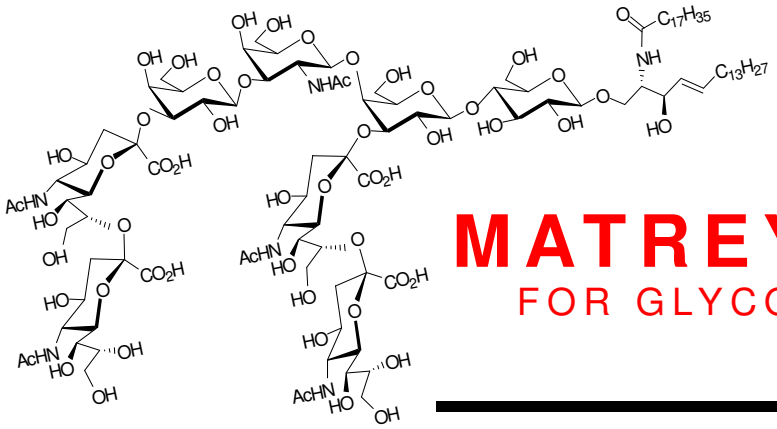

MATREYA NEWSLETTER

FOR GLYCO/SPHINGOLIPID RESEARCH

JANUARY 2012

Sphingolipidoses: Sphingolipid Lysosomal Storage Diseases

In 1881 Tay-Sachs disease became the first of the lysosomal storage diseases to be described. A description of Gaucher's disease soon followed in 1882 and the identification of over 50 lysosomal storage disorders began over the next 130 years. Lysosomal storage diseases are a group of rare inherited disorders that result in the accumulation of compounds within the lysosome as a result of inherited genetic mutations. Most of these diseases are autosomal recessive, with a few being X-linked recessive, and occur in about 1:8000[1] cases.

The lysosome is an organelle within the cell that is responsible for catabolizing and recycling many lipid compounds and has a significant role in maintaining a cells proper balance of compounds. Lysosomes have a low pH and the enzymes present within lysosomes mostly only function in this acidic environment. Enzyme deficiencies within the lysosome result in the accumulation of various lipids, which are toxic at high concentrations.

The lysosomal storage diseases are classified according to the compounds accumulated in the lysosomes and include sphingolipidoses, oligosaccharidoses, mucolipidoses, mucopolysaccharidoses, lipoprotein storage disorders, lysosomal transport defects and neuronal ceroid lipofuscinoses. The accumulation of substrates in the lysosomes can result because the lysosome lacks sufficient enzyme activity to metabolize a particular lipid compound. It can also result from an inability to transport a particular lipid out of the lysosome. Both of these result from specific mutations in the gene's codes for enzymes.

For many years these lysosomal storage diseases were untreatable but, with a clearer understanding of the mechanisms involved, several effective therapies have been developed[2]. There are two approaches to treating these diseases: replacing the defective enzymes or inhibiting the synthesis of the accumulated lipid. The most promising and most common treatment for many of these storage disorders is enzyme replacement therapy, although it remains very expensive. It is difficult to transport enzymes across the blood-brain barrier, which limits the effectiveness of enzyme replacement therapy in cases involving the central nervous system. Another treatment being developed is stem cell transplantation, either on its own or along with enzyme replacement therapy; however, bone marrow transplant has limited applications and cannot be applied to as many cases as enzyme replacement therapy. A third treatment option, inhibiting the synthesis of the accumulated lipid, has seen some success in treating type I Gaucher's disease by reducing the synthesis of glucosylceramide. This option affects the synthesis of other downstream lipids, which are also critical for cellular functions. Due to the complexity of the diseases encountered, it appears that a combination of therapeutic approaches will be needed[3].

