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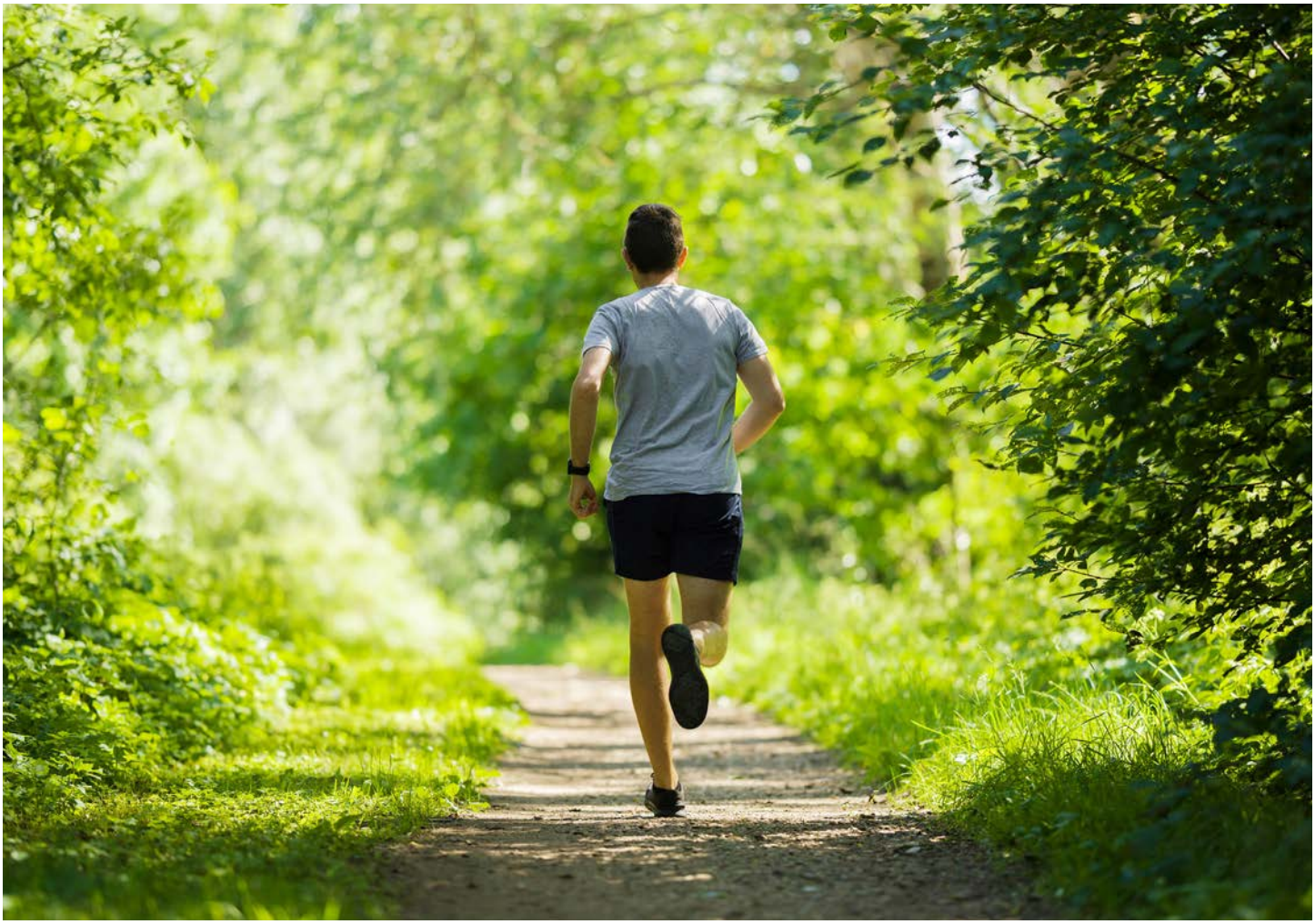
RESEARCH PRODUCTS

Stable Isotope-Labeled Mixtures, Sets, and Kits

For Mass Spectrometric Applications



Cambridge Isotope Laboratories, Inc.
North America: 1.800.322.1174 cilsales@isotope.com | **International:** +1.978.749.8000 intlsales@isotope.com | fax: 1.978.749.2768 | isotope.com

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The global and targeted measurement of biomolecules continues to be two areas of growing focus in analytical chemistry and biomedicine. Drivers for this research include efforts to better understand the underlying mechanisms of disease pathogenesis and to improve precision medicine through the qualitative/quantitative screening of candidate biomarkers. To address these objectives, mass spectrometry (MS)-based approaches are increasingly utilized and have been aided by advancements in experimental methodologies, instrumentation technologies, and bioinformatic tools.

To help advance research in MS 'omics and MS/MS screening, Cambridge Isotope Laboratories, Inc. (CIL) is pleased to offer the largest variety of stable isotope-labeled sets, mixtures, and kits. The mixes are formulated neat and/or as solutions and are readily available for immediate use. In addition to the packaged mix(es), the kits include a user manual and shipping documents (e.g., certificate of analysis, safety data sheet). The manual outlines general procedures and processing examples for user reference, as well as troubleshooting notes and analysis results. Please see **isotope.com** for product details, pricing, and to inquire about customized mixes.

Benefits

- easy to implement
- offers end user flexibility
- reduces development time and cost
- enhances data quality
- improves reproducibility
- renders confidence in analytical results

Features Overview

- mixes supplied in neat and/or solution form
- preferentially ^{13}C- and/or ^{15}N-enriched
- site-specific or uniform labeling
- established specification guidelines
- procedural guides in kit manuals
- broad-spanning applications (from QC to quantification)

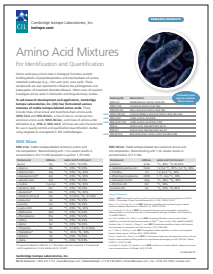
Mixtures and Sets

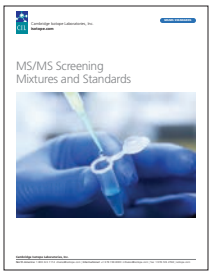
The mixtures available off-the-shelf are class- or pathway-specific for 'omics and MS/MS screening applications. These mixes are amenable for use in quality control and qualification/quantification exercises using targeted, semi-targeted, or untargeted MS-based methodologies. Outlined below is an overview of our current mix offerings, as well as details into their compositions and usage specifications (i.e., reconstitution guidelines, storage, and stability). For reference purposes, example results and published manuscripts are also provided.

Class-Specific Mixes

Amino Acid Mixes and Sets

Amino acids (AAs) play critical roles in biological functions as both building blocks of peptides/proteins and intermediates of various metabolic pathways (e.g., citric acid cycle, urea cycle). These compounds are also reported to influence the pathogenesis and propagation of metabolic disorders/disease. To aid continued development and application, CIL has formulated a number of stable isotope-labeled (and unlabeled) AA mixtures. These include mixes of the canonical amino acids (MSK-A2 and MSK-CAA), the rare or unnatural non-canonical amino acids (MSK-NCAA), and a series of reference standard AA mixes (e.g., NSK-A).





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Overview

Catalog No.	Description	No. of Metabolites	Unit Size
MSK-A2	Metabolomics Amino Acid Mix	17	1.2 mL
MSK-CAA	Canonical Amino Acid Mix	20	1 vial
MSK-NCAA	Non-canonical Amino Acid Mix	7	1 vial
MSK-CNCAA	Canonical/Non-canonical Amino Acid Mix Sets	20 (in CAA), 7 (in NCAA)	2 × 1 vial
NSK-AA3	3-Plex Amino Acid Standard Mix	3	1 vial
NSK-AA3-10X	3-Plex Amino Acid Standard Mix (10X)	3	1 vial
NSK-A	Amino Acid Standard Mix Set A	12	1 vial, 10 vials
NSK-A1	Amino Acid Standard Mix Set A1	12	1 vial, 10 vials
NSK-AB	Standard Mix Sets A and B	12 (in NSK-A), 8 (in NSK-B)	2 × 10 vials
NSK-BCAA	Branched-chain Amino Acid Standard Mix	4	1 vial

MSK-A2 and MSK-CAA Mixes

Compositions

The A2 mix (in 0.1 M HCl) consists of 17 amino acids (in solution), and the CAA mix (dried down) comprises 20. Reconstituting the CAA mix in 1 mL solvent (e.g., water) results in 2.5 mM concentrations (exception: L-cystine at 1.25 mM). **Note:** This CAA mix should not be reconstituted in 0.1 M HCl as Asn and Gln are unstable in acid.

Compound	Abbrev.	Label and Enrichment	Conc. (mM)
L-Alanine	Ala	$^{13}C_3$, 99%; ^{15}N, 99%	2.5
L-Arginine·HCl	Arg	$^{13}C_6$, 99%; $^{15}N_4$, 99%	2.5
L-Asparagine*	Asn	$^{13}C_4$, 99%; $^{15}N_2$, 99%	2.5
L-Aspartic acid	Asp	$^{13}C_4$, 99%; ^{15}N, 99%	2.5
L-Cystine	Cys-Cys	$^{13}C_6$, 99%; $^{15}N_2$, 99%	1.25
L-Glutamic acid	Glu	$^{13}C_5$, 99%; ^{15}N, 99%	2.5
L-Glutamine*	Gln	$^{13}C_5$, 99%; $^{15}N_2$, 99%	2.5
Glycine	Gly	$^{13}C_2$, 99%; ^{15}N, 99%	2.5
L-Histidine·HCl	His	$^{13}C_6$, 97-99%; $^{15}N_3$, 97-99%	2.5
L-Isoleucine	Ile	$^{13}C_6$, 99%; ^{15}N, 99%	2.5
L-Leucine	Leu	$^{13}C_6$, 99%; ^{15}N, 99%	2.5
L-Lysine·2HCl	Lys	$^{13}C_6$, 99%; $^{15}N_2$, 99%	2.5
L-Methionine	Met	$^{13}C_5$, 99%; ^{15}N, 99%	2.5
L-Phenylalanine	Phe	$^{13}C_9$, 99%; ^{15}N, 99%	2.5
L-Proline	Pro	$^{13}C_5$, 99%; ^{15}N, 99%	2.5
L-Serine	Ser	$^{13}C_3$, 99%; ^{15}N, 99%	2.5
L-Threonine	Thr	$^{13}C_4$, 97-99%; ^{15}N, 97-99%	2.5
L-Tryptophan*	Trp	$^{13}C_{11}$, 99%; $^{15}N_2$, 99%	2.5
L-Tyrosine	Tyr	$^{13}C_9$, 99%; ^{15}N, 99%	2.5
L-Valine	Val	$^{13}C_5$, 99%; ^{15}N, 99%	2.5

**Compounds absent in MSK-A2.*

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

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Example Results

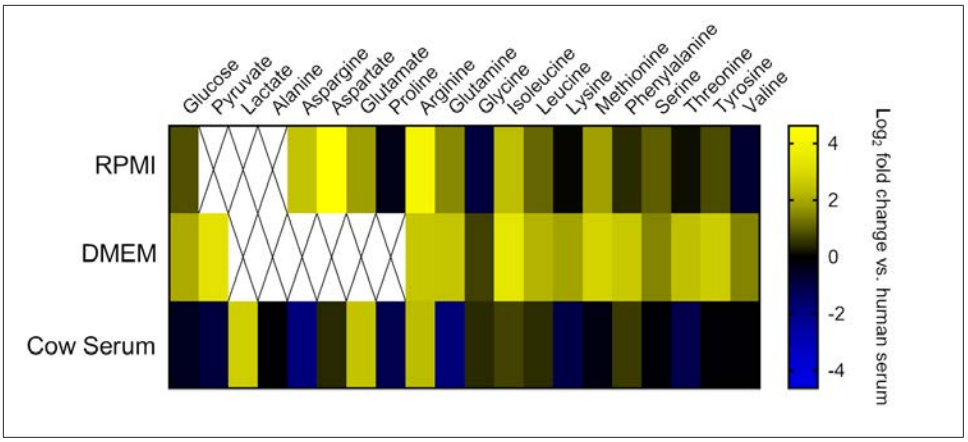

Figure. Application of the MSK-A2 mix to compare the quantitative profiles of cow serum and standard media (see **PMID: 28826492** for additional information).

Example References

Morley, S.A.; Ma, F.; Alazem, M.; et al. **2023**. Expression of malic enzyme reveals subcellular carbon partitioning for storage reserve production in soybeans. *New Phytol, in press*.

McNabney, D.W.G.; Mangal, V.; Kirkwood, A.E.; et al. **2023**. Phytoplankton metabolite profiles from two Lake Ontario areas of concern reveal differences associated with taxonomic community composition. *Sci Total Environ, 871,* 162042-162053.

Handzlik, M.K.; Gengatharan, J.M.; Frizzi, K.E.; et al. **2023**. Insulin-regulated serine and lipid metabolism drive peripheral neuropathy. *Nature, 614(7946),* 118-124.

Shen, J.L.; Doherty, J.; Allen, E.; et al. **2022**. Atg6 promotes organismal health by suppression of cell stress and inflammation. *Cell Death Differ, 29(11)*, 2275-2287.

Fuenzalida, K.; Leal-Witt, M.J.; Guerrero, P.; et al. **2021**. NTBC treatment monitoring in Chilean patients with tyrosinemia type 1 and its association with biochemical parameters and liver biomarkers. *J Clin Med, 10(24),* 5832-5845.

Gao, J.; Chung, T-S. **2021**. Membranes made from nonsolvent-thermally induced phase separation (N-TIPS) for decellularization of blood in dry plasma spot (DPS) applications. *Chem Eng Sci, 229. doi.org/10.1016/j.ces.2020.116010.*

van Gastel, N.; Spinelli, J.B.; Sharda, A.; et al. **2020**. Induction of a timed metabolic collapse to overcome cancer chemoresistance. *Cell Metab, 32(3),* 391-403.

Røst, L.M.; Thorfinnsdottir, L.B.; Kumar, K.; et al. **2020**. Absolute quantification of the central carbon metabolome in eight commonly applied prokaryotic and eukaryotic model systems. *Metabolites, 10(2),* 74.

Alcock, R.D.; Shaw, G.C.; Tee, N.; et al. **2019**. Plasma amino acid concentrations after the ingestion of dairy and collagen proteins, in healthy active males. *Front Nutr, 6,* 163.

Sullivan, M.R; Danai, L.V.; Lewis, C.A.; et al. **2019**. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *Elife, 8,* e44235.

Chen, W.W.; Freinkman, E.; Sabatini, D.M. **2017**. Rapid immunopurification of mitochondria for metabolite profiling and absolute quantification of matrix metabolites. *Nat Protoc, 12(10),* 2215-2231.

Muir, A.; Danai, L.V.; Gui, D.Y.; et al. **2017**. Environmental cystine drives glutamine anaplerosis and sensitizes cancer cells to glutaminase inhibition. *Elife, 6,* e27713.

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

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MSK-NCAA Mix

Composition

Reconstituting the dried-down NCAA mix with 1 mL solvent (e.g., 1:1 v/v methanol:water) results in 2.5 mM concentrations for each compound.

Compound	Abbrev.	Label and Enrichment
β-Alanine	β-Ala	$^{13}C_3$, 98%; ^{15}N, 96-99%
L-Azidohomoalanine·HCl	hAHA	1,2,3,4-$^{13}C_4$, 99%; 2,4-$^{15}N_2$, 98%
L-Citrulline	Cit	1,2,3,4,5-$^{13}C_5$, 98%
L-Dihydroxyphenylalanine	DOPA	1-^{13}C, ring-$^{13}C_6$, 99%
L-Homoarginine·HCl	Harg	$^{13}C_7$, 98%; $^{15}N_4$, 98%
L-Ornithine·HCl	Orn	$^{13}C_5$, 98%
Sarcosine·HCl	Sar	$^{13}C_3$, 99%; ^{15}N, 98%

"I use several of CIL's metabolomics mixes in my LC-MS analysis. They make quantitative metabolomic work convenient with a single internal standard mix spike and provide the corresponding unlabeled mix for absolute quantitation. The ready mixes save time from the tedious task of making up individual solutions of each analyte for quantitation. I find the different mixes applicable to a variety of analyses in complicated matrices that provide metabolic insight to my studies."

