIT>3.6
<UNITS>MPA.S

Hypromello

HYPROMELLOSE 2910 (3 MPA.S)	0VUT3PMY82
HYPROMELLOSE 2910 (5 MPA.S)	R75537T0T4
HYPROMELLOSE 2910 (6 MPA.S)	0WZ8WG20P6
HYPROMELLOSE 2910 (15 MPA.S)	36SFW2JZ0W
HYPROMELLOSE 2910 (50 MPA.S)	1IVH67816N
HYPROMELLOSE 2910 (4000 MPA.S)	RN3152OP35
HYPROMELLOSE 2910 (15000 MPA.S)	288VBX44JC
HYPROMELLOSE 2906 (50 MPA.S)	612E703ZUQ
HYPROMELLOSE 2906 (4000 MPA.S)	5EYA69XGAT
HYPROMELLOSE 2208 (3 MPA.S)	9H4L916OBU
HYPROMELLOSE 2208 (100 MPA.S)	B1QE5P712K
HYPROMELLOSE 2208 (4000 MPA.S)	39J80LT57T
HYPROMELLOSE 2208 (15000 MPA.S)	Z78RG6M2N2
HYPROMELLOSE 2208 (100000 MPA.S)	VM7F0B23ZI



1. C14:0	6. C18:1 n-9	11. C20:0	15. C20:4 n-3	20. C22:5 n-6
2. C16:0	7. C18:1 n-7	12. C20:1 n-9	16. C20:5 n-3	21. C22:5 n-3
3. C16:1 n-7	8. C18:2 n-6	12a. C20:1 n-11	17. C22:1 n-11	22. C22:6 n-3
4. C16:4 n-1	9. C18:3 n-3	13. C20:1 n-7	18. C22:1 n-9	
5. C18:0	10. C18:4 n-3	14. C20:4 n-6	19. C21:5 n-3	

Figure 1912.-2. – *Chromatogram for the assay of total omega-3 acids in fish oil rich in omega-3 acids*

Fish oil

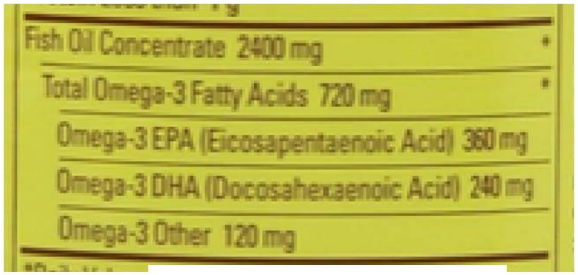
From Wikipedia, the free encyclopedia

Fish oil is oil derived from the tissues of oily fish. Fish oils contain the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), precursors of certain eicosanoids that are known to reduce inflammation in the body,[1][2] and have other health benefits.