INSIDE THIS ISSUE

Sphingolipidoses (sphingolipid lysosomal storage Sphingolipidoses (sphingolipid lysosomal storage disorders) result in an accumulation of various sphingolipids in the lysosome. Ten main sphingolipidoses affect the glycosphingolipid pathway: Farber, Krabbes, Gaucher's, Metachromatic Leukodystrophy, Fabry, Sandhoff, Niemann-Pick, Sialidosis, Tay-Sachs, and GM_1 gangliosidosis. In all of these disorders multiple sphingolipids accumulate in the lysosome. The outline of these disorders is illustrated in the charts on page 3 and 4.

Matreya offers a large number of glycosphingolipids, both natural and well-defined, that are ideal for studies involving these sphingolipisoses.

Sphingolipidoses: Sphingolipid Lysosomal Storage Diseases (Continued)

Farber disease is characterized by an accumulation of ceramides due to a lack in the activity of the enzyme acid ceramidase. Disorders in many organs, including the central nervous system, can occur. Hematopoietic stem cell transplantation is being developed as a therapeutic treatment for this disease and is showing promising results for patients without CNS involvement[4].

Krabbe disease is characterized by an accumulation of galactosylcerebroside due to a lack in the activity of the enzyme *beta*-galactosidase. The accumulation of these lipids negatively affects the myelin of the nerve cells causing severe nervous system deterioration. Psychosine (galactosylsphingosine, the deacylated form of galactosylcerebroside) is also accumulated in this disorder and may significantly contribute to the degeneration of axons. Bone marrow transplantation may be an effective therapeutic approach to slow down the disease in cases of early detection.

Fabry disease is characterized by an accumulation of globotriaosylceramide (CTH) due to a lack in the activity of the enzyme *alpha*-galactosidase A and is a length-dependent peripheral neuropathy[5]. Fabry disease has recently become of great interest due to its implication in cardiac and cerebrovascular disease as well as in initial ischemic stroke[6].

Sandhoff disease is characterized by an accumulation of globoside (GL4) and monosialoganglioside GM_2 due to a lack in the activity of the enzyme *beta*-hexosaminidase A and B and is a neuropathic disease. Enzyme replacement therapy is not effective against Sandhoff disease; it is a neuropathy of the central nervous system. Therefore glycolipid inhibitors or viral vectors expressing *beta*-hexosaminidase subunits may be a therapeutic approach for this disorder[7].

Niemann-Pick disease types A and B are characterized by an accumulation of sphingomyelin due to a lack in the activity of the enzyme acid sphingomyelinase. Type A is a neurodegenerative disease while type B is a nonneurologic, visceral form. The accumulation of sphingomyelin, and subsequent lyso-sphingomyelin, can cause extensive damage to neurons and organs[8].

Sialidosis is characterized by an accumulation of various gangliosides as well as sialic acid containing glycoproteins and oligosaccharides due to a lack in the activity of the sialidase (*alpha*-N-acetyl neuraminidase) enzymes[9]. It significantly affects the nervous system[10].

Tay-Sachs disease is characterized by an accumulation of ganglioside GM_2 due to a lack in the activity of the enzyme *beta*-hexosaminidase A and results in severe neurodegeneration. Enzyme replacement therapy has been shown to have a good potential for widespread correction of the underlying lysosomal defect in this disease[11].

GM_1 gangliosidosis is characterized by an accumulation of ganglioside GM_1 and asialoganglisoide GM_1 due to a lack in the activity of the enzyme acid *beta*-galactosidase. This leads to neurodegeneration and brain dysfunction. Both enzyme replacement therapies and substrate reduction therapies have been shown to be effective interventions for this disorder[12].