– Andrew Downey
Senior Scientist, Axcella Health Inc. (USA)

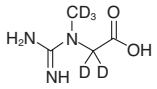
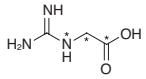
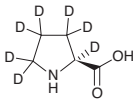
Usage Specifications

Mix Type	MSK-A2	MSK-CAA	MSK-NCAA
Form	1.2 mL solution	dried down	
Before reconstitution:			
Storage	-5 to 5°C; protect from light		
Recommended retest	2 years from date of manufacture		
Upon reconstitution:			
Storage	N/A	-5 to 5°C; protect from light	
Recommended retest	N/A	4 weeks	

NSK-AA3 Mix

Composition

Reconstituting the AA3 mix in 1 mL of solvent (e.g., 50% acetonitrile) will produce the tabulated concentrations below. **Note**: NSK-AA3-10X has 10× the specified concentrations.

Standard (Abbreviation)	Label and Enrichment	MW (Da)	Conc. (µM)	Structure
Creatine (Cre)	*N*-Methyl-D_3; glycine-2,2-D_2, 99%	154.18	500	
Guanidinoacetic acid (GAA)	1,2-$^{13}C_2$, 97-99%; 3-^{15}N, 97-99% (CP 97%)	120.09	50	
L-Proline (Pro)	D_7, 97-98%	122.17	500	

Usage Specifications

Criteria	Recommendation		
Before reconstitution:		*After reconstitution:**	
Storage	-5 to 5°C; protect from light	Storage	-20°C
Recommended retest	2 years from date of manufacture	Recommended retest	3 months

**Represents minimum stability period when AA3 mix is reconstituted with 1:1 purified water:acetonitrile.*

Companion unlabeled standard mixes and kits may be available; please inquire.

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NSK-BCAA Mix

Composition

Reconstituting the BCAA mix in 1 mL of solvent (e.g., 0.1 M HCl) will produce the tabulated concentrations below.

Standard (Abbreviation)	Label and Enrichment	Conc. (µM)	Q1 *m/z*	Q3 *m/z*
L-Allo-isoleucine (Alle)	$^{13}C_6$, 97-99%; ^{15}N, 97-99%	400	139.2	92.2
L-Isoleucine (Ile)	D_{10}, 98%	400	142.2	96.2
L-Leucine (Leu)	5,5,5-D_3, 99%	400	135.2	89.2
L-Valine (Val)	$^{13}C_5$, 99%; ^{15}N, 99%	400	124.1	77.1

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	≤25°C; protect from light and moisture
Recommended retest	5 years from date of manufacture
*After reconstitution:**	
Storage	4°C
Recommended retest	5 weeks

**Represents minimum stability period when the BCAA mix is reconstituted with 100% water.*

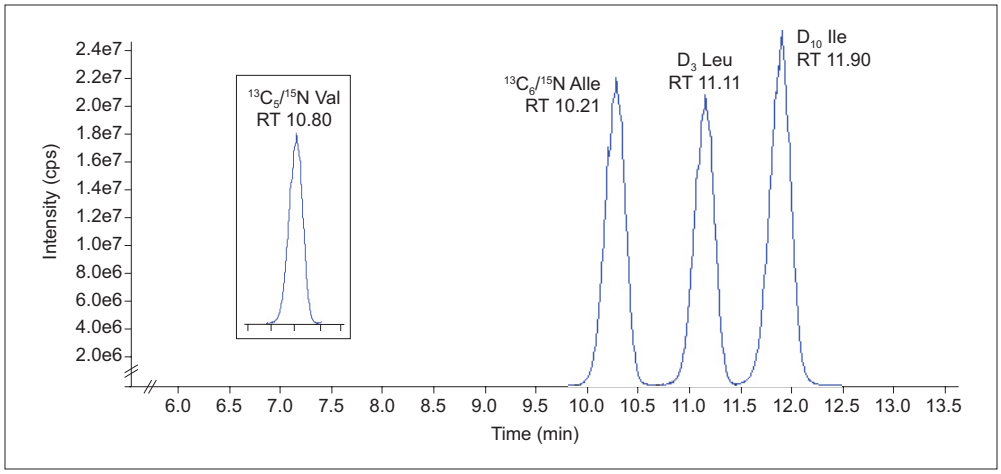

Figure. Representative XICs of the BCAA mix metabolites measured by RPLC-MRM/MS (ESI+, 5500+ QqQ). Separation of the isobaric metabolites is shown in the main plot, with Val in the inset. Displayed are the $[M+H]^+$ ions (see **Table** for precursor and product ion values).

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

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NSK-A Mix

Composition

Reconstituting a given NSK-A vial's contents in 1 mL of high-purity solvent (1:1 water:methanol recommended) will produce the tabulated concentrations below. To facilitate complete dissolution, it is recommended to vortex manually for 1 minute then auto-vortex for a minimum of 30 seconds. **Note:** A combined set of NSK-A and NSK-B – the carnitine/acylcarnitine reference standard mix – is also available (NSK-AB).

Compound	Abbrev.	Label and Enrichment	Conc. (µM)
L-Alanine	Ala	2,3,3,3-D_4, 98%	500
L-Arginine·HCl	Arg	5-^{13}C, 99%; 4,4,5,5-D_4, 95%	500
L-Aspartatic acid	Asp	2,3,3-D_3, 98%	500
L-Citrulline	Cit	5,5-D_2, 98%	500
DL-Glutamic acid	Glu	2,4,4-D_3, 98%	500
Glycine	Gly	2-^{13}C, 99%; ^{15}N, 98%	2500
L-Leucine	Leu	5,5,5-D_3, 99%	500
L-Methionine	Met	methyl-D_3, 98%	500
L-Ornithine·HCl*	Orn	5,5-D_2, 98%	500
L-Phenylalanine	Phe	ring-$^{13}C_6$, 99%	500
L-Tyrosine	Tyr	ring-$^{13}C_6$, 99%	500
L-Valine	Val	D_8, 98%	500

**NSK-A1 contains Orn 3,3,4,4,5,5,-D_6, 98% instead of 5,5-D_2, 98%. The remaining components and concentrations are equivalent.*

Usage Specifications

Criteria	Recommendation
No. of uses	960 samples/vial
Before reconstitution:	
Storage	≤25°C; protect from light
Recommended retest	4 years from date of manufacture
Upon reconstitution:	
Storage	5±3°C in a tightly sealed vial **Note:** Storing the sealed vial in a second sealed container helps maintain the integrity of the solution.
Recommended retest	4 weeks

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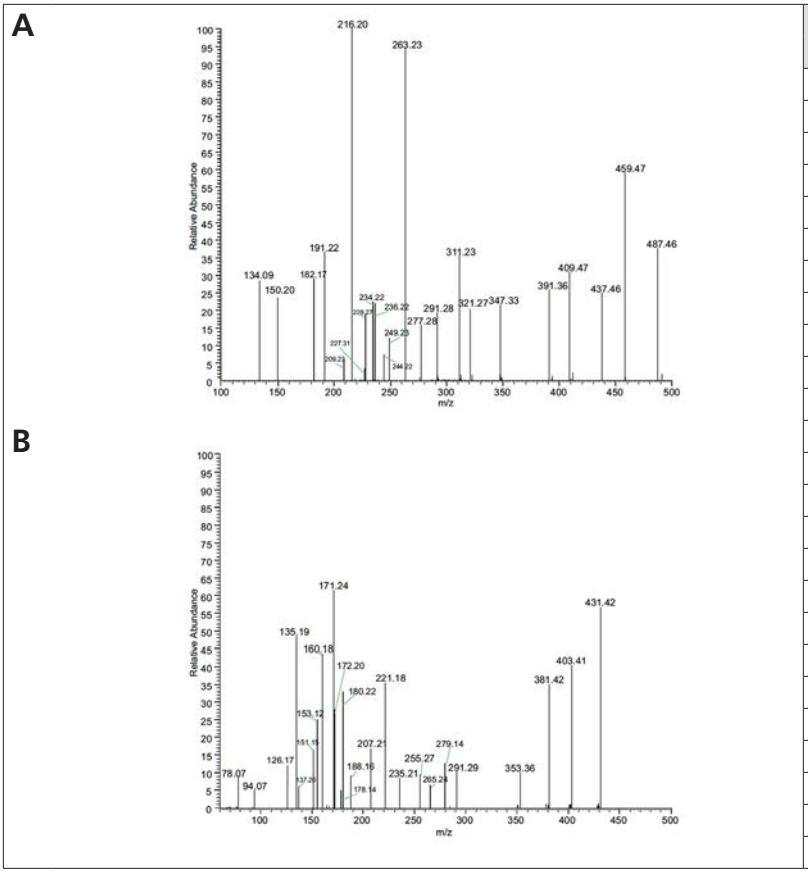
Example Results



Standard	Precursor *m/z*	
	Derivatized	Nonderivatized
Ala (D_4)	150.20	94.07
Arg ($^{13}C/D_4$)	236.22	180.22
Asp (D_3)	249.23	137.20
Cit (D_2)	234.22	178.14
Glu (D_3)	263.23	151.15
Gly ($^{13}C/^{15}N$)	134.09	78.07
Leu (D_3)	191.22	135.19
Met (D_3)	209.23	153.12
Orn (D_2)	191.22	135.19
Phe ($^{13}C_6$)	228.27	172.20
Tyr ($^{13}C_6$)	244.22	188.16
Val (D_8)	182.17	126.17
SUAC ($^{13}C_5$)	216.20	160.18
C0 (D_9)	227.31	171.24
C2 (D_3)	263.23	207.21
C3 (D_3)	277.28	221.18
C4 (D_3)	291.28	235.21
C5 (D_9)	311.23	255.27
C5-DC (D_3)	391.36	279.14
C5-OH (D_3)	321.27	265.24
C8 (D_3)	347.33	291.29
C12 (D_9)	409.47	353.36
C14 (D_9)	437.46	381.42
C16 (D_3)	459.47	403.41
C18 (D_3)	487.46	431.42

Figure. Full scan MS1 spectra of the DBS internal standards, with the derivatized standards shown in **A** and the nonderivatized in **B**. The standard mixture consists of stable isotope-labeled amino acids (NSK-A and -T) and carnitine/acylcarnitines (NSK-B and NSK-B-G). Please refer to Thermo Scientific technical note #73398 for method and application details.

Example References

Li, S.; Huang, B.; Liu, M; et al. **2022**. The association between leucine and diabetic retinopathy in different genders: a cross-sectional study in Chinese patients with type 2 diabetes. *Front Endocrinol, 13,* 806807-806815.

Habib, A.; Azize, N.A.A.; Rahman, S.A.; et al. **2021**. Novel mutations associated with carnitine-acylcarnitine translocase and carnitine palmitoyl transferase 2 deficiencies in Malaysia. *Clin Biochem, 98,* 48-53.

Zhang, S.; Li, X.; Luo, H.; et al. **2020**. Role of aromatic amino acids in pathogeneses of diabetic nephropathy in Chinese patients with type 2 diabetes. *J Diabetes Complications, 34(10),* 107667.

Wang, L.; Liu, D.; Shen, H.; et al. **2020**. Analysis of amino acid patterns with nutrition regimens in preterm infants with extrauterine growth retardation. *Front Pediatr, 8,* 184.

Brennenstuhl, H.; Kohlmüller, D.; Gramer, G.; et al. **2020**. High throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency by analysis of concentrations of 3-*O*-methyldopa from dried blood spots. *J Inherit Metab Dis, 43(3)*, 602-610.

Cao, Y-F.; Li , J.; Zhang, Z; et al. **2019**. Plasma levels of amino acids related to urea cycle and risk of type 2 diabetes mellitus in Chinese adults. *Front Endocrinol, 10,* 50.

Jing, F.; Hu, X.; Cao, Y.; et al. **2018**. Discriminating gastric cancer and gastric ulcer using human plasma amino acid metabolic profile. *UBMB Life, 70(6),* 553-562.

Technical Note

Xie, X.; Kozak, M. **2020**. Simultaneous analysis of amino acids, acylcarnitines, and succinylacetone in dried blood spots for research using nonderivatized and derivatized methods. (Thermo Scientific technical note #73398)

"We have been using CIL's NSK-A and NSK-B reference standards in our LC-MS/MS method for newbom screening tests since 2001. From that time more than 4,000,000 newborns have been screened. The products maintain good stability after dissolution and the high analysis repeatability enabled us to stabilize their use as internal standards. We appreciate the high-quality products, timely deliveries, and excellent customer relations."

– Mariusz Oltarzewski

Head of Department of Screening Tests and Metabolic Diagnostics, Institute of Mother and Child (Poland)

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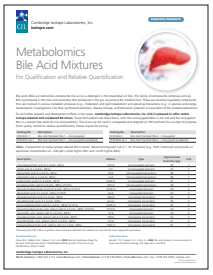
Bile Acid Mixes



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Bile acids (BAs) are steroid-like compounds that act as a detergent in the breakdown of fats. This family of compounds comprises primary BAs (synthesized in the liver) and secondary BAs (produced in the gut by bacteria). These are essential regulatory compounds that are involved in various metabolic processes (e.g., cholesterol and lipid metabolism) and signaling interactions (e.g., in glucose and energy homeostasis). Investigations into their synthesis/metabolism, disease linkage, and biomarker potential are examples of the type of research studies being undertaken. To aid further research and development efforts in this space, CIL has formulated stable isotope-labeled (and unlabeled) BA mixes. These dried-down mixes are constructed with the unconjugated BAs in one vial and the conjugated BAs in a second.

Overview

Catalog No.	Description	No. of Metabolites	Unit Size
MSK-BA1	Bile Acid Standard Mix 1 – Unconjugated	6	1 vial
MSK-BA2	Bile Acid Standard Mix 2 – Conjugated	10	1 vial

Compositions

Reconstituting a given BA mix in 1 mL of solvent (e.g., 1:1 v/v methanol:water) yields a concentration of ~100 µM.

Unconjugated BA Mix (MSK-BA1)				
Compound	**Abbrev.**	**Type of BA**	**Label and Enrichment**	**~Qty. (µg)**
Chenodeoxycholic acid	CDCA	Primary	2,2,4,4-D_4, 98%	40
Cholic acid	CA	Primary	2,2,4,4-D_4, 98%	41
Deoxycholic acid	DCA	Secondary	2,2,4,4-D_4, 98%	40
Lithocholic acid	LCA	Secondary	2,2,4,4-D_4, 98%	38
β-Muricholic acid	β-MCA	Primary	2,2,3,4,4-D_5, 99%	41
Ursodeoxycholic acid	UDCA	Secondary	2,2,4,4-D_4, 98% (CP 95%)	40

Conjugated BA Mix (MSK-BA2)				
Compound	**Abbrev.**	**Type of BA**	**Label and Enrichment**	**~Qty. (µg)**
Glycochenodeoxycholic acid	GCDCA	Primary	2,2,4,4-D_4, 98% (CP 97%)	45
Glycocholic acid	GCA	Primary	2,2,4,4-D_4, 98% (CP 96%)	47
Glycodeoxycholic acid	GDCA	Secondary	2,2,4,4-D_4, 98%	45
Glycolithocholic acid	GLCA	Secondary	2,2,4,4-D_4, 98%	44
Glycoursodeoxycholic acid	GUDCA	Secondary	2,2,4,4-D_4, 98% (CP 97%)	45
Taurochenodeoxycholic acid, sodium salt	TCDCA	Primary	2,2,4,4-D_4, 98% (CP 97%)	53
Taurocholic acid, sodium salt	TCA	Primary	2,2,4,4-D_4, 98%	54
Taurodeoxycholic acid, sodium salt	TDCA	Secondary	2,2,4,4-D_4, 98%	53
Taurolithocholic acid, sodium salt	TLCA	Secondary	2,2,4,4-D_4, 98%	51
Tauroursodeoxycholic acid, sodium salt	TUDCA	Secondary	2,2,4,4-D_4, 98%	53

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	-20°C; protect from light
Recommended retest	2 years from date of manufacture
After reconstitution:	
Storage	4°C
Recommended retest	4 weeks

Example Reference

Foley, M.H.; Walker, M.E.; Stewart, A.K.; et al. **2023**. Bile salt hydrolases shape the bile acid landscape and restrict *Clostridioides difficile* growth in the murine gut. *Nat Microbiol, 8(4),* 611-628.