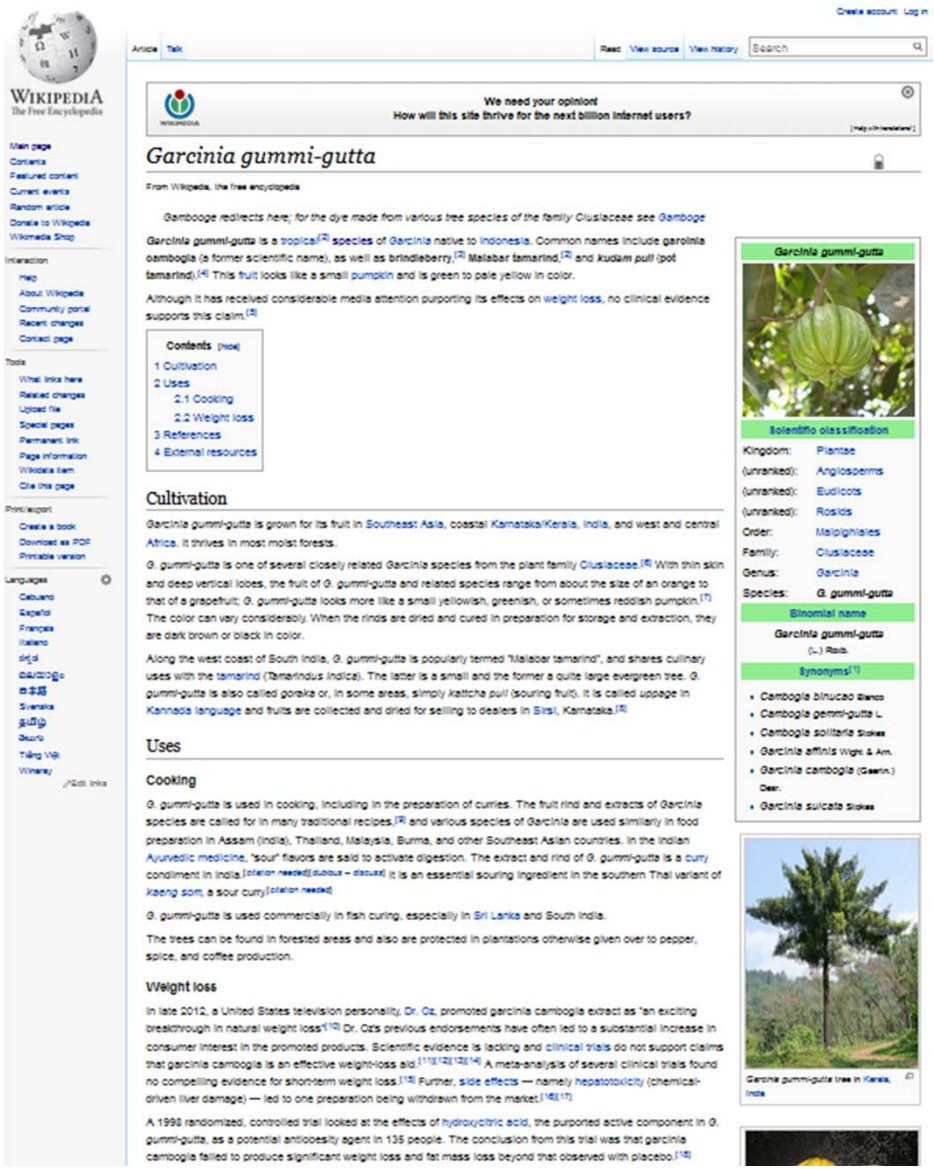
The fish used as sources do not actually produce omega-3 fatty acids, but instead accumulate them by consuming either microalgae or prey fish that have accumulated omega-3 fatty acids, together with a high quantity of antioxidants such as iodide and selenium, from microalgae, where these antioxidants are able to protect the fragile polyunsaturated lipids from peroxidation.[3][4][5]

Fatty predatory fish like sharks, swordfish, tilefish, and albacore tuna may be high in omega-3 fatty acids, but due to their position at the top of the food

A typical fish oil softgel



Garcinia Cambogia



Create account Log in

Article Talk Read View source View history Search

WIKIPEDIA
The Free Encyclopedia

Main page
Contents
Featured content
Current events
Random article
Donate to Wikipedia
Wikimedia Shop

Interaction
Help
About Wikipedia
Community portal
Recent changes
Contact page

Tools
What links here
Related changes
Upload file
Special pages
Permanent link
Page information
Wikidata item
Cite this page

Print/export
Create a book
Download as PDF
Printable version

Languages
Cebuano
Español
Français
Italiano
Svenska
Tiếng Việt
Winaray
Edit links

We need your opinion!
How will this site thrive for the next billion internet users?

Garcinia gummi-gutta

From Wikipedia, the free encyclopedia

Gambooge redirects here; for the dye made from various tree species of the family Clusiaceae see Gamboge

Garcinia gummi-gutta is a tropical[2] species of Garcinia native to Indonesia. Common names include **garcinia cambogia** (a former scientific name), as well as **brindleberry**,[3] **Malabar tamarind**,[2] and *kudam puli* (**pot tamarind**).[4] This fruit looks like a small pumpkin and is green to pale yellow in color.

Although it has received considerable media attention purporting its effects on weight loss, no clinical evidence supports this claim.[5]

Contents [hide]
1 Cultivation
2 Uses
2.1 Cooking
2.2 Weight loss
3 References
4 External resources

Cultivation

Garcinia gummi-gutta is grown for its fruit in Southeast Asia, coastal Karnataka/Kerala, India, and west and central Africa. It thrives in most moist forests.

G. gummi-gutta is one of several closely related *Garcinia* species from the plant family Clusiaceae.[6] With thin skin and deep vertical lobes, the fruit of *G. gummi-gutta* and related species range from about the size of an orange to that of a grapefruit; *G. gummi-gutta* looks more like a small yellowish, greenish, or sometimes reddish pumpkin.[7] The color can vary considerably. When the rinds are dried and cured in preparation for storage and extraction, they are dark brown or black in color.