References:
1. B. Manger, *Z Rheumatol*, Lysosomal storage diseases, 69(6):527-38 (2010)
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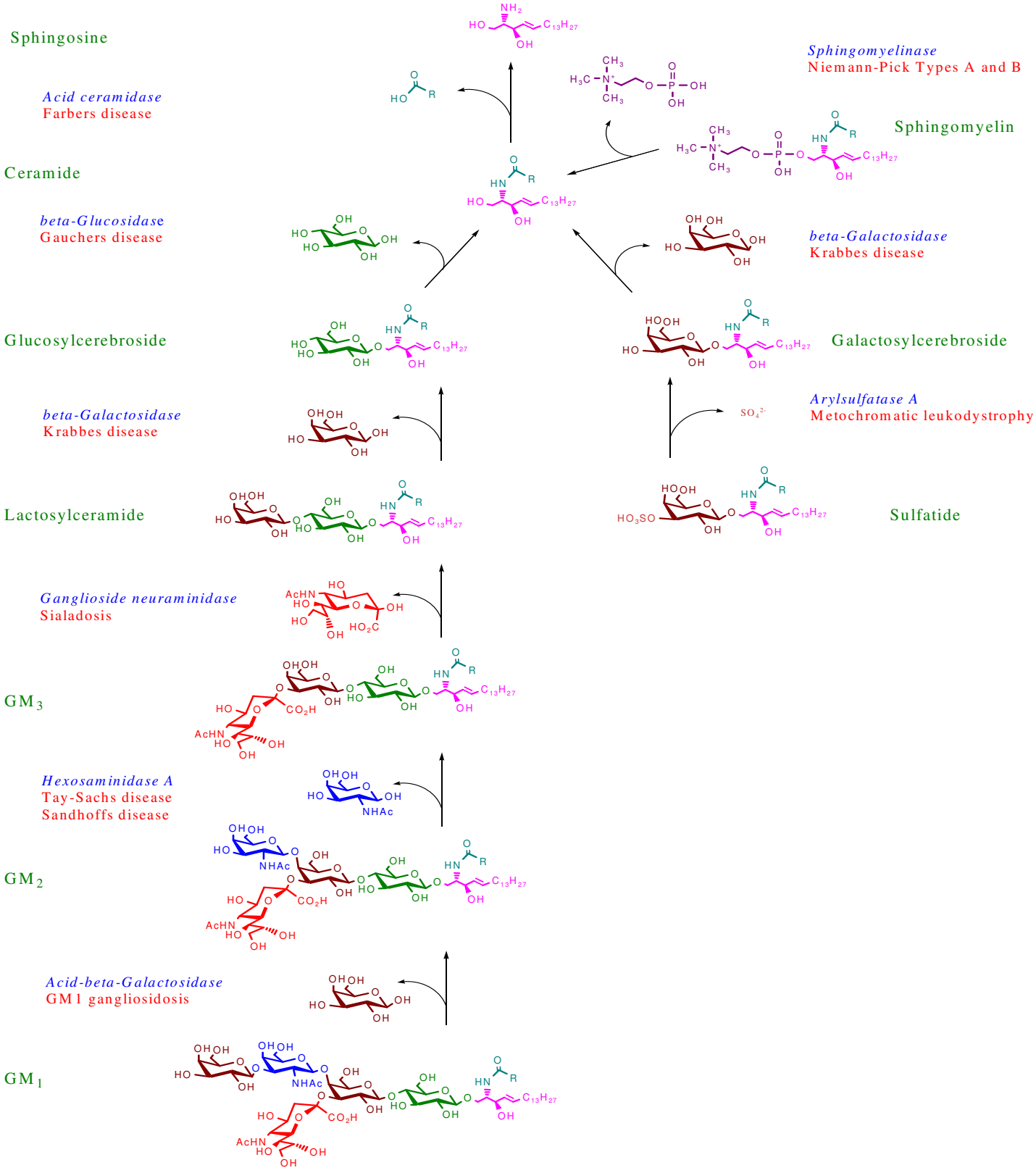
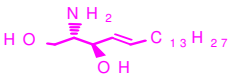
4. K. Ehlert et al. *Pediatric Rheumatology*, Farber disease: clinical presentation, pathogenesis and a new approach to treatment, 5:1-7 (2007)
5. K. Toyooka, *Current Opinion in Neurology*, Fabry disease, 24(5):463-468 (2011)
6. M. Wozniak et al., *Stroke*, Frequency of Unrecognized Fabry Disease Among Young European-American and African-American Men With First Ischemic Stroke, 41:78-81 (2010)
7. K. Ashe et al. *PloS ONE*, Iminosugar-Based Inhibitors of Glucosylceramide Synthase Increase Brain Glycosphingolipids and Survival in a Mouse Model of Sandhoff Disease, 6:1-11 (2011)
8. J. Desnick et al. *Mol Med*., Identification and Characterization of Eight Novel *SMPD1* Mutations Causing Types A and B Niemann-Pick Disease, 16(7-8):316–321 (2010)
9. B Ulrich-Bott et al. *Enzyme*, Lysosomal sialidase deficiency: increased ganglioside content in autopsy tissues of a sialidosis patient, 38(1-4):262-266 (1987)
10. V. Seyrantepe et al., *J. Biol. Chem.*, Neu4, a Novel Human Lysosomal Lumen Sialidase, Confers Normal Phenotype to Sialidosis and Galactosialidosis Cells, 279(35):37021-37029 (2004)
11. M. Cachon-Gonzalez et al., *PNAS*, Effective gene therapy in an authentic model of Tay-Sachs-related diseases, 103(27):10373-10378 (2006)