Application Note

Horvath, T.D.; Engevik, A.C.; Percy, A.J. **2022**. Bile acid analysis in mouse samples to study liver cholestasis etiology. (CIL application note #52)

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results

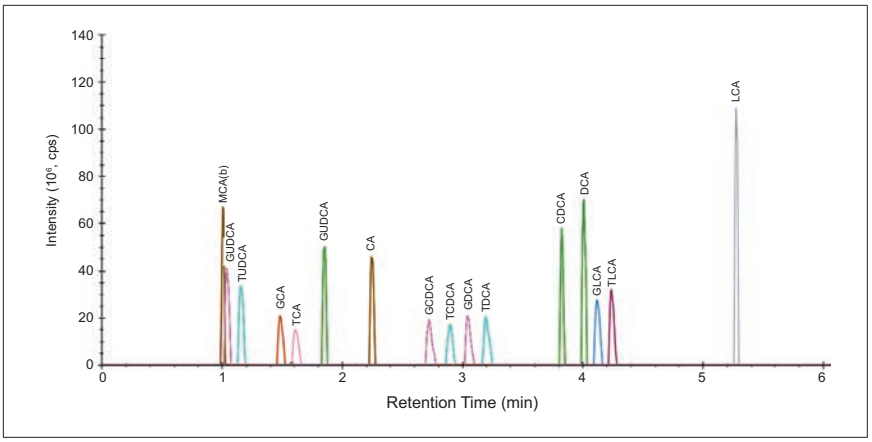


Figure. Chromatographic overview of a combined BA mix (6 unconjugates and 10 conjugates) analysis measured by RPLC-MS (Orbitrap ID-X, negative ESI). The *m/z* displayed are the $[M-H]^-$ ions. Procedurally, the labeled/unlabeled BA mixes were reconstituted in 50% methanol before aliquot mixing and MS1 measurement. **Note:** The labeled and unlabeled BAs coeluted.

"The materials that Cambridge Isotope Laboratories (CIL) supply are always of the highest quality in terms of chemical and isotopic purity. Recently, we have embarked on two new major research areas involving the analyses of bile acids (BAs) and per- and polyfluorinated alkylsubstances (PFAS). The standards/mixes from CIL that enable these, and other, projects are precisely what we have come to expect – perfection!"

– David C. Muddiman, PhD
Jacob and Betty Belin Distinguished Professor, Department of Chemistry, North Carolina State University
Director of Molecular Education, Technology, and Research Innovation Center (METRIC)

Carnitine/Acylcarnitine Mixes and Sets

Carnitine and acylcarnitines play an essential role in fatty acid metabolism. Metabolism disorders of fatty acid oxidation and several organic acidurias impose major clinical manifestations (e.g., hypoketotic hypoglycemia, skeletal myopathy, liver disease, and/or failure). These are largely attributed to enzymatic deficiencies and can be monitored through carnitine/acylcarnitine measurement. To aid MS/MS screening studies, CIL has formulated stable isotope-labeled (and unlabeled) standard carnitine/acylcarnitine mixes.

Click on the thumbnail or visit **isotope.com/applications/** for more information.

Overview

Catalog No.	Description	No. of Metabolites	Unit Size
NSK-B	Carnitine/Acylcarnitine Standard Mix Set B	8	1 vial, 10 vials
NSK-B-G1	Carnitine/Acylcarnitine Standard Mix Supplement to NSK-B	5	1 vial, 10 vials
NSK-AB	Standard Mix Sets A and B	12 (in NSK-A), 8 (in NSK-B)	2 × 10 vials

"In clinical chemistry-based applications of mass spectrometry, the first lesson the laboratory learns is the requisite nature of stable isotope-enriched standards for quantification of metabolites in biological fluids. In newborn screening of amino acids and acylcarnitines, Cambridge Isotope Laboratories, Inc., set the standard for quantification of these metabolites in dried blood spots. As research and development of the newborn screening analysis by mass spectrometry progressed, it was clear that a half dozen isotope-labeled internal standards would not be adequate for the analysis of an amino acid and acylcarnitine profile, together comprising a range of 500 separate mass units and more than 30 important metabolites, most of which require accurate quantification. When screening began to expand beyond research, it was clear that weighing out small quantities of individual standards would reduce accuracy and introduce unnecessary error. Therefore, together, we set out to develop sets of standards for amino acids and acylcarnitine analysis that would enable quantification. We started this development more than 20 years ago adding, changing and improving these standards. CIL, together with the early developers of tandem mass spectrometry-based newborn screening, set the standard by which all other laboratories follow. CIL's commitment to supporting the metabolic and newborn screening community is exceptional. It is our good fortune in the clinical chemistry and mass spectrometry community to have CIL as part of our laboratory solutions."

– Donald H. Chace, PhD MSFS FACB
Medolac Laboratories (USA)

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Compositions

Reconstituting a given NSK-B or NSK-B-G1 vial's contents in 1 mL of highly pure methanol will produce the tabulated concentrations below. To facilitate complete dissolution, it is recommended to vortex manually for 1 minute then auto-vortex for a minimum of 30 seconds. **Note:** A combined set of NSK-B and NSK-A – the amino acid reference standard mix – is also available (NSK-AB).

NSK-B			
Compound	Abbrev.	Label and Enrichment	Conc. (µM)
L-Carnitine	C0	trimethyl-D_9, 98%	152
O-Acetyl-L-carnitine·HCl	C2	*N*-methyl-D_3, 98%	38
O-Propionyl-L-carnitine·HCl	C3	*N*-methyl-D_3, 98%	7.6
O-Butyryl-L-carnitine·HCl	C4	*N*-methyl-D_3, 98%	7.6
O-Isovaleryl-L-carnitine·HCl	C5	*N,N,N*-trimethyl-D_9, 98%	7.6
O-Octanoyl-L-carnitine·HCl	C8	*N*-methyl-D_3, 98%	7.6
O-Myristoyl-L-carnitine·HCl	C14	*N,N,N*-trimethyl-D_9, 98%	7.6
O-Palmitoyl-L-carnitine·HCl	C16	*N*-methyl-D_3, 98%	15.2

NSK-B-G1			
Compound	Abbrev.	Label and Enrichment	Conc. (µM)
O-Glutaryl-L-carnitine·ClO_4	C5-DC	*N*-methyl-D_3, 98% (CP 97%)	15.2
3-Hydroxyisovaleryl-L-carnitine·ClO_4	C5-OH	*N*-methyl-D_3, 98%	7.6
O-Dodecanoyl-L-carnitine·HCl	C12	*N,N,N*-trimethyl-D_9, 98%	7.6
O-3-DL-Hydroxypalmitoyl-L-carnitine·ClO_4	C16-OH	*N*-methyl-D_3, 98%	15.2
O-Octadecanoyl-L-carnitine·HCl	C18	*N*-methyl-D_3, 98%	15.2

Usage Specifications

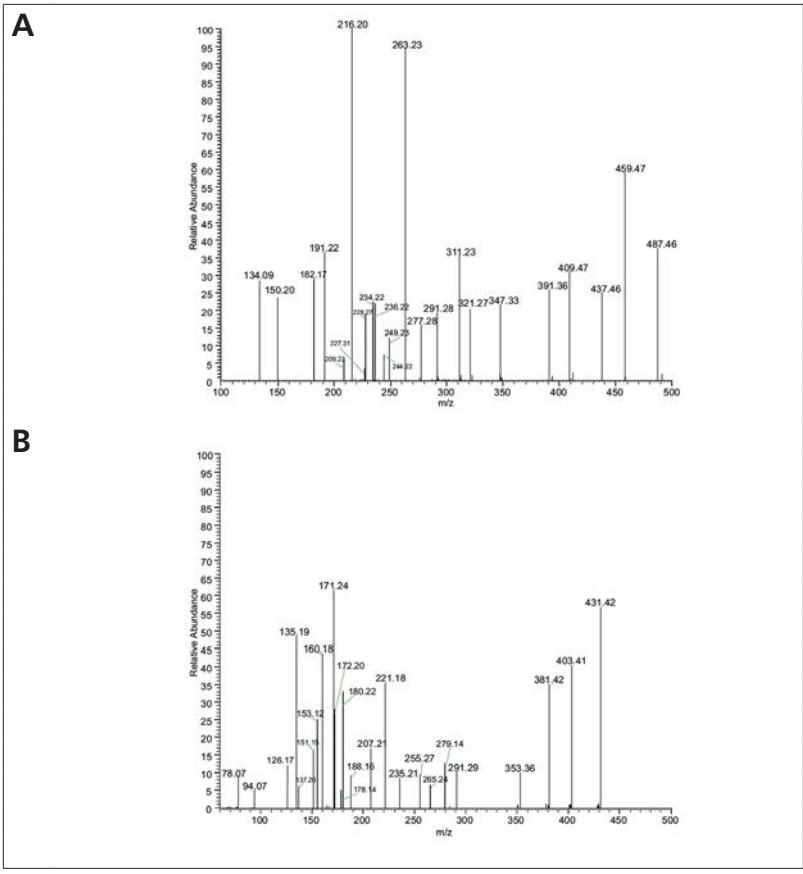
Mix Type	NSK-B	NSK-B-G1
No. of uses	960 samples/vial	
Before reconstitution:		
Storage	≤8°C; protect from light	
Recommended retest	1 year from date of manufacture	2 years from date of manufacture
After reconstitution:		
Storage	5±3°C in a tightly sealed vial	5±3°C in a tightly sealed vial
	Note: Storing the sealed vial in a second sealed container helps maintain the integrity of the solution	
Recommended retest	4 weeks	

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results



Standard	Precursor *m/z*	
	Derivatized	Nonderivatized
Ala (D_4)	150.20	94.07
Arg ($^{13}C/D_4$)	236.22	180.22
Asp (D_3)	249.23	137.20
Cit (D_2)	234.22	178.14
Glu (D_3)	263.23	151.15
Gly ($^{13}C/^{15}N$)	134.09	78.07
Leu (D_3)	191.22	135.19
Met (D_3)	209.23	153.12
Orn (D_2)	191.22	135.19
Phe ($^{13}C_6$)	228.27	172.20
Tyr ($^{13}C_6$)	244.22	188.16
Val (D_8)	182.17	126.17
SUAC ($^{13}C_5$)	216.20	160.18
C0 (D_9)	227.31	171.24
C2 (D_3)	263.23	207.21
C3 (D_3)	277.28	221.18
C4 (D_3)	291.28	235.21
C5 (D_9)	311.23	255.27
C5-DC (D_3)	391.36	279.14
C5-OH (D_3)	321.27	265.24
C8 (D_3)	347.33	291.29
C12 (D_9)	409.47	353.36
C14 (D_9)	437.46	381.42
C16 (D_3)	459.47	403.41
C18 (D_3)	487.46	431.42

Figure. Full scan MS1 spectra of the DBS internal standards, with the derivatized standards shown in **A** and the nonderivatized in **B**. The standard mixture consists of stable isotope-labeled amino acids (NSK-A and -T) and carnitine/acylcarnitines (NSK-B and NSK-B-G). Please refer to Thermo Scientific technical note #73398 for method and application details.

Example References

Mak, J.; Peng, G.; Le, A.; et al. **2023**. Validation of a targeted metabolomics panel for improved second-tier newborn screening. *J Inherit Metab Dis, 46(2),* 194-205.

Daas, S.; Salah, N.A.; Anikster, Y.; et al. **2023**. Addition of galactose-1-phosphate measurement enhances newborn screening for classical galactosemia. *J Inherit Metab Dis, 46(2),* 232-242.

Habib, A.; Azize, N.A.A.; Rahman, S.A.; et al. **2021**. Novel mutations associated with carnitine-acylcarnitine translocase and carnitine palmitoyl transferase 2 deficiencies in Malaysia. *Clin Biochem, 98,* 48-53.

Brailova, M.; Clerfond, G.; Trésorier, R.; et al. **2020**. Inherited metabolic diseases and cardiac pathology in adults: diagnosis and prevalence in a cardiometabo study. *J Clin Med, 9(3),* 694-707.

Varkey, A.; Devi, S.; Mukhopadhyay, A.; et al. **2020**. Metabolome and microbiome alterations related to short-term feeding of a micronutrient-fortified, high-quality legume protein-based food product to stunted school age children: a randomized controlled pilot trial. *Clin Nutr, 39(11),* 3251-3261.

Brennenstuhl, H.; Kohlmüller, D.; Gramer, G.; et al. **2020**. High throughput newborn screening for aromatic ι-amino-acid decarboxylase deficiency by analysis of concentrations of 3-*O*-methyldopa from dried blood spots. *J Inherit Metab Dis, 43(3)*, 602-610.

Cao, B.; Wang, D.; Pan, Z.; et al. **2019**. Characterizing acylcarnitine biosignatures for schizophrenia: a longitudinal pre- and post-treatment study. *Transl Psychiatry, 9(1),* 19.

Puskarich, M.A.; Evans, C.R.; Karnovsky, A.; et al. **2018**. Septic shock nonsurvivors have persistently elevated acylcarnitines following carnitine supplementation. *Shock, 49(4),* 412-419.

Technical Note

Xie, X.; Kozak, M. **2020**. Simultaneous analysis of amino acids, acylcarnitines, and succinylacetone in dried blood spots for research using nonderivatized and derivatized methods. (Thermo Scientific technical note #73398)

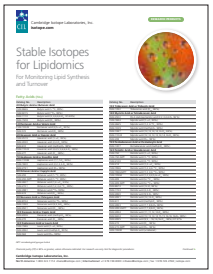
Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Fatty Acid/Lipid Mixes

Fatty acids and lipids are important biological compounds that are essential to the regulation and control of cellular functions and metabolic pathways. These biomolecules are also tied to the energetic balance of an organism. Their qualitative/quantitative analysis has emerged to better understand the underlying pathophysiology, as well as to identify new biomarkers or diagnose existing ones. To aid such initiatives, CIL offers an array of mixed fatty acids and triglycerides. These dried-down mixes are uniformly labeled and available in different forms (i.e., free acid, methyl ester) as research-grade material.



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Overview

Catalog No.	Description	No. of Metabolites	Unit Size
CLM-8455	Fatty Acid Mix (U-^{13}C, 98%)	5-10	0.25 g, 1 g
DLM-8572	Fatty Acid Mix (U-D, 96-98%)	5-10	Please inquire
CDLM-8376	Fatty Acid Mix (U-^{13}C, 98%; U-D, 97%)	5-10	0.25 g, 1 g
CLM-8381	Fatty Acid, Methyl Ester Mix (U-^{13}C, 98%) (unlabeled terminal ester) CP 95%	5-10	0.25 g, 1 g
DLM-2497	Fatty Acid, Methyl Ester Mix (U-D, 96-98%)	5-10	Please inquire
DLM-8375	Triglyceride Mix (U-D, 97%)	5-10	0.25 g, 1 g

Compositions

The mixed fatty acid and triglyceride products are derived from the *Agmenelum quadriplicatum* algal source. Please inquire for details as the mix compositions can vary by lot.

Usage Specifications

Mix Type	Catalog No.	Before Reconstitution	
		Storage	Recommended Retest
Fatty acids	CLM-8455 DLM-8572 CDLM-8376	-5 to 5°C; protect from light	2 years
Fatty acid, methyl esters	CLM-8381 DLM-2497	-5 to 5°C; protect from light	5 years
Triglycerides	DLM-8375	-5 to 5°C; protect from light	5 years

Example References

Chen, J.; Zou, L.; Lu, G.; et al. **2022**. PFKP alleviates glucose starvation-induced metabolic stress in lung cancer cells via AMPK-ACC2 dependent fatty acid oxidation. *Cell Discov, 8(1),* 52-67.

Hernandez-Saavedra, D.; Sanders, L.; Freeman, S.; et al. **2020**. Stable isotope metabolomics of pulmonary artery smooth muscle and endothelial cells in pulmonary hypertension and with TGF-beta treatment. *Sci Rep, 10(1),* 413-426.

He, C.; Weston, T.A.; Jung, R.S.; et al. **2018**. NanoSIMS analysis of intravascular lipolysis and lipid movement across capillaries and into cardiomyocytes. *Cell Metab, 27(5),* 1055-1066.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Nucleic Acid Sets

Nucleic acids are necessary biomolecules of living systems, being fundamentally important to a multitude of cellular processes. Its basic building blocks are nucleobases (e.g., adenine, cytosine), nucleosides (e.g., adenosine, guanosine), and nucleotides (e.g., ATP, CDP). The qualification/quantification of these compounds is conducted for a number of purposes. This includes the screening of metabolic errors and evaluating the efficacy of drug treatments (be it anticancer, antiviral, or immunosuppressive), among other target areas. CIL offers a variety of stable isotope-labeled nucleic acid sets to help advance MS- and/or NMR-based research. The sets consist of deoxyribonucleoside monophosphates (dNMPs), deoxyribonucleoside triphosphates (dNTPs), and ribonucleoside triphosphate (rNTPs) in different unit configurations.