Along the west coast of South India, *G. gummi-gutta* is popularly termed "Malabar tamarind", and shares culinary uses with the tamarind (*Tamarindus indica*). The latter is a small and the former a quite large evergreen tree. *G. gummi-gutta* is also called *goraka* or, in some areas, simply *kattcha puli* (souring fruit). It is called *uppage* in Kannada language and fruits are collected and dried for selling to dealers in Sirsi, Karnataka.[8]

Uses

Cooking

G. gummi-gutta is used in cooking, including in the preparation of curries. The fruit rind and extracts of *Garcinia* species are called for in many traditional recipes,[9] and various species of *Garcinia* are used similarly in food preparation in Assam (India), Thailand, Malaysia, Burma, and other Southeast Asian countries. In the Indian Ayurvedic medicine, "sour" flavors are said to activate digestion. The extract and rind of *G. gummi-gutta* is a curry condiment in India,[citation needed][dubious – discuss] it is an essential souring ingredient in the southern Thai variant of *kaeng som*, a sour curry.[citation needed]

G. gummi-gutta is used commercially in fish curing, especially in Sri Lanka and South India.

The trees can be found in forested areas and also are protected in plantations otherwise given over to pepper, spice, and coffee production.

Weight loss

In late 2012, a United States television personality, Dr. Oz, promoted garcinia cambogia extract as "an exciting breakthrough in natural weight loss"[10] Dr. Oz's previous endorsements have often led to a substantial increase in consumer interest in the promoted products. Scientific evidence is lacking and clinical trials do not support claims that garcinia cambogia is an effective weight-loss aid.[11][12][13][14] A meta-analysis of several clinical trials found no compelling evidence for short-term weight loss.[15] Further, side effects — namely hepatotoxicity (chemical-driven liver damage) — led to one preparation being withdrawn from the market.[16][17]

A 1998 randomized, controlled trial looked at the effects of hydroxycitric acid, the purported active component in *G. gummi-gutta*, as a potential antiobesity agent in 135 people. The conclusion from this trial was that garcinia cambogia failed to produce significant weight loss and fat mass loss beyond that observed with placebo.[18]

Garcinia gummi-gutta

Scientific classification

Kingdom:	Plantae
(unranked):	Angiosperms
(unranked):	Eudicots
(unranked):	Rosids
Order:	Malpighiales
Family:	Clusiaceae
Genus:	Garcinia
Species:	*G. gummi-gutta*

Binomial name

Garcinia gummi-gutta
(L.) Robs.

Synonyms:[1]

- *Cambogia binucao* Blanco
- *Cambogia gemmi-gutta* L.
- *Cambogia solitaria* Sickes
- *Garcinia affinis* Wight & Arn.
- *Garcinia cambogia* (Gaertn.) Desr.
- *Garcinia suicata* Sickes

Garcinia gummi-gutta tree in Kerala, India

Medicinal Plants Name Service

http://apps.kew.org/mpns-portal/

Accepted scientific name:

Garcinia gummi-gutta **(L.) Roxb., Hort. Bengal.: 42 (1814).**

Taxonomic source: World Checklist - unpublished

Family: Clusiaceae

Non-scientific names and plant parts | Scientific synonyms | Published in medicinal plant references as | Further information

Non-scientific names for this plant and parts used:

Non-scientific name:	Class of name:	Trade forms:	Plant parts:	Medicinal plant reference:
brindall berry	Other			Herbs of Commerce (McGuffin et al., 2000)
garcinia	Other			Herbs of Commerce (McGuffin et al., 2000)
Garcinia cambogia	Other	dried pericarp of the fruits	fruit	U.S. Pharmacopoeia USP 37 (2013)
Malabar tamarind	Other			Herbs of Commerce (McGuffin et al., 2000)
Powdered Garcinia Hydroxycitrate Extract	Other	powdered extract	fruit	U.S. Pharmacopoeia USP 37 (2013)

Need for Specified Substance

- Need to tie material to a manufacturer and a process
- Need to tie material to a specific grade
- Need to obtain specification information
- Need to obtain information about processing materials
- Need to establish and monitor the supply chain

Specified Substance

- To be implemented with the GInAS Application
- An explicit grouping of elements and concepts put forward in ISO IDMP
  - Group-1 Multiple substance materials (Coatings, Colorants, Flavorants); Physical Form; Extracts
  - Group-2 Manufacturer and minimal manufacturing information
  - Group-3 Grade of material (USP, EP, technical, standardized etc.)
  - Group-4 Detailed manufacturing information, impurities, degradents etc.

Why IDMP?

- No other approach can meet the regulatory need for substance/ingredient identity codes
- Precise at the molecular level
- Consistent and standardized dataset
- UNIIs are free to use, highly searchable and possess internal validation