Sphingolipidsosis Chart (Gangliosides, Sulfatides, and Sphingomyelin)



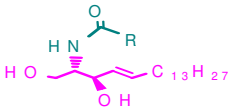
Sphingolipidsosis Chart (Globosides)

Sphingosine

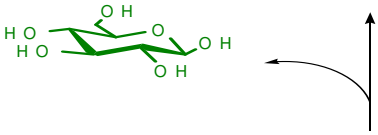


Acid ceramidase
Farbers disease

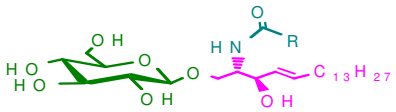
Ceramide



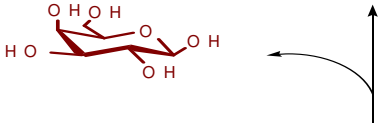
beta-Glucosidase
Gauchers disease



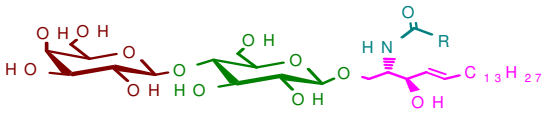
Glucosylcerebroside



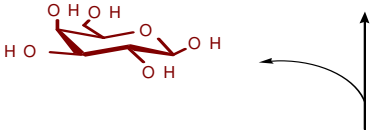
beta-Galactosidase
Krabbes disease



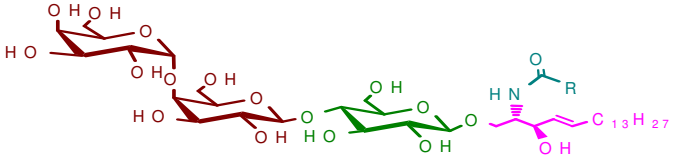
Lactosylceramide



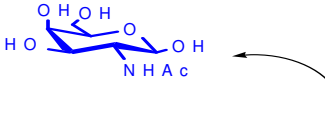
alpha-Galactosidase A
Fabrys disease



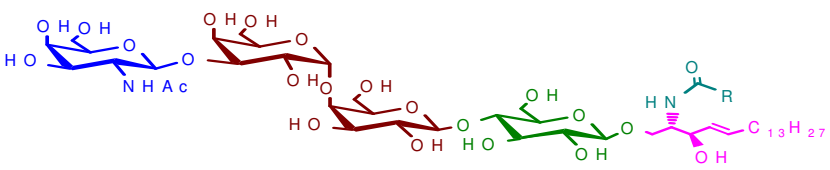
Gb3 (CTH)



beta-Hexosaminidase A + B
Sandhoffs disease



Gb4



Biomarkers for Lysosomal Storage Diseases

Matreya's glycosphingolipid standards can be used for TLC, HPLC, and Mass Spectrometry