Overview

Catalog No.	Description	No. of Metabolites	Unit Size
CNLM-7871-SL	Set of 4 2′-deoxyribonucleoside 5′-monophosphates, lithium salt (^{13}C, 98%; ^{15}N, 98%) (in solution) CP 95%	4	10 mg
NLM-7512-SL	Set of 4 2′-deoxyribonucleoside 5′-triphosphates, lithium salt (^{15}N, 98%) (in solution) CP 95%	4	10 mg, 50 mg
DLM-7511-SL	Set of 4 2′-deoxyribonucleoside 5′-triphosphates, lithium salt (D, 98%) (in solution) CP 95%	4	10 mg, 50 mg
CNLM-7513-SL	Set of 4 2′-deoxyribonucleoside 5′-triphosphates, lithium salt (^{13}C, 98%; ^{15}N, 98%) (in solution) CP 95%	4	10 mg, 50 mg
NLM-7519-SL	Set of 4 ribonucleoside 5′-triphosphates, lithium salt (^{15}N, 98%) (in solution) CP 95%	4	10 mg, 50 mg
DLM-7518-SL	Set of 4 ribonucleoside 5′-triphosphates, lithium salt (D, 98%) (in solution) CP 95%	4	10 mg, 50 mg
CNLM-7503-SL	Set of 4 ribonucleoside 5′-triphosphates, lithium salt (^{13}C, 98%; ^{15}N, 98%) (in solution) CP 95%	4	10 mg, 50 mg
NLM-7519-CA	Set of 4 ribonucleoside 5′-triphosphates, ammonium salt (^{15}N; 98%) (in solution) CP 90%	4	4 × 20 µmol 4 × 100 µmol
DLM-7518-CA	Set of 4 ribonucleoside 5′-triphosphates, ammonium salt (D, 98%) (in solution) CP 95%	4	4 × 20 µmol 4 × 50 µmol 4 × 100 µmol
CNLM-7503-CA	Set of 4 ribonucleoside 5′-triphosphates, ammonium salt (^{13}C, 98%; ^{15}N, 98%) (in solution) CP 95%	4	4 × 20 µmol 4 × 50 µmol 4 × 100 µmol

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

dNMP

Composition and Specification

Catalog No.	dNMP	Conc. (mM)
CNLM-7871-SL	AMP, CMP, GMP, TMP	80

- Supplied on dry ice as a solution of 5 mM Tris-HCl (pH 7.5) in water.
- Store below -20°C; protect from light.

dNTPs

Compositions and Specifications

Catalog No.	dNTP	Conc. (mM)
NLM-7512-SL	dATP, dCTP, dGTP, dTTP	50-100
DLM-7511-SL		
CNLM-7513-SL		

- Supplied on dry ice as a solution of 5 mM Tris-HCl (pH 7.5) in water (for NLM-7512-SL and CNLM-7513-SL) or D_2O (for DLM-7511-SL)
- Store below -20°C; protect from light.

Example References

Liu, B.; Winkler, F.; Herde, M.; et al. **2019**. A link between deoxyribonucleotide metabolites and embryonic cell-cycle control. *Curr Biol, 29(7),* 1187-1192.

Song, Y.; Marmion, R.A.; Park, J.O.; et al. **2017**. Dynamic control of dNTP synthesis in early embryos. *Dev Cell, 42(3),* 301-308.

rNTPs

Compositions and Specifications

Catalog No.	rNTP	Conc. (mM)
NLM-7519-SL	rATP, rCTP, rGTP, rTTP	50-100
DLM-7518-SL		
CNLM-7503-SL		

- Supplied on dry ice as a solution of 5 mM Tris-HCl (pH 7.5) in water (for NLM-7519-SL and CNLM-7503-SL) or D_2O (for DLM-7518-SL)
- Store below -20°C; protect from light.

Catalog No.	rNTP	Conc. (mM)
NLM-7519-CA	rATP, rCTP, rGTP, rUTP	20, 50, and/or 100
DLM-7518-CA		
CNLM-7503-CA		

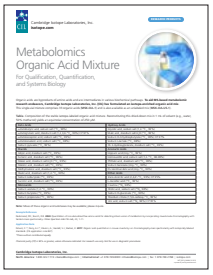
- Supplied on dry ice as a solution (e.g., 100 mM – contains 100 µmol of each rNTP in 1 mL water, pH ~7.5).
- Store at -20°C; protect from light. Recommended retest is 5 years from date of manufacture.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Organic Acid Mixes

Organic acids are byproducts of amino acids and are intermediates in various biochemical pathways. To aid MS-based metabolomic research endeavors, CIL has formulated an isotope-enriched organic acid mix. This single-vial mixture comprises 33 organic acids (**MSK-OA-1**) and is also available as an unlabeled mix (**MSK-OA-US-1**).



Click on the thumbnail or visit **isotope.com/applications/** for more information.

Overview

Catalog No.	Description	No. of Metabolites	Unit Size
MSK-OA	Organic Acid Mix	33	1 vial

Compositions

Composition of the stable isotope-labeled organic acid mixture. Reconstituting this dried-down mix in 1 mL of solvent (e.g., water, 1:1 v/v methanol:water) yields an equimolar concentration of 250 µM. **Note:** Mixes of these organic acid subclasses may be available; please inquire.

Keto Acids	Hydroxy Acids
α-Ketobutyric acid, sodium salt ($^{13}C_4$, 98%)	Glycolic acid, sodium salt (1,2-$^{13}C_2$, 99%)
α-Ketoglutaric acid, disodium salt (1,2,3,4-$^{13}C_4$, 99%) CP 97%	Malic acid, disodium salt·H_2O ($^{13}C_4$, 99%)
α-Ketoisocaproic acid, sodium salt ($^{13}C_6$, 99%)	Sodium D-3-hydroxybutyrate ($^{13}C_4$, 99%) CP 97%
α-Ketoisovaleric acid, sodium salt ($^{13}C_5$, 98%)	Sodium L-lactate ($^{13}C_3$, 98%)
Sodium pyruvate ($^{13}C_3$, 99%)	DL 2-Hydroxyglutarate, disodium salt ($^{13}C_5$, 99%)
Diacids	**Aromatic Acids**
Adipic acid, disodium salt ($^{13}C_6$, 99%)	Hippuric acid (ring-$^{13}C_6$, 99%)
Fumaric acid, disodium salt ($^{13}C_4$, 99%)	Homovanillic acid, sodium salt (1,2-$^{13}C_2$, 98-99%)
Maleic acid, disodium salt·H_2O ($^{13}C_4$, 99%)	Phthalic acid, disodium salt ($^{13}C_4$, 99%)
Malonic acid, disodium salt ($^{13}C_3$, 99%)	Sodium benzoate (ring-$^{13}C_6$, 99%)
Methylmalonic acid, disodium salt ($^{13}C_4$, 99%)	DL-Vanilmandelic acid (ring-$^{13}C_6$, 99%)
Oxalic acid, disodium salt (1,2-$^{13}C_2$, 99%)	**Other Acids**
Sodium isobutyrate ($^{13}C_4$, 99%)	*trans*-Aconitic acid (2,4,4'-$^{13}C_3$, 99%) CP 95%
Succinic acid, disodium salt ($^{13}C_4$, 99%)	L-Ascorbic acid ($^{13}C_6$, 99%)
Monoacids	Creatine ($^{15}N_3$, 98%)
Sodium acetate (1,2-$^{13}C_2$, 99%)	Orotic acid, sodium salt ($^{15}N_2$, 98%)
Sodium butyrate ($^{13}C_4$, 99%)	Sodium D-gluconate ($^{13}C_6$, 99%)
Sodium propionate ($^{13}C_3$, 99%)	Trisodium citrate (1,5,6-carboxy-$^{13}C_3$, 99%)
	Uric acid, sodium salt ($^{15}N_2$, 98%) CP 95%

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	-5 to 5°C; protect from light
Recommended retest	2 years from date of manufacture
After reconstitution:	
Storage	4°C
Recommended retest	4 weeks

Note: Extended mix stabilities have been demonstrated when solubilized in 50% methanol and stored as specified above.

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results

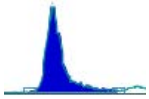
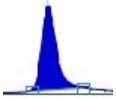
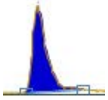
Butyrate ($^{13}C_4$, *m/z* 91.0586)	α-Ketoisovalerate ($^{13}C_5$, *m/z* 120.0568)	Hippuric acid ($^{13}C_6$, *m/z* 184.0709)	Orotate ($^{15}N_2$, *m/z* 157.0039)	Lactate ($^{13}C_3$, *m/z* 92.0345)
RT: 1.55  Time (min)	RT: 1.55  Time (min)	RT: 2.20  Time (min)	RT: 2.39  Time (min)	RT: 3.06  Time (min)
Creatine ($^{15}N_3$, *m/z* 133.0534)	Malonate ($^{13}C_2$, *m/z* 106.0138)	2-Hydroxyglutarate ($^{13}C_5$, *m/z* 152.0466)	Oxalate ($^{13}C_2$, *m/z* 90.9948)	*trans*-Aconitate ($^{13}C_3$, *m/z* 176.0193)
RT: 4.19  Time (min)	RT: 4.86  Time (min)	RT: 4.98  Time (min)	RT: 5.16  Time (min)	RT: 5.60  Time (min)

Figure. XICs of example metabolites measured in the labeled OA master mix by HILIC-MS (Orbitrap ID-X, negative ESI). Shown are a collection of OAs from a variety of subset classes. The *m/z* displayed are the $[M-H]^-$ ions. Procedurally, the dried-down master mix was reconstituted in 1 mL of 50% methanol then an aliquot 10-fold diluted before MS1 analysis.

Example Reference

DeArmond, P.D.; Bunch, D.R. **2022**. Quantitation of non-derivatized free amino acids for detecting inborn errors of metabolism by incorporating mixed-mode chromatography with tandem mass spectrometry. *J Mass Spectrom Adv Clin Lab, 25,* 1-11.

Application Note

Petucci, C.*; Percy, A.J.*; Zelenin, A.; Gardell, S.J.; Backiel, K. **2017**. Organic acid quantitation in mouse muscle by ion chromatography-mass spectrometry with isotopically labeled standards. (CIL application note #47)

**These authors contributed equally.*

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Other Mixes

A number of additional stable isotope-labeled mixes are also available at CIL (see overview). Included in this collection is a lysophosphatidylcholine (LPC or lysoPC) mix (NSK-LPC), a metabolomics standard mix (MSK-MET1), and MS/MS screening mixes for basic and translational MS research. The details of these mix offerings are outlined below.

Click on the thumbnails or visit **isotope.com/applications/** for more information.

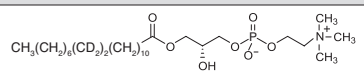
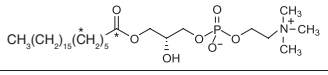
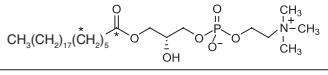
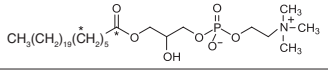
Overview

Catalog No.	Description	No. of Metabolites	Unit Size
NSK-LPC	Lysophosphatidylcholine Mix	4	1 vial
NSK-NI	Acid Sphingomyelinase Substrate and Internal Standard Mix	1 (S + IS)	1 vial
NSK-KR	Galactocerebrosidase Substrate and Internal Standard Mix	1 (S + IS)	1 vial
NSK-FA	α-Galactosidase Substrate and Internal Standard Mix	1 (S + IS)	1 vial
NSK-GA	Glucocerebrosidase Substrate and Internal Standard Mix	1 (S + IS)	1 vial
NSK-MP	α-L-Iduronidase Substrate and Internal Standard Mix	1 (S + IS)	1 vial
NSK-PO	Acid α-Glucosidase Substrate and Internal Standard Mix	1 (S + IS)	1 vial
MSK-MET1	Metabolomics Standard Mix 1	11	1 vial, 5 vials, 10 vials

NSK-LPC Mix

Composition

Reconstituting a given LysoPC mix (labeled, NSK-LPC; unlabeled, NSK-LPC-US) in 1 mL of high-purity solvent (e.g., 95:5 v/v methanol:water) will produce the concentrations specified below. To facilitate complete dissolution, it is recommended to sonicate the vial for 3 minutes then auto-vortex for a minimum of 10 seconds.

Standard (Abbreviation)	Label and Enrichment	Conc. (µM)	Structure
Lysophosphatidylcholine 20:0 (LysoPC 20:0)	eicosanoyl-12,12,13,13-D_4, 98%	5.5	
Lysophosphatidylcholine 22:0 (LysoPC 22:0)	docosanoyl-1,2,3,4,5,6-$^{13}C_6$, 99%	5.5	
Lysophosphatidylcholine 24:0 (LysoPC 24:0)	tetracosanoyl-1,2,3,4,5,6-$^{13}C_6$, 99%	5.5	
Lysophosphatidylcholine 26:0 (LysoPC 26:0)	hexacosanoyl-1,2,3,4,5,6-$^{13}C_6$, 99%	5.5	

Usage Specifications

Criteria	Recommendation		
No. of uses	~765 samples/vial		
Before reconstitution:		*After reconstitution:*	
Storage	≤20°C; protect from light	Storage	5±3°C or -20±5°C
Recommended retest	2 years from date of manufacture	Recommended retest	6 weeks

"Testing 1,200 to 2,000 newborn specimens every day is a challenging job. In order to ensure high data quality and proper efficacy of an MS-based screening assay (1st and 2nd tier), we utilize CIL's lyophilized LysoPC mix. This 4-plex cocktail helps reduce significantly our laboratory day-to-day variation and preparation time. We also use the LysoPC mixes (both unlabeled and isotope-labeled) in the tuning of our mass spectrometers and in determining response factors. This ensures that the concentrations rendered for each LysoPC is accurately obtained and can be cross-checked from platform-to-platform."

– Kuldeep Dhillon, Research Scientist Supervisor I
California Department of Public Health (USA)

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results

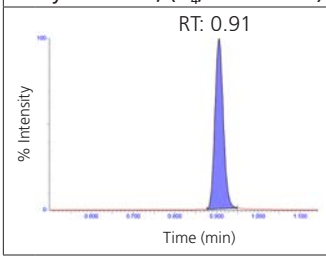
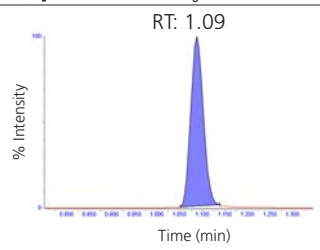
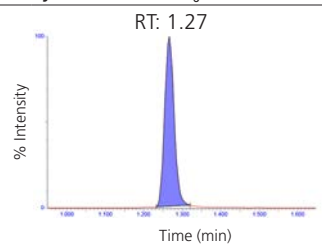
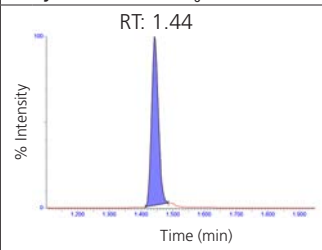
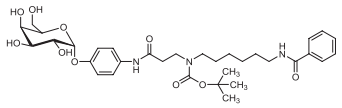
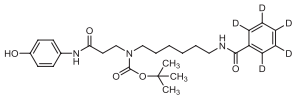
Lysophosphatidylcholine 20:0 LysoPC 20:0; (D_4, *m/z* 555.77)	Lysophosphatidylcholine 22:0 LysoPC 22:0; ($^{13}C_6$, *m/z* 585.75)	Lysophosphatidylcholine 24:0 LysoPC 24:0; ($^{13}C_6$, *m/z* 613.81)	Lysophosphatidylcholine 26:0 LysoPC 26:0; ($^{13}C_6$, *m/z* 641.85)
			

Figure. XICs of four labeled LysoPCs from the NSK-LPC mix measured by LC-MS/MS (positive ESI, Xevo-TQS). These serve as individual calibrators for their unlabeled counterparts in sample screening experiments. Data courtesy of CA Department of Public Health.

MS/MS Screening Mixes

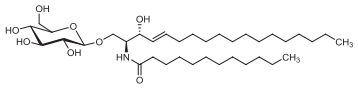
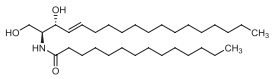
α-Galactosidase Substrate and Internal Standard (NSK-FA-1)

Each vial contains the following compounds at a molar ratio of 500:1.

Substrate	Internal Standard
(6-Benzoylamino-hexyl)-{2-[4-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenylcarbamoyl]-ethyl}-carbamic acid *t*-butyl ester	(6-D_5-Benzoylamino-hexyl)-[2-(4-hydroxy-phenyl-carbamoyl)-ethyl]-carbamic acid *t*-butyl ester
$C_{33}H_{47}N_3O_{10}$ MW: 645.7 Da	$C_{27}H_{32}N_3O_5D_5$ MW: 488.5 Da
	

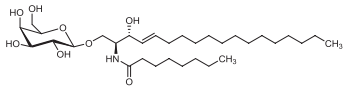
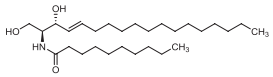
Glucocerebrosidase Substrate and Internal Standard (NSK-GA-1)

Each vial contains the following compounds at a molar ratio of 50:1.

Substrate	Internal Standard
D-Glucosyl-β1-1′-*N*-dodecanoyl-D-*erythro*-sphingosine [C12-glucocerebroside]	*N*-Myristoyl-D-*erythro*-sphingosine [C14-ceramide]
$C_{36}H_{69}NO_8$ MW: 643.9 Da	$C_{32}H_{63}NO_3$ MW: 509.8 Da
	

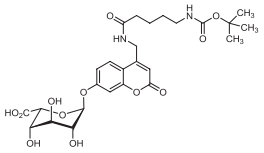
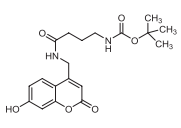
Galactocerebrosidase Substrate and Internal Standard (NSK-KR-1)

Each vial contains the following compounds at a molar ratio of 150:1.

Substrate	Internal Standard
D-Galactosyl-β1-1′-octanoyl-D-*erythro*-sphingosine [C8-galactosylceramide]	*N*-Decanoyl-D-*erythro*-sphingosine [C10-ceramide]
$C_{32}H_{61}NO_8$ MW: 587.8 Da	$C_{28}H_{55}NO_3$ MW: 453.7 Da
	

α-L-Iduronidase Substrate and Internal Standard (NSK-MP-1)

Each vial contains the following compounds at a molar ratio of 150:1.

Substrate	Internal Standard
(7-(1-Iduronic acid)-oxycoumarin-4-methylamine-(5′-*N*-boc-aminopentanoyl)-amide)	(7-Hydroxycoumarin-4-methylamine-(4′-*N*-boc-aminobutanoyl)-amide)
$C_{26}H_{34}N_2O_{12}$ MW: 566.6 Da	$C_{19}H_{24}N_2O_6$ MW: 376.4 Da
	

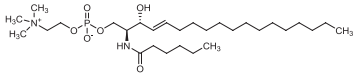
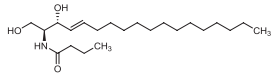
Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

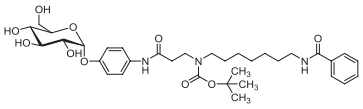
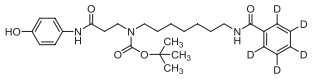
Acid Sphingomyelinase Substrate and Internal Standard (NSK-NI-1)

Each vial contains the following compounds at a molar ratio of 50:1.

Substrate	Internal Standard
N-Hexanoyl-D-*erythro*-sphingosylphosphorylcholine [C6-sphingomyelin]	*N*-Butyroyl-D-*erythro*-sphingosine [C4-ceramide]
$C_{29}H_{59}N_2O_6P$ MW: 562.8 Da	$C_{22}H_{43}NO_3$ MW: 369.6 Da
	

Acid α-Glucosidase Substrate and Internal Standard (NSK-PO-1)

Each vial contains the following compounds at a molar ratio of 100:1.

Substrate	Internal Standard
(7-Benzoylamino-heptyl)-{2-[4-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenylcarbamoyl]-ethyl}-carbamic acid *t*-butyl ester	(7-D_5-Benzoylamino-heptyl)-[2-(4-hydroxy-phenyl-carbamoyl)-ethyl]-carbamic acid *t*-butyl ester
$C_{34}H_{49}N_3O_{10}$ MW: 659.8 Da	$C_{28}H_{34}N_3O_5D_5$ MW: 502.7 Da
	

Usage Specifications

Criteria	Recommendation
Use	~600 samples/vial
Before reconstitution:	
Storage	-20°; protect from light
Recommended retest	2 years from date of manufacture
After reconstitution:	
Storage	5±3°C or -20±5°C
Recommended retest	4 weeks

Example References

Ribas, G.; De Mari, J.F.; Civallero, G.; et al. **2017**. Validation of a multiplex tandem mass spectrometry method for the detection of selected lysosomal storage diseases in dried blood spots. *JIMES, 5,* 1-7.

Tortorelli, S.; Turgeon, C.T.; Gavrilov, D.K.; et al. **2016**. Simultaneous testing for 6 lysosomal storage disorders and x-adrenoleukodystrophy in dried blood spots by tandem mass spectrometry. *Clin Chem, 62(9),* 1248-1254.

Cho,S.E.; Kwak, J.R.; Lee, H.; et al. **2016**. Triplex tandem mass spectrometry assays for the screening of 3 lysosomal storage disorders in a Korean population. *Clin Chim Acta, 454,* 20-27.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

MSK-MET1 Mix

Composition

Reconstituting a given vial in 1 mL of solvent (e.g., water) will produce the tabulated concentrations below. **Note**: The unlabeled 2DG was included to examine its metabolic uptake in tracer studies.

Compound	Abbrev.	Label and Enrichment	Conc. (mM)
L-Alanine	Ala	2,3,3,3-D_4, 98%	20
L-Carnitine	C0	trimethyl-D_9, 98%	0.4
Creatinine	Crn	*N*-methyl-D_3, 98%	0.7
2-Deoxy-D-glucose	2DG	unlabeled	50
D-Glucose	Glc	U-$^{13}C_6$, 99%	400
L-Glutamine	Gln	2,3,3,4,4-D_5, 97%	8
L-Leucine	Leu	5,5,5-D_3, 99%	5
L-Phenylalanine	Phe	ring-D_5, 98%	0.5
Sodium butyrate	BTA	D_7, 98%	2
Sodium propionate	PA	D_5, 98%	2
Urea	UR	$^{15}N_2$, 98%	20

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	4°C; protect from light
Recommended retest	2 years from date of manufacture

Example Results

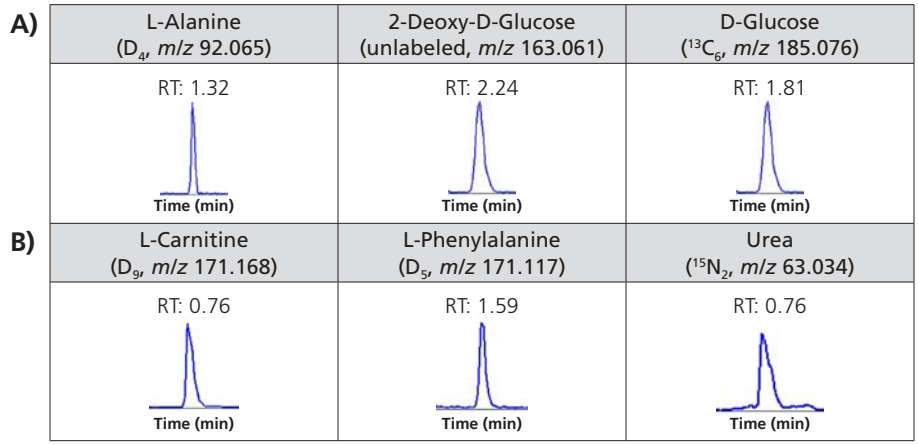


Figure. Representative XICs of example metabolites in the MET1 mix measured in mouse plasma by LC-MS analysis. A TripleTOF 6600 was fronted by a Hypercarb™ Porous Graphitic Carbon HPLC column (100 × 4.6 mm, 3 µm) in **A)** and a Kinetex F5 HPLC column (100 × 2.1 mm, 2.6 µm) in **B)** operated under negative and positive ESI, respectively. Data was courtesy of the Kibbey lab at Yale School of Medicine.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Steroid Mixes and Sets

Steroids play vital roles in the regulation of a diverse array of cellular functions and physiological processes. These pertain to development, reproduction, homeostasis, and metabolism, among others. Accurate quantification of this compound class is essential for basic and translation research. To aid MS-based research endeavors in this space, CIL is pleased to offer a few different types of stable isotope-labeled steroid mixes.

Click on the thumbnail or visit **isotope.com/applications/** for more information.

Overview

Catalog No.	Description	No. of Metabolites	Unit Size
NSK-S	Steroid Mix Set S	5	1 vial, 10 vials
NSK-S-40X	Steroid Mix Set S (40X)	5	1 vial, 10 vials
NSK-S-EXP	Expanded Steroid Mix Set S	9	1 vial, 10 vials

NSK-S Mix

Composition

Reconstituting a given vial's contents in 1 mL of highly pure methanol will produce the concentrations listed in the table below. To facilitate complete dissolution, it is recommended to vortex manually for 1 minute then auto-vortex for a minimum of 30 minutes. **Note**: NSK-S-40X has 40**×** the specified concentrations.

Compound	Abbrev.	Label and Enrichment	Conc. (nM)
4-Androstene-3,17-dione	A4	2,2,4,6,6,16,16-D_7, 97%	20
Cortisol	F	9,11,12,12-D_4, 98%	100
11-Deoxycortisol	11-S	2,2,4,6,6-D_5, 98%	20
21-Deoxycortisol	21-S	2,2,4,6,6,21,21,21-D_8, 97%	20
17α-Hydroxyprogesterone	17-OHP	2,2,4,6,6,21,21,21-D_8, 98%	20

Usage Specifications

Criteria	Recommendation
No. of uses	48 samples/vial
Before reconstitution:	
Storage	-5 to 5°C; protect from light
Recommended retest	5 years from date of manufacture
Upon reconstitution:	
Storage	Store in a tightly sealed vial at 5±3°C. **Note:** Storing the sealed vial in a second sealed container helps maintain the integrity of the solution.
Recommended retest	4 weeks

Example References

Gervasoni, J.; Schiattarella, A.; Primiano, A.; et al. **2016**. Simultaneous quantification of 17-hydroxyprogesterone, androstenedione, testosterone and cortisol in human serum by LC-MS/MS using TurboFlow online sample extraction. *Clin Biochem, 49(13-14),* 998-1003.

Hicks, R.A.; Yee, J.K.; Mao, C.S.; et al. **2014**. Precursor-to-product ratios reflect biochemical phenotype in congenital adrenal hyperplasia. *Metabolomics, 10(1),* 123-131.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

NSK-S-EXP Mix

Composition

Reconstituting a given vial's contents in 1 mL of highly pure methanol will produce the concentrations listed in the table below. To facilitate complete dissolution, it is recommended to vortex manually for 1 minute then auto-vortex for a minimum of 30 minutes.

Compound	Abbrev.	Label and Enrichment	MW (Da)	Conc. (µM)
Aldosterone	A	D_7, 98%	367.49	0.52
4-Androstene-3,17-dione	A4	2,2,4,6,6-D_5, 98%	291.44	0.12
Corticosterone	B	2,2,4,6,6,17α,21,21-D_8, 97-98%	354.51	1.58
Cortisol	F	9,12,12-D_3, 98%	365.48	2.57
Dehydroepiandrosterone sulfate·sodium salt·$2H_2O$	DHEAS	2,2,3,4,4,6-D_6, 95%	432.54	21.69
11-Deoxycortisol	11-S	2,2,4,6,6-D_5, 98% (CP 97%)	351.49	0.54
17-α-Hydroxyprogesterone	17-OHP	2,2,4,6,6,21,21,21-D_8, 98%	338.51	0.27
Progesterone	P	2,2,4,6,6,17α,21,21,21-D_9, 98%	323.52	0.14
Testosterone	T	2,2,4,6,6-D_5, 98%	293.46	0.12

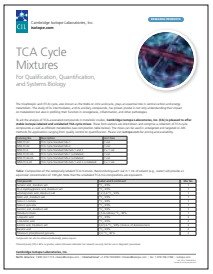
Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	-5 to 5°C; protect from light
Recommended retest	1 year from date of manufacture

Pathway-Specific Mixes

TCA Mixes and Sets

The tricarboxylic acid (TCA) cycle plays an essential role in central carbon and energy metabolism. The study of TCA cycle intermediates (e.g., citrate, α-ketoglutarate, succinate) and its offshoot metabolites (e.g., itaconate and 2-hydroxyglutarate), have proven pivotal in not only understanding their impact on metabolism, but also in profiling their cellular function/fate in oncogenesis, inflammation, and other pathologies (e.g., necrosis, cirrhosis). To aid the analysis of TCA cycle-associated compounds in metabolomic studies, we offer stable isotope-labeled and unlabeled TCA cycle mixes. These mixes are dried down and comprise a collection of TCA cycle and offshoot metabolites.



Click on the thumbnails or visit **isotope.com/applications/** for more information.

Overview

Catalog No.	Description	No. of Metabolites	Unit Size
MSK-TCA1	TCA Cycle Standard Mix 1	8	1 vial
MSK-TCA2	TCA Cycle Standard Mix 2	5	1 vial
MSK-TCA	TCA Cycle Standard Mix Sets 1 and 2	8 (in mix 1), 5 (in mix 2)	2 × 1 vials

Compositions

Composition of the stable isotope-labeled TCA mixtures. Reconstituting a given vial in 1 mL of solvent (e.g., water) will produce an equimolar concentration of 100 µM.

Compound	Abbrev.	Label and Enrichment	Mix No.
Fumaric acid, disodium salt	Fum	$^{13}C_4$, 99%	1
DL-2-Hydroxyglutaric acid, disodium salt	HG	$^{13}C_5$, 99%	1
α-Ketoglutaric acid, disodium salt	α-KG	1,2,3,4-$^{13}C_4$, 99%	1
Malic acid, disodium salt	Mal	$^{13}C_4$, 99%	1
Sodium L-lactate	Lac	$^{13}C_3$, 98%	1
Sodium pyruvate	Pyr	$^{13}C_3$, 99%	1
Succinic acid, disodium salt	SA	$^{13}C_4$, 99%	1
Trisodium citrate	CA	1,5,6-carboxy-$^{13}C_3$, 99%	1
L-Aspartic acid	Asp	$^{13}C_4$, 99%	2
L-Glutamic acid	Glu	$^{13}C_5$, 99%	2
Isocitric acid, trisodium salt	Iso	3,4,5,6-$^{13}C_4$, 98% (mixture of diastereomers)	2
Itaconic acid	IA	$^{13}C_5$, 99%	2
Potassium phosphoenol pyruvate	PEP	2,3-$^{13}C_2$, 99%	2

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	ambient temperature; protect from light and moisture
Recommended retest	2 years from date of manufacture
After reconstitution:	
Storage	4°C
Recommended retest	4 weeks

Note: Extended mix stabilities have been demonstrated when solubilized in water and stored as specified above.

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results

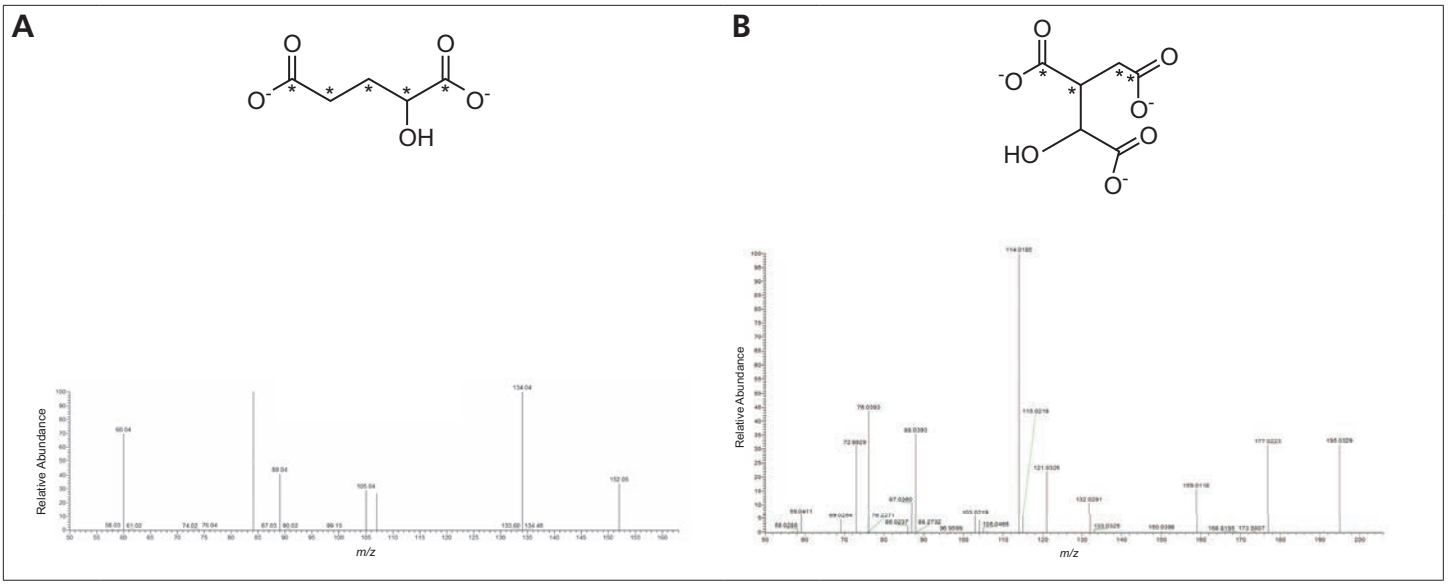


Figure. Example MS/MS spectra of the TCA mixes. These were obtained from the IC-MS analysis (negative ESI, Orbitrap Fusion Tribrid) of 10 µM working solutions. The compounds are $^{13}C_5$ 2-hydroxyglutarate (from mix 1) in **A)** and $^{13}C_4$ isocitrate (from mix 2) in **B)**. Their complete, unfragmented structures ($^{13}C_5$ hydroxyglutarate, precursor *m/z* 152.05; $^{13}C_4$ isocitrate, precursor *m/z* 195.03) are illustrated for reference. Data was courtesy of the Metabolomics Facility at MD Anderson Cancer Center.