SPHINGOLIPID	CATALOG NO.	ASSOCIATED DISORDER
Sphingosines and Ceramides		***Farber disease***
D-erythro-Sphingosine	1802	
N-Acetyl-D-erythro-sphingosine	1901	
N-Hexanoyl-D-erythro-sphingosine	1900	
N-Octanoyl-D-erythro-sphingosine	1903	
N-Decanoyl-D-erythro-sphingosine	1333	
N-Pentadecanoyl-D-erythro-sphingosine	2037	
N-Hexadecanoyl-D-erythro-sphingosine	1915	
N-Heptadecanoyl-D-erythro-sphingosine	2038	
N-Octadecanoyl-D-erythro-sphingosine	1832	
N-Nonadecanoyl-D-erythro-sphingosine	2039	
N-Tetacosanoyl-D-erythro-sphingosine	1916	
N-Tetracosenoyl-D-erythro-sphingosine	1930	
N-Hexanoyl-NBD-D-erythro-sphingosine	1618	
N-Dodecanoyl-NBD-D-erythro-sphingosine	1841	
Sphingosylphosphorylcholines		***Niemann-Pick Type A and B***
D-erythro-Sphingosylphosphorylcholine	1318	
N-Acetyl-sphingosylphosphorylcholine	1907	
N-Hexanoyl-sphingosylphosphorylcholine	1909	
N-Heptadecanoyl-sphingosylphosphorylcholine	1890	
N-Octadecanoyl-sphingosylphosphorylcholine	1911	
N-Eicosanoyl-sphingosylphosphorylcholine	1917	
N-Docosanoyl-sphingosylphosphorylcholine	1918	
N-1-^{13}C-Palmitoyl-sphingosylphosphorylcholine	2200	
N-Hexanoyl-NBD-sphingosylphosphorylcholine	1912	
N-Dodecanoyl-NBD-sphingosylphosphorylcholine	1619	
Galactosylceramides		***Krabbe disease***
Cerebrosides (bovine)	1050	
Psychosine	1305	
N-Acetyl-psychosine	1325	
N-Octanoyl-psychosine	1334	
N-Heptadecanoyl-psychosine	1335	
N-Stearoyl-D_{35}-psychosine	1914	
N-Hexanoyl-NBD-psychosine	1621	
N-Dodecanoyl-NBD-psychosine	1633	

Biomarkers for Lysosomal Storage Diseases
(Continued)

SPHINGOLIPID	CATALOG NO.	ASSOCIATED DISORDER
Glucosylceramides		***Gaucher's disease***
Glucocerebrosides (bovine buttermilk)	1521	
Glucocerebrosides (plant)	1522	
Glucocerebrosides (Gaucher's spleen)	1057	
Glucopsychosine (bovine buttermilk)	1306	
Glucopsychosine (plant)	1310	
N-Docosanoyl-glucopsychosine	1531	
N-Palmitoyl-D_3-glucopsychosine	1533	
N-Hexanoyl-NBD-glucopsychosine	1622	
Sulfatides		***Metachromatic Leukodystrophy***
Sulfatides (bovine)	1049	
lyso-Sulfatides	1904	
N-Acetyl-sulfatide	2076	
N-Hexadecanoyl-sulfatide	1875	
N-Tetracosanoyl-sulfatide	1888	
N-Octadecanoyl-D_3-sulfatide	1536	
N-Dodecanoyl-NBD-sulfatide	1632	
Lactosylceramides		***Krabbe disease***
Lactosylceramides (porcine)	1500	
Lactosylceramides (bovine buttermilk)	1507	
lyso-Lactosylceramide	1517	
N-Palmitoyl-lactosylceramide	1532	
N-Palmitoyl-D_3-lactosylceramide	1534	
N-Hexanoyl-NBD-lactosylceramide	1629	
N-Dodecanoyl-NBD-lactosylceramide	1630	
Ceramide Trihexosides (Globotriaosylceramides)		***Fabry disease***
Ceramide trihexoside (CTH) (porcine)	1067	
lyso-Ceramide trihexoside (*lyso*-CTH)	1520	
N-Heptadecanoyl-ceramide trihexoside	1523	
N-Tricosanoyl-ceramide trihexoside	1524	
N-Octadecanoyl-D_3-ceramide trihexoside	1537	
N-Dodecanoyl-NBD-ceramide trihexoside	1631	
Globosides (Globotetrahexosylceramides)		***Sandhoff disease***
Globosides (porcine)	1068	
Gangliosides		***Sialidosis***
Monosialoganglioside GM_1	1061	***GM_1 gangliosidosis***
lyso-Monosialoganglioside GM_1	1518	
N-*omega*-CD_3-Octadecanoyl monosialoganglioside GM_1 (NH_4^+ salt)	2050	
N-*omega*-CD_3-Octadecanoyl monosialoganglioside GM_2 (NH_4^+ salt)	2051	***Tay-Sachs and Sandhoff***
N-*omega*-CD3-Octadecanoyl monosialoganglioside GM_3 (NH_4^+ salt)	2052	