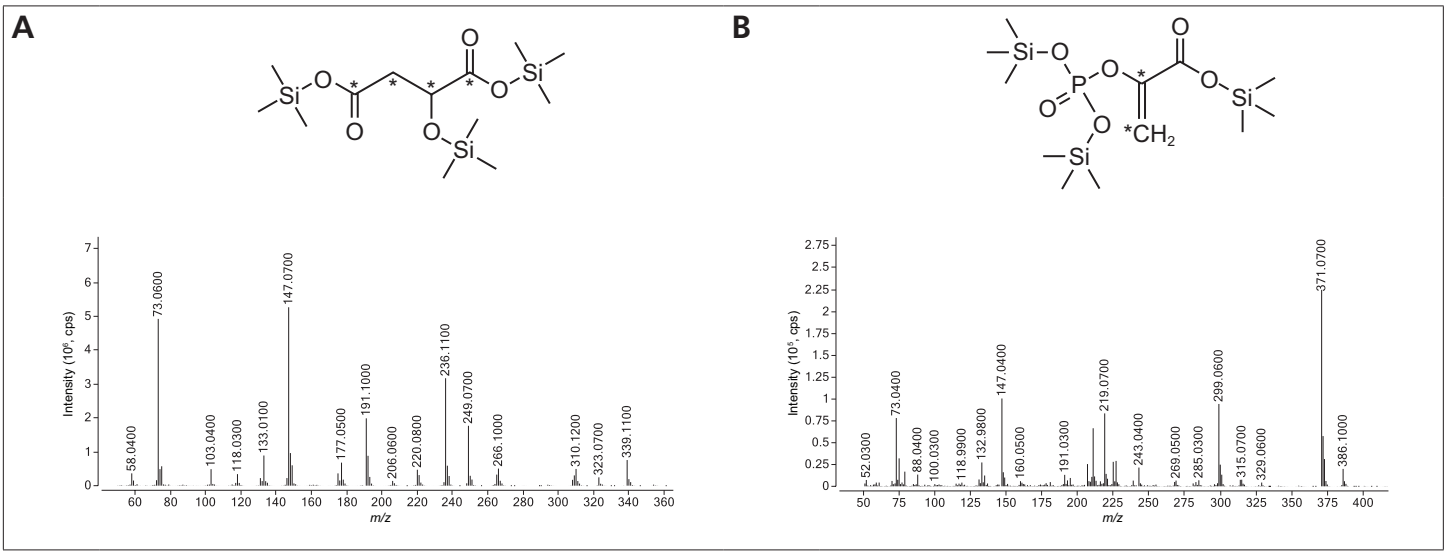


Figure. Example spectra of the labeled TCA mixes. These were obtained from the analysis of 50 µM working solutions by GC-MS (BSTFA with TMCS, EI ionization, scan mode on single quadrupole). The compounds are $^{13}C_4$ malate (from mix 1) in **A)** and $^{13}C_2$ phosphenol pyruvate (from mix 2) in **B)**. Their complete, unfragmented structures ($^{13}C_4$ malate, exact mass 354.15; $^{13}C_2$ phosphenol pyruvate, exact mass 386.11) are illustrated for reference. Data was courtesy of the University of Chicago Metabolomics Facility.

"The metabolomic compound mixes by Cambridge Isotope Laboratories have expedited several processes in our GC-MS analysis pipeline. We have used these products, including their novel TCA mixes, to verify metabolite retention times, test derivatization reaction conditions, and to confirm fragmentation patterns detected in biological samples. CIL's metabolite mixes are ready to go, easy to use, and consistently of high quality!"

– Ashley M. Sidebottom, PhD
Metabolomics Platform Director, University of Chicago (USA)
Host-Microbe Metabolomics Facility, Duchossois Family Institute

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

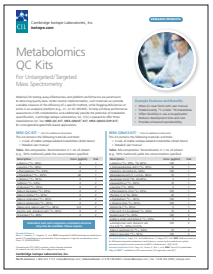
For research use only. Not for use in diagnostic procedures.

Kits

To help facilitate product application, a number of the CIL mix offerings are accompanied with a user manual. The kit manual provides a guide to the preparation and processing possibilities for product implementation, as well as supplying further resources for additional user reference. The majority of the kits supply the supporting documents through a QR code (via product label on kit materials box); the exceptions are the PeptiQuant™ Plus kits (documents on USB) and the IROA kits (documents delivered in email). The accompanying documents minimally include a user manual, certificate of analysis (CoA), safety data sheet (SDS), and product flyer. Overall, the mixes are amenable for use in quality control and qualification/quantification exercises in the MS 'omics space using targeted, semitargeted, or untargeted LC-MS methodologies. Note that the individual mixes may be obtained separately without the manual. Please inquire.

Metabolomic QC Kits

To ensure high-quality metabolomics results, the method and instrument platform must be qualified as being fit-for-purpose. This involves testing for losses or errors in the analytical workflow. To aid such performance assessments in MS metabolomics and potentially other applications (e.g., qualification, quantification), CIL offers three types of QC kits: MSK-QC-KIT, MSK-QReSS-KIT, and MSK-QReSS-EXP-KIT (see details below). These kits comprise vials of dried-down metabolite mixes (see composition tables below) and have been qualified on both low- and high-resolution mass spectrometers operated under an untargeted/targeted metabolomics regimen (see example results below).



Click on the thumbnail or visit **isotope.com/applications/** for more information.

Overview

Catalog No.	Description	No. of Metabolites	Kit Contents
MSK-QC-KIT	Metabolomics QC Kit	5 (in mix 1) 9 (in mix 2)	• 2 vials of ^{13}C-labeled metabolites • document package (user manual, CoA, SDS, product flyer)
MSK-QReSS-KIT*	Metabolomics QReSS Kit	12 (in mix 1) 6 (in mix 2)	• 2 vials of isotope-labeled metabolites • document package (user manual, CoA, SDS, product flyer)
MSK-QReSS-EXP-KIT ***COMING SOON!***	Expanded Metabolomics QReSS Kit	12 (in mix 1) 6 (in mix 2) 9 (in mix 3)	• 3 vials of isotope-labeled metabolites • document package (user manual, CoA, SDS, product flyer)

**QReSS™ stands for Quantification, Retention, and System Suitability. This kit was developed and matrix tested in collaboration with SCIEX.*

MSK-QC Kit

Mix Compositions

Reconstituting in 1 mL of solvent (e.g., 0.1% FA in 5% ACN) will yield the specified compound concentrations.

Compound	Abbrev.	Label and Enrichment	Conc. (µg/mL)	Mix No.
L-Alanine	Ala	$^{13}C_3$, 99%	4	1
L-Leucine	Leu	$^{13}C_6$, 99%	4	1
L-Phenylalanine	Phe	$^{13}C_6$, 99%	4	1
L-Tryptophan	Trp	$^{13}C_{11}$, 99%	40	1
L-Tyrosine	Tyr	$^{13}C_6$, 99%	4	1
D-Glucose	Glc	$^{13}C_6$, 99%	4	2
D-Sucrose	Suc	$^{13}C_6$, 98%	4	2
Caffeine	CAF	$^{13}C_3$, 99%	4	2
Stearic acid, sodium salt	18:0	$^{13}C_{18}$, 98%	0.4	2
Sodium octanoate	8:0	$^{13}C_8$, 99%	4	2
Sodium propionate	PA	$^{13}C_3$, 99%	4	2
Sodium benzoate	BZA	$^{13}C_6$, 99%	4	2
Sodium citrate	CA	$^{13}C_3$, 99%	4	2
Succinic acid, disodium salt	SA	$^{13}C_4$, 99%	4	2

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	ambient temperature; protect from light and moisture
Recommended retest	2 years from date of manufacture

Example References

Kossack, M.E.; Manz, K.E.; Martin, N.R.; et al. **2023**. Environmentally relevant uptake, elimination, and metabolic changes following early embryonic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in zebrafish. *Chemosphere, 310,* 136723-136754.

Barco, S.; Lavarello, C.; Cangelosi, D.; et al. **2022**. Untargeted LC-HRMS based-plasma metabolomics reveals 3-O-methyldopa as a new biomarker of poor prognosis in high-risk neuroblastoma. *Front Oncol, 12,* 845936-845946.

Example Results

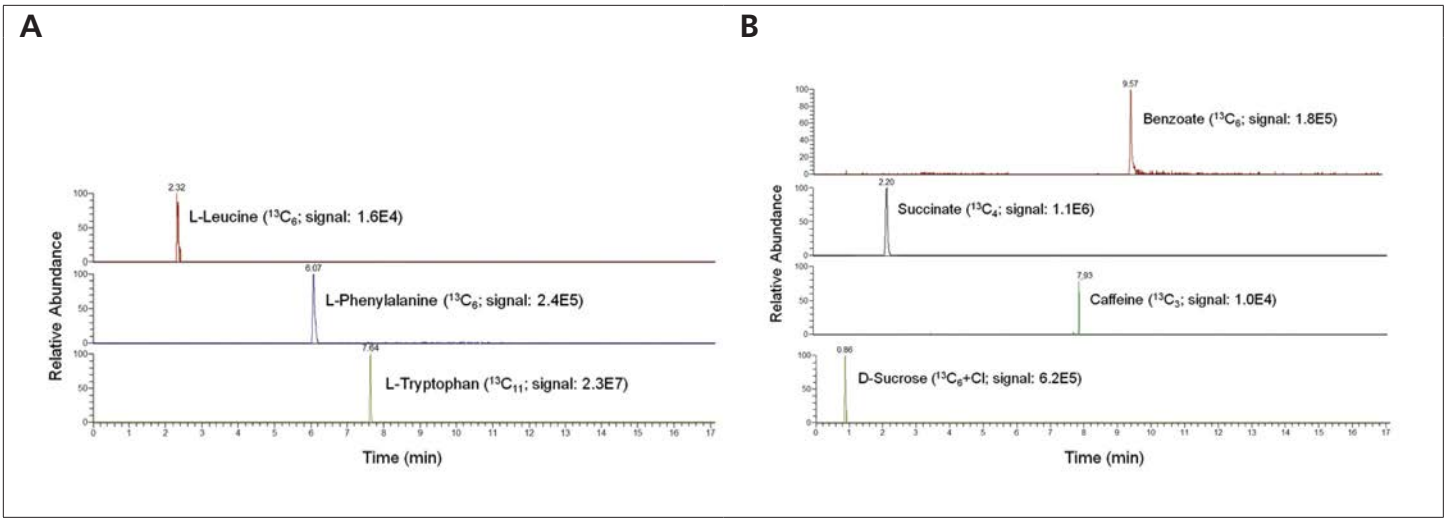


Figure. Representative XICs of a subset of kit metabolites – vial 1 in **A** and vial 2 in **B** – measured in human plasma by RPLC-MS (negative ESI, Q Exactive). Note that all isotopically labeled metabolites in the mixes co-eluted with their endogenous analytes in the plasma analyses and their *m/z* were predominantly $[M-H]^-$.

"I have used products from Cambridge Isotope Laboratories (CIL) for well over 15 years because of the high quality provided. I have collaborated with CIL to develop a new product that would enable improved quality control in MS metabolomics. This process was exciting and engaging. Through collaboration, I found CIL to be a cutting-edge vendor that seeks opportunities to enable scientific discovery and data quality. They seek advice from clients to learn how to better serve them. I always look forward to talking with CIL at conferences and often seek out their booth to visit, not just to talk science, but to also see how their team is doing."

– Timothy J. Garrett, PhD
Associate Professor in Department of Pathology, Immunology, and Laboratory Medicine, University of Florida (USA)

MSK-QReSS Kit

Mix Compositions

Reconstituting a given QReSS mix in 1 mL of solvent (e.g., 1:1 v/v methanol:water) will yield the specified compound concentrations.

Compound	Abbrev. or Alt. Name	Label and Enrichment	Conc. (µg/mL)	Mix No.
L-Alanine	Ala	$^{13}C_3$, 99%; ^{15}N, 99%	100	1
1,4-Butanediamine·2HCl	putrescine	$^{13}C_4$, 99%	10	1
Creatinine	Crn	N-methyl-D_3, 98%	100	1
Ethanolamine·HCl	ETA	1,1,2,2-D_4, 98%	10	1
Guanosine·2H_2O	Guo	$^{15}N_5$, 96-98%	2	1
Hypoxanthine	HPX	$^{13}C_5$, 99%	10	1
L-Leucine	Leu	$^{13}C_6$, 99%	5	1
L-Phenylalanine	Phe	ring-$^{13}C_6$, 99%	100	1
Thymine	T	1,3-$^{15}N_2$, 98%	20	1
L-Tryptophan	Trp	$^{13}C_{11}$, 99%	100	1
L-Tyrosine	Tyr	ring-$^{13}C_6$, 99%	100	1
Vitamin B_3	nicotinamide	$^{13}C_6$, 99%	5	1
Citric acid	CA	1,5,6-carboxyl-$^{13}C_3$, 99%	10	2
Fumaric acid	FA	$^{13}C_4$, 99%	100	2
Indole-3-acetic acid	IAA	phenyl-$^{13}C_6$, 99%	5	2
α-Ketoglutaric acid, disodium salt	α-KG	1,2,3,4-$^{13}C_4$, 99% (CP 97%)	100	2
Sodium palmitate	16:0	U-$^{13}C_{16}$, 98%	10	2
Sodium pyruvate	Pyr	$^{13}C_3$, 99%	100	2

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Usage Specifications

Criteria	Recommendation
Before reconstitution:	
Storage	ambient temperature; protect from light and moisture
Recommended retest	2 years from date of manufacture
Upon reconstitution:	
Storage	4°C
Recommended retest	4 weeks

Example Results

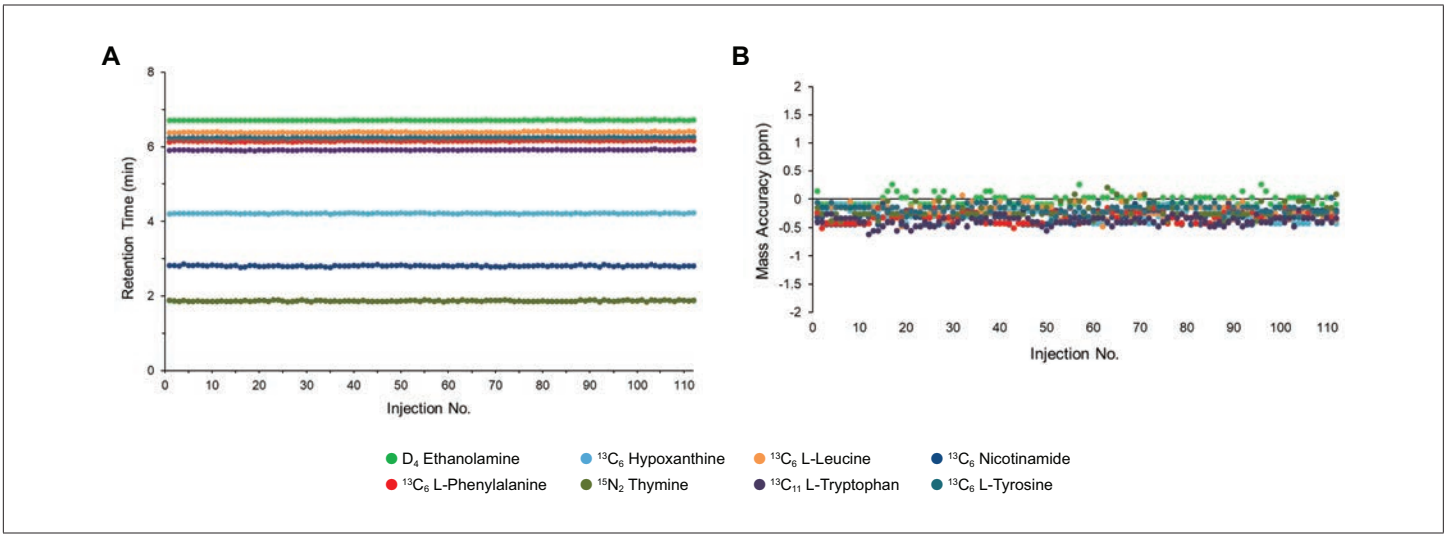
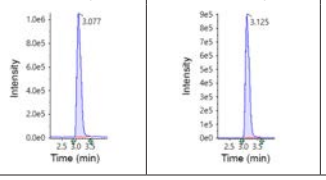


Figure.QC results for a subset of stable isotope-labeled QReSS metabolites measured across calibrants, QCs, and FBS samples. Acquisitions were by HILIC-MS (ESI+, Orbitrap Exploris™ 120). Variability of retention times are shown in **A** and mass accuracy in **B**. For additional information on the application, see **CIL application note #51**.

Metabolite	MRM Transition (Precursor → Product Ion *m/z*)
Hypoxanthine ($^{13}C_5$)	142 → 124



Metabolite	MRM Transition (Precursor → Product Ion *m/z*)
Phenylalanine ($^{13}C_6$)	172 → 126

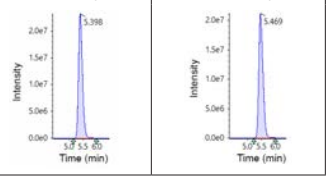


Figure. Example XICs for a subset of labeled QReSS metabolites measured in buffer and human plasma by RPLC-MRM/MS (positive ESI, QTRAP 6500+). In the buffer analysis, a vial of a working stock mix was stored in on autosampler rack (maintained at 4°C) and processed eight days apart. Such measurements, when performed and metric tracked routinely, would constitute a system suitability test. In the human plasma analysis, an aliquot of the working stock mix was matrix spiked and subjected to a metabolomics workflow. The relative signals to its corresponding endogenous analyte (not shown for simplicity) is within an order of magnitude and can be used for relative quantitative applications, with absolute quantitation likely involving calibration curves. For additional information and application demonstrations see **CIL application note #49**.

Companion unlabeled standard mixes and kits may be available; please inquire.

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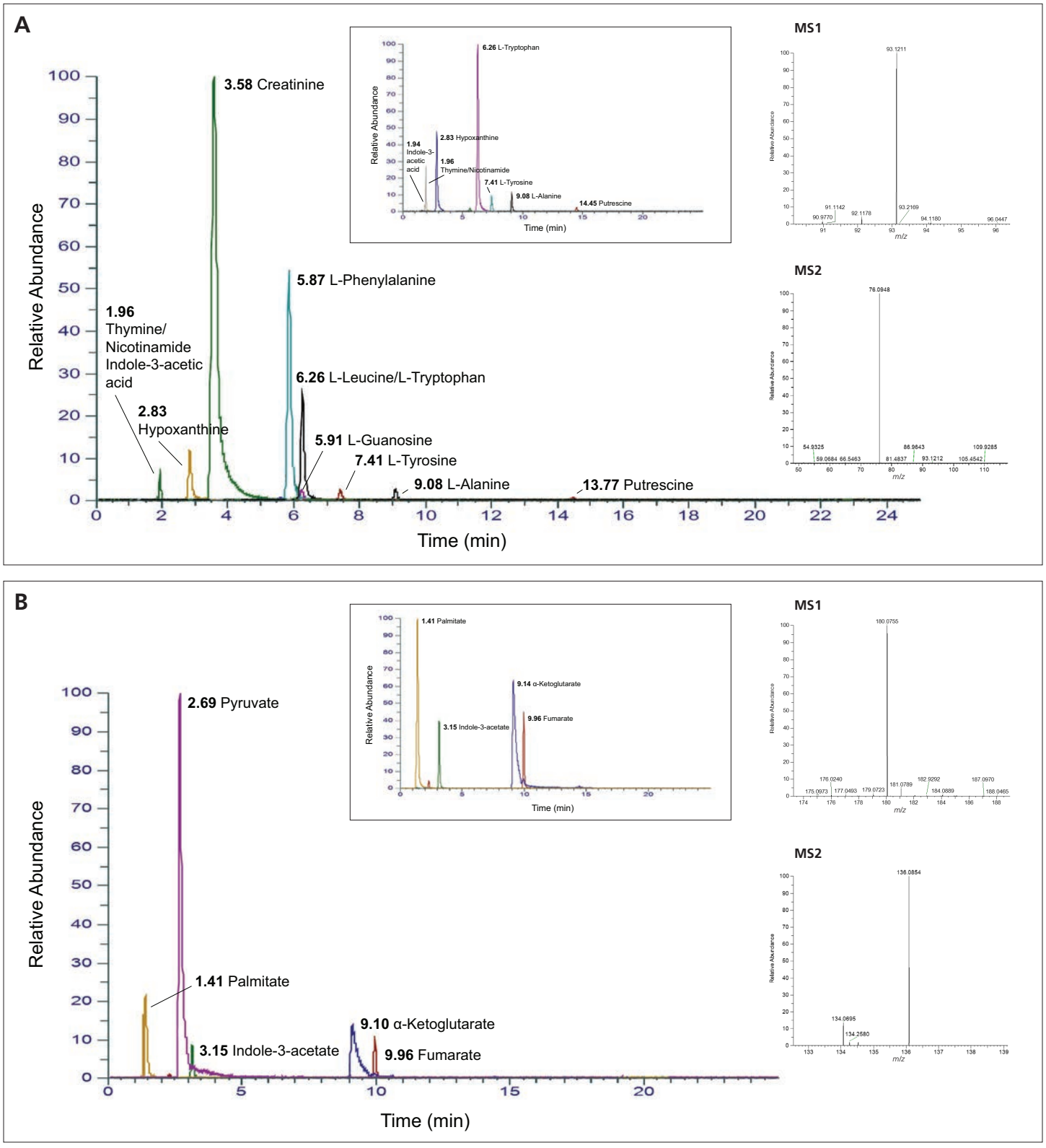

Figure. XIC overview of stable isotope-labeled QReSS metabolites measured matrix-free by HILIC-MS (Q Exactive), with ESI+ in **A** and ESI- in **B**. Chromatographic insets reflect zoomed-in snapshots of lower-abundance metabolites, while the MS1/MS2 spectra reflect putrescine in **A** and indole-3-acetate in **B**. For clarity, the following higher-abundance metabolites were removed in the insets – creatinine (RT 3.58 min), phenylalanine (RT 5.87 min), and leucine (RT 6.26 min) in **A** and pyruvate (RT 2.69 min) in **B**. Data is courtesy of the Jackson Laboratory.

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Reference

Brown, J.I.; Wang, P.; Wong, A.Y.L.; et al. **2023**. Cycloguanil and analogues potently target DHFR in cancer cells to elicit anti-cancer activity. *Metabolites, 13(2),* 151-172.

Lippa, K.A.; Aristizabal-Henao, J.J.; Beger, R.D.; et al. **2022**. Reference materials for MS-based untargeted metabolomics and lipidomics: a review by the metabolomics quality assurance and quality control consortium (mQACC). *Metabolomics, 18(4),* 24-52.

Heppler, L.N.; Attarha, S.; Persaud, R.; et al. **2022**. The antimicrobial drug pyrimethamine inhibits STAT3 transcriptional activity by targeting the enzyme dihydrofolate reductase. *J Biol Chem, 298(2),* 101531-10548.

Application Notes

Percy, A.J.; Souza, A.; Ntai, I.; et al. **2022**. From QC to quantitation: Utility of QReSS™ metabolites in FBS measurements. (CIL application note #51)

Percy, A.J.; Proos, R.; Demianova, Z.; et al. **2021**. Standardizing quantitative metabolomics analyses through the QReSS kit. (CIL application note #49)

"The unique feature of our media analysis workflow is the use of the QReSS standard mix. We spike this into media samples before extraction, which helps normalize variabilities in metabolite extraction efficiencies and combat matrix effects. The QReSS mix consists of 18 isotope-labeled metabolites, which spans a multitude of metabolic classes and mimics the largely diverse chemical composition of cell culture media. This serves as an excellent choice for an internal standard mix and helps to improve the accuracy, precision, and robustness of our cell culture method."

– Hari Kosanam, PhD
Associate Principal Scientist, Vaccine Process Development and Commercialization
Merck & Co. (USA)

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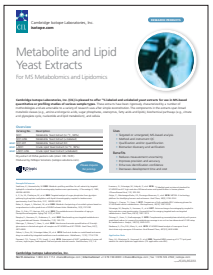
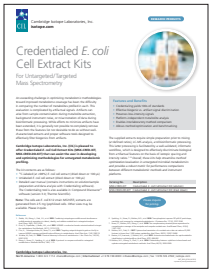
Extract Kits

Expanded qualification remains a necessity in MS 'omics today. Validated identifications are desired that can be used to springboard in-depth profiling studies and selective quantifications in preclinical screening studies. To aid method benchmarking (e.g., through a credentialing approach) and improved qualification/quantification studies, CIL offers two types of cell extracts: yeast (*Pichia pastoris*, strain CBS 7435) and *E. coli* (K12 strain MG1655), as outlined in the overview table below. Upon careful and precise solubilization (see reconstitution guidelines below), 100s of metabolites are potentially observable in their U-^{13}C and unlabeled form. The metabolites span a broad class range (see example identification tables), having linkage to various biochemical pathways (e.g., citrate and glyoxylate cycle, nucleotide and lipid metabolism) and cellular/molecular processes (e.g., intracellular signaling, immune system, blood coagulation, lipolysis). Please refer to the sample results and references below for examples of the product-specific applications.





Click on the thumbnails or visit **isotope.com/applications/** for more information.

Overview

Catalog No.	Description	No. of Analytes	Kit Contents
L-ISO1	Crude Lipid Yeast Extract (U-^{13}C, 99%)	100s	• 1 vial of U-^{13}C crude lipid yeast extract • document package (user manual, CoA, SDS, product flyer)
L-ISO1-UNL	Crude Lipid Yeast Extract (unlabeled)	100s	• 1 vial of unlabeled crude lipid yeast extract • document package (user manual, CoA, SDS, product flyer)
ISO1	Metabolite Yeast Extract (U-^{13}C, 98%)	100s	• 1 vial of U-^{13}C metabolite yeast extract • document package (user manual, CoA, SDS, product flyer)
ISO1-UNL	Metabolite Yeast Extract (unlabeled)	100s	• 1 vial of unlabeled metabolite yeast extract • document package (user manual, CoA, SDS, product flyer)
ISO1-KIT	Metabolite Yeast Extract Kit	100s	• 1 vial of U-^{13}C metabolite yeast extract • 1 vial of unlabeled metabolite yeast extract • document package (user manual, CoA, SDS, product flyer)
MSK-CRED-DD-KIT	Credentialed *E. coli* Cell Extract Kit (dried down)	100s	• 1 vial (blue cap) of ^{13}C-labeled *E. coli* cell extract (dried down) • 1 vial (yellow cap) of unlabeled *E. coli* cell extract (dried down) • document package (user manual, CoA, SDS, product flyer)
MSK-CRED-KIT	Credentialed *E. coli* Cell Extract Kit (solution)	100s	• 1 vial (black) of ^{13}C-labeled *E. coli* cell extract (solution) • 1 vial (red) of unlabeled *E. coli* cell extract (solution) • document package (user manual, CoA, SDS, product flyer)

Lipid Yeast Extracts

Compositions

Tabulated is a reproducibly identified panel of fatty acids and lipids measured in the lipid yeast extracts (U-^{13}C, L-ISO1; unlabeled, L-ISO1-UNL) using one general RPLC-MS method. **Note:** Additional analytes have been measured with alternate methods and analysis techniques.

Category	Class	Examples (Fatty Acid Level)		
Glycerolipids	Diglyceride (DG)	34:1 (16:0/18:1) 34:4 (16:2/18:2) 36:3 (18:1/18:2)	34:2 (16:1/18:1) 36:1 (18:0/18:1) 36:4 (18:1/18:3)	34:3 (16:1/18:2) 36:2 (18:0/18:2) 36:5 (18:2/18:3)
	Triglyceride (TG)	50:1 (16:0/16:0/18:1) 50:4 (16:1/16:1/18:2) 52:2 (16:0/18:1/18:1) 52:5 (16:1/18:2/18:2) 54:1 (18:0/18:1/18:0) 54:4 (18:1/18:1/18:2) 54:7 (18:1/18:3/18:3)	50:2 (16:0/18:2/16:0) 50:5 (16:1/16:1/18:3) 52:3 (16:1/18:1/18:1) 52:6 (16:1/18:2/18:3) 54:2 (18:0/18:1/18:1) 54:5 (18:1/18:2/18:2) 54:8 (18:3/18:2/18:3)	50:3 (16:1/16:1/18:1) 52:1 (18:0/16:0/18:1) 52:4 (18:2/18:2/16:0) 52:7 (18:3/18:3/16:1) 54:3 (18:1/18:1/18:1) 54:6 (18:2/18:2/18:2) 54:9 (18:3/18:3/18:3)

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

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Category	Class	Examples (Fatty Acid Level)
Glycerophospholipids	Phosphatidic acid (PA)	34:1 (16:0/18:1) 34:2 (16:0/18:2) 34:3 (16:0/18:3) 36:1 (18:0/18:1) 36:2 (18:0/18:2) 36:3 (18:1/18:2)
	Phosphatidylcholine (PC)	34:1 (16:0/18:1) 34:2 (16:0/18:2) 34:3 (16:0/18:3) 34:4 (16:1/18:3) 36:2 (18:0/18:2) 36:3 (18:1/18:2) 36:4 (18:1/18:3) 36:5 (18:2/18:3) 36:6 (18:3/18:3)
	Phosphatidylethanolamine (PE)	34:1 (16:0/18:1) 34:2 (16:0/18:2) 34:3 (16:0/18:3) 36:1 (18:0/18:1) 36:2 (18:0/18:2) 36:3 (18:1/18:2) 36:4 (18:1/18:3) 36:5 (18:2/18:3) 36:6 (18:3/18:3)
	Phosphatidylglycerol (PG)	34:1 (16:0/18:1) 34:2 (16:1/18:1)
	Phosphatidylinositol (PI)	34:1 (16:0/18:1) 34:2 (16:0/18:2) 36:1 (18:0/18:1) 36:2 (18:1/18:1)
	Phosphatidylserine (PS)	34:1 (16:0/18:1) 34:2 (16:0/18:2) 34:3 (16:0/18:3) 36:1 (18:0/18:1) 36:2 (18:0/18:2) 36:3 (18:0/18:3)
Lysophospholipids	Lysophosphatidylcholine (LPC)	16:1 18:1 18:2 18:3
	Lysophosphatidylethanolamine (LPE)	18:1 18:2 18:3
Sphingolipids	Ceramide (Cer)	d34:1 (d18:1/16:0) d36:1 (d18:1/18:0) t34:1 (t18:1/16:0) t36:0 (t18:0/18:0) t36:2 (t18:1/18:1)
	Hexosyl ceramide (HexCer)	t36:2 (t18:1/18:1)
Other	Acylcarnitines (AC)	16:1
	Coenzyme (Co)	Q8
	Fatty acid (FA)	18:2 18:3

Usage Specifications

Extract Type	L-ISO1	L-ISO1-UNL
No. of uses	~50*	
Before reconstitution:		
Storage	-80°C; protect from light	
Recommended retest	every 12 months	
Expiration	2 years from date of manufacture	

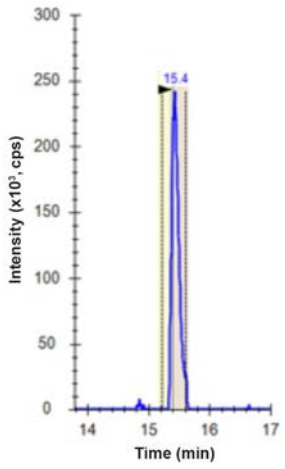
**Conservative estimate, with numbers varying depending on method and application.*

Solution Preparation Procedure

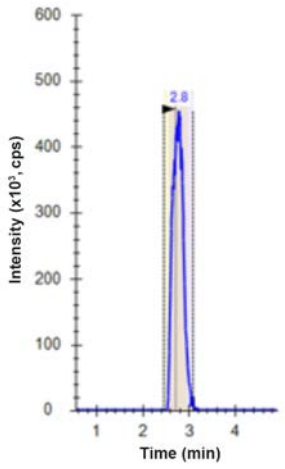
1. Reconstitute the lipid yeast extract (L-ISO1 or L-ISO1-UNL) in 1 mL solvent (e.g., isopropanol).
2. Following a high-speed vortex and brief centrifuge, the resulting clear solution can then be matrix-spiked, diluted (1/10 v/v), or prepared further for calibrant, QC, and/or sample addition.

Example Results

A



DG 34:1
$[M+NH_4]^+$; *m/z* 649.68028



LPC 18:2
$[M+H]^+$; *m/z* 546.426992

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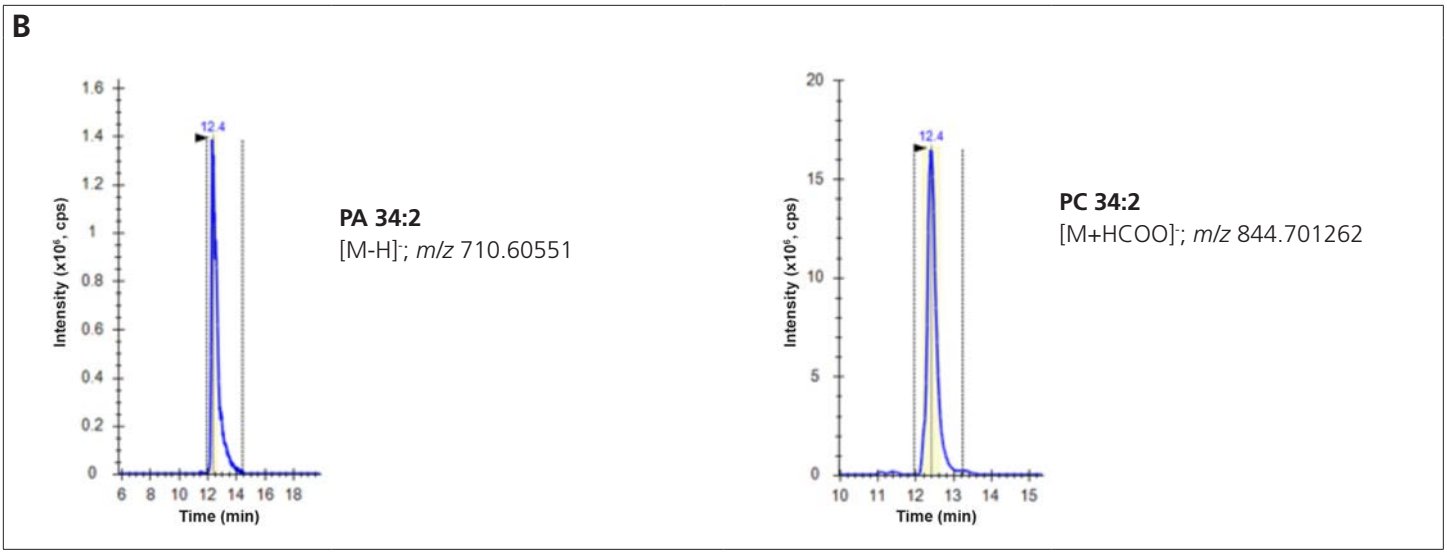

Figure. Representative XICs of example lipids measured in the U-^{13}C lipid yeast extract by RPLC-MS (ACQUITY HSS T3, Orbitrap ID-X). The ionization mode was ESI+ in **A** and ESI- in **B**. Data is courtesy of the Patti lab at Washington University.

Table. Example set of identified fatty acids and lipids measured by RPLC-IM-MS (ACQUITY™ Premier CSH™ C18 column, SYNAPT™ XS). Tabulated is analytical data for unlabeled and U-^{13}C lipids acquired under ESI+ and ESI- (in blue) polarities. Error tolerances on the ion mobility-derived collision cross-sections (CCS) are ±3%. Data is courtesy of Waters (Manchester, UK).

		Precursor *m/z*			CCS (Å²)	
Lipid (Fatty Acid Level)	RT (min)	Unlabeled Lipids	U-^{13}C Lipids	Adduct	Unlabeled Lipids	U-^{13}C Lipids
Cer d34:1 (d18:1/16:0)	3.31	560.5023	594.6124	$[M+Na]^+$	257.79	258.44
Cer d34:1 (d18:1/16:0)	3.31	536.5059	570.6159	$[M-H]^-$	252.85	253.30
PC 34:2 (16:0/18:2)	2.85	758.5700	800.7074	$[M+H]^+$	293.16	294.46
PC 36:4 (18:1/18:3)	2.53	782.5697	826.7160	$[M+H]^+$	300.69	301.52
PE 34:2 (16:0/18:2)	2.96	716.5220	755.6510	$[M+H]^+$	279.92	280.33
PE 34:2 (16:0/18:2)	2.96	738.5032	777.6310	$[M+Na]^+$	286.03	286.47
LPC(16:1)	0.82	494.3223	518.4045	$[M+H]^+$	229.29	229.61
LPC(16:1)	0.82	538.3145	562.3950	$[M+HCOO]^-$	238.29	239.23

Metabolite Yeast Extracts

Compositions

Tabulated are the routinely identified analytes in the metabolite yeast extracts (U-^{13}C, ISO1; unlabeled, ISO1-UNL). **Note:** Additional metabolites have been measured with alternate methods and analysis techniques. This includes cofactors (e.g., NMN, ADPR, NADPH) and coenzymes (e.g., acetyl and malonyl coenzyme A).

Amino Acids and Derivatives (L enantiomer where applicable)		
S-Adenosyl-homocysteine (SAH)	Glutamate (Glu)	Methionine (Met)
Alanine (Ala)	Glutamine (Gln)	(±)-3-Methyl-2-oxovalerate (K-IVal)
α-Aminoadipate (AAD)	Glycine (Gly)	Ornithine (Orn)
Arginine (Arg)	Guanidineacetate (GAA)	Phenylalanine (Phe)
Argininosuccinate (ASA)	Histidine (His)	Proline (Pro)
Asparagine (Asn)	Homoserine (Hse)	Sarcosine (Sar)
Aspartate (Asp)	Isoleucine (Ile)	Serine (Ser)
Betaine (BET)	α-Ketoisovalerate (KIV)	Threonine (Thr)
Citrulline (Cit)	Kynurenine (KYN)	Tryptophan (Trp)
Cystathionine (CYS)	Leucine (Leu)	Tyrosine (Tyr)
Dihydroxyisovalerate (DIHV)	Lysine (Lys)	Valine (Val)

Nucleobases, Nucleosides, and Nucleotides		
Adenine (Ade)	Cytidine triphosphate (CTP)	Inosine (Isin)
Adenosine (Asin)	Deoxyadenosine monophosphate (dAMP)	Inosine monophosphate (IMP)
Adenosine diphosphate (ADP)	5′-Deoxy-5′-methylthioadenosine (MTAP)	5-Methyluridine (m^5U)
Adenosine monophosphate (AMP)	Guanine (Gnin)	Pseudouridine (PsU)
Adenosine triphosphate (ATP)	Guanosine (Gsin)	Uridine (Uri)
Cyclic adenosine monophosphate (cAMP)	Guanosine diphosphate (GDP)	Uridine diphosphate (UDP)
Cyclic guanosine monophosphate (cGMP)	Guanosine monophosphate (GMP)	Uridine monophosphate (UMP)
Cytidine monophosphate (CMP)	Guanosine triphosphate (GTP)	Uridine triphosphate (UTP)
Organic Acids		
cis-Aconitate (*cis*-Ac)	DL-2-Hydroxyglutarate (2-HG)	Malate (Mal)
Citrate (CA)	Isocitrate (Iso)	Pyruvate (Pyr)
Fumarate (Fum)	α-Ketoglutarate (α-KG)	Succinate (SA)
Gluconate (GA)	Lactate (Lac)	
Sugar and Sugar Phosphates (D enantiomer where applicable)		
Dihydroxyacetone phosphate (DHAP)	Glucose (Glc)	6-Phosphogluconate (6PGA)
Erythritol (Erthrit)	Glucose-6-phosphate (G6P)	Ribose (RIB)
Fructose (Fuc)	Mannitol (Man-Ol)	Ribose-5-phosphate (R5P)
Fructose-1,6-bisphosphate (FBP)	Mannose (Man)	Sedoheptulose-7-phosphate (S7P)
Fructose-6-phosphate (F6P)	Mannose-6-phosphate (M6P)	Trehalose (TRE)
Galactose (Gal)	2-Phosphoglycerate (2PG)	
Vitamins and Coenzymes		
Biotin (B_7)*	Nicotinamide (NAM)	Nicotinamide adenine dinucleotide, reduced (NADH)
Choline (CHOL)	Nicotinamide adenine dinucleotide, oxidized (NAD^+)	Nicotinamide adenine dinucleotide phosphate, oxidized ($NADP^+$)
Other Small Molecules		
Glutamylcysteine (Glu-Cys)	Glutathione, reduced (GSH)	
Glutathione, oxidized (GSSG)	Mevalonate (MVA)	

**Identified in ISO1-UNL only.*

Usage Specifications

Extract Type	ISO1	ISO1-UNL
No. of uses	~50*	
Before reconstitution:		
Storage	-80°C; protect from light	
Recommended retest	every 12 months	
Expiration	4 years from date of manufacture	
Upon reconstitution:		
Storage	4°C	
Recommended retest	4 weeks	

**Conservative estimate, with numbers varying depending on method and application.*

Solution Preparation Procedure

1. Reconstitute the metabolite yeast extracts (ISO1 or ISO1-UNL) with 2 mL solvent (e.g., water, 50% methanol).
2. Vigorously shake by hand with intermittent high-speed vortexing (2 minute minimum).
3. Centrifuge at 20°C for 5 min at 4000 rcf.
4. The clear standard solution can then be diluted (1/10 v/v) for direct use or prepared further for calibration and matrix addition. If particulate matter remains after steps 2) and 3), repeat with extra intense vortexing and shaking until complete dissolution.

A video demonstration of this procedure can be obtained here, as well as in the resources section of the Metabolite Yeast Extracts application page (see isotope.com/applications/metabolic research/metabolomics mixtures and kits).

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results

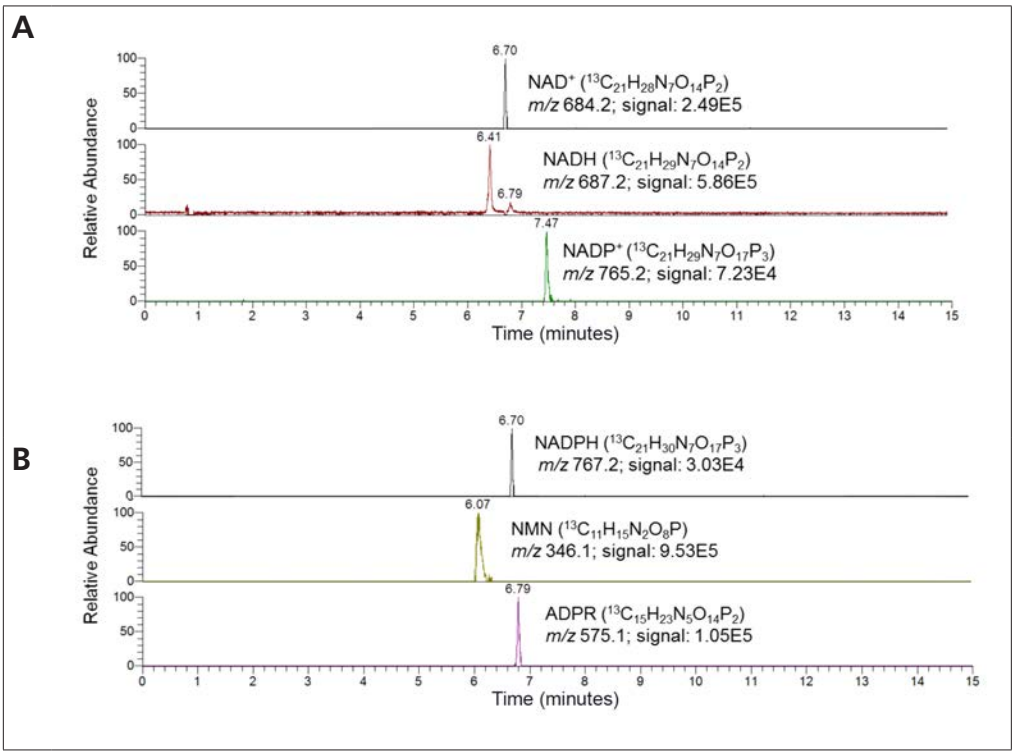

Figure. Representative XICs of ^{13}C-labeled cofactors measured by HILIC-MS (positive ESI, Q Exactive HF). Shown in **A** are the routinely identified metabolites and **B** the additionally observed cofactors. Procedurally, the extract was reconstituted in 2 mL water then diluted 1:10 before analysis. The HILIC separation utilized an Acquity UPLC BEH Amide column (100 × 2.1 mm, 1.7 µm particles).

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Application Notes

Percy, A.J.; Munjoma, N.; Heywood, D.; et al. **2022**. Targeted MRM screening of U-^{13}C lipid yeast extracts for robust lipidomics applications. (CIL application note #54)

Mohsin, S.B.; Batoon, P. **2022**. Absolute quantitation of fragile metabolites by isotope dilution mass spectrometry on the Agilent 6495 Triple Quadrupole LC/MS. (Agilent application no. 5994-4439EN)

E. coli Cell Extracts

Compositions

Condensed table of example metabolites detected in the *E. coli* extract samples (see **PMID: 29256075** for application details). The spread of logPs (source: ALOGPS) highlights the breadth of physicochemical diversity.

Compound (Abbrev. or Alt. Name)	LogP	Metabolite Class
Adenine (Ade)	-0.38	Nucleobase
Adenosine monophosphate (AMP)	-2.30	Nucleotide
Biotin (vitamin B_7)	0.30	Vitamin
Coenzyme Q10 (CoQ10; ubiquinone)	9.94	Coenzyme
Diacylglycerol (DG) 17:0/17:0	10.16	Lipid
Diacylglycerol (DG) 18:0/18:2	10.28	Lipid
Diacylglyercol (DG) 18:1/18:1	10.26	Lipid
Elaidic acid (EA; *trans* 18:1)	7.68	Fatty acid
Glutathione (GSH)	-2.70	Peptide
Oleic acid (OA; 18:1)	7.68	Fatty acid
Palmitic acid (PAL; 16:0)	7.23	Fatty acid
Palmitoyl CoA (PAL-CoA)	2.35	Coenzyme
Phosphatidylcholine (PC) 18:2/18:2	5.68	Lipid
Phosphatidylethanolamine (PE) 16:1/16:1	7.89	Lipid
Phosphatidylethanolamine (PE) 18:1/18:1	8.81	Lipid
Phenethylamine (PEA)	1.41	Neurotransmitter
Proline (Pro)	-2.70	Amino acid
Phosphatidylserine (PS) 18:1/18:1	4.96	Lipid
Retinol (vitamin A)	6.38	Vitamin
Stearic acid (STE; 18:0)	8.02	Fatty acid
Thymidine (Thd)	-1.30	Nucleoside
Tryptophan (Trp)	1.04	Amino acid
Uracil (U)	-1.20	Nucleobase
Uridine (Uri)	-1.80	Nucleoside

Usage Specifications

Criteria	Recommendation
No of sample runs	≤20 (with 5 µL LC-MS injections)
Storage	-80°C; protect from light, air, and moisture
Recommended retest	2 years

Solution Preparation Procedure

1. Reconstitute the dried-down extracts in 100 µL of ACN:water (e.g., 1:1 v/v). **Note:** Alternate solvent ratios are possible without impact to the credentialing approach. Changing the ratio to increase ACN or water will simply increase the coverage of organic or water-soluble metabolites, respectively.
2. Sonicate briefly the solutions (equates to 40 µL/mg of *E. coli* extract) then centrifuge (e.g., for 15 min at 13,000 RPM and 4°C) and incubate overnight at 4°C. This results in a clear solution.
3. Mix aliquots of the unlabeled and ^{13}C-labeled extracts (at 99% isotopic enrichment) into autosampler vials at distinct ratios (e.g., 1:2 and 1:1 v/v). Vortex briefly.
4. Load the vials onto an autosampler rack for the benchmarking optimizations.

Companion unlabeled standard mixes and kits may be available; please inquire.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example Results