AOCS Reference Standards for Edible Oils

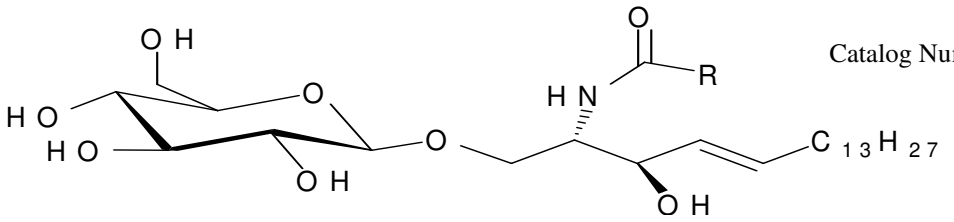
Matreya offers many lipid mixtures that are ideal as GC standards. These mixtures are carefully and accurately prepared using great precautions. The individual components are carefully analyzed before being combined with the mixture and are stored under inert gas at -20°C. Each component is carefully measured using calibrated instruments. After the mixture is prepared it is re-analyzed to ensure that it meets all quality standards. After passing rigorous inspection the mixture is carefully packaged under inert gas and stored at -20°C.

By studying problems with the quantitative analysis of animal and vegetable oils and fats, the American Oil Chemists' Society has found certain mixtures to be useful as reference standards. The composition of each mixture (see the table below for weight composition) is similar to the fatty acid distribution of certain oils. All mixtures are in methyl ester form and are ready for GC analysis. If you need a mixture that is not listed we will be happy to prepare one that will meet your specifications.

Each methyl ester mixture is carefully prepared by weight and the composition verified by gas chromatography. The weight percentage of each component is indicated in the Table.

Mix No. Catalog No.	**RM-1 1084**	**RM-2 1085**	**RM-3 1086**	**Rapeseed 1083**	**RM-4 1087**	**RM-5 1088**	**RM-6 1089**
C8:0 Caprylate						7.0	
C10:0 Caprate						5.0	
C12:0 Laurate						48.0	
C14:0 Myristate			1.0	1.0		15.0	2.0
C16:0 Palmitate	6.0	7.0	4.0	4.0	11.0	7.0	30.0
C16:1 Palmitoleate							3.0
C18:0 Stearate	3.0	5.0	3.0	3.0	3.0	3.0	14.0
C18:1 Oleate	35.0	18.0	45.0	60.0	80.0	12.0	41.0
C18:2 Linoleate	50.0	36.0	15.0	12.0	6.0	3.0	7.0
C18:3 Linolenate	3.0	34.0	3.0	5.0			3.0
C20:0 Arachidate	3.0		3.0	3.0			
C20:1 Eicosenoate				1.0			
C22:0 Behenate			3.0	3.0			
C22:1 Erucate			20.0	5.0			
C24:0 Lignocerate			3.0	3.0			
*These are the oils that the mixtures are suitable for.	Corn Cottonseed Soybean Safflower Sesame Poppy seed Walnut Kapok Rice	Linseed Perilla Hempseed Rubberseed	Peanut Rapeseed Mustard	Rapeseed	Olive Teaseed Neatsfoot	Coconut Palm Babassu Ouri-ouri	Lard Beef tallow Mutton tallow Palm

Glucocerebrosides (Gaucher's spleen)



Catalog Number 1057

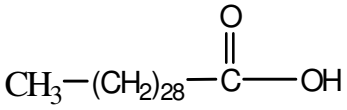
This cerebroside product is a glycosphingolipid containing a glucose attached to a ceramide (glucocerebroside) acylated with hydroxy and non-hydroxy fatty acids. It is a major constituent of skin lipids where it has an important role in lamellar body formation and in maintaining the water permeability barrier. Glucocerebroside is very important due to its function as the biosynthetic precursor for lactosylceramide and from which most of the **neutral oligoglycolipids** and **gangliosides**[1] are derived. Glucocerebroside is the only **glycosphingolipid** that is found in plants, fungi, and animals and is one of the most abundant glycosphingolipid in plants. Due to the relatively high melting point of cerebroside (much greater than physiological body temperature) they have a para-crystalline structure. Glucocerebroside tends to be concentrated in the outer leaflet of the plasma membrane in lipid rafts. It has been reported that glucocerebroside is essential for the activity of tyrosinase (a key enzyme in melanin biosynthesis), to elicit defense responses in plants, and to help the plasma membrane in plants to withstand stresses brought about by cold and drought. In **Gaucher's** disease glucocerebroside accumulates in the spleen, liver, lungs, bone marrow, and brain due to a deficiency of the enzyme glucocerebrosidase.[2,3] This accumulation of glucocerebroside has been associated with chemotherapy resistance. Glucocerebroside has been shown to be able to modulate membrane traffic along the endocytic pathway.[4]

	Catalog Number	Product Name	Unit	Purity
New!	1057; 1057-25	Glucocerebrosides (Gaucher's spleen)	5 mg; 25 mg	98+%

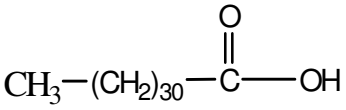
References:
1. D. Sillence et al. "Assay for the transbilayer distribution of glycolipids: selective oxidation of glucosylceramide to glucuronylceramide by TEMPO nitroxyl radicals" *Journal of Lipid Research*, Vol. 41(8) pp. 1252-1260, *2000*
2. C. Walden et al. "Accumulation of Glucosylceramide in Murine Testis, Caused by Inhibition of β-Glucosidase 2: IMPLICATIONS FOR SPERMATOGENESIS" *The Journal of Biological Chemistry*, Vol. 282 pp. 32655-32664, *2007*
3. R. Brady "Gaucher's disease: past, present and future" *Baillieres Clin Haematol*, Vol. 10:4 pp. 621-634, *1997*
4. D. Sillence et al. "Glucosylceramide modulates membrane traffic along the endocytic pathway" *Journal of Lipid Research*, Vo. 43(11) pp. 1837-1845, *2002*

Long-Chain Fatty Acids

Triacontanoic acid



Dotriacontanoic acid



	Catalog Number	Product Name	Unit	Purity
	1038	Methyl tetracosanoate	100mg	98+%
	1252	Methyl hexacosanoate	25mg	98+%
New!	1271	Methyl octacosanoate	50mg	98+%
New!	1273	Methyl triacontanoate	50mg	98+%
New!	1275	Methyl dotriacontanoate	50mg	98+%
New!	2011	Long Chain Fatty Acid Methyl Ester Mix (C24:0, C26:0, C28:0, C30:0, C32:0 methyl esters)	25mg/ml	98+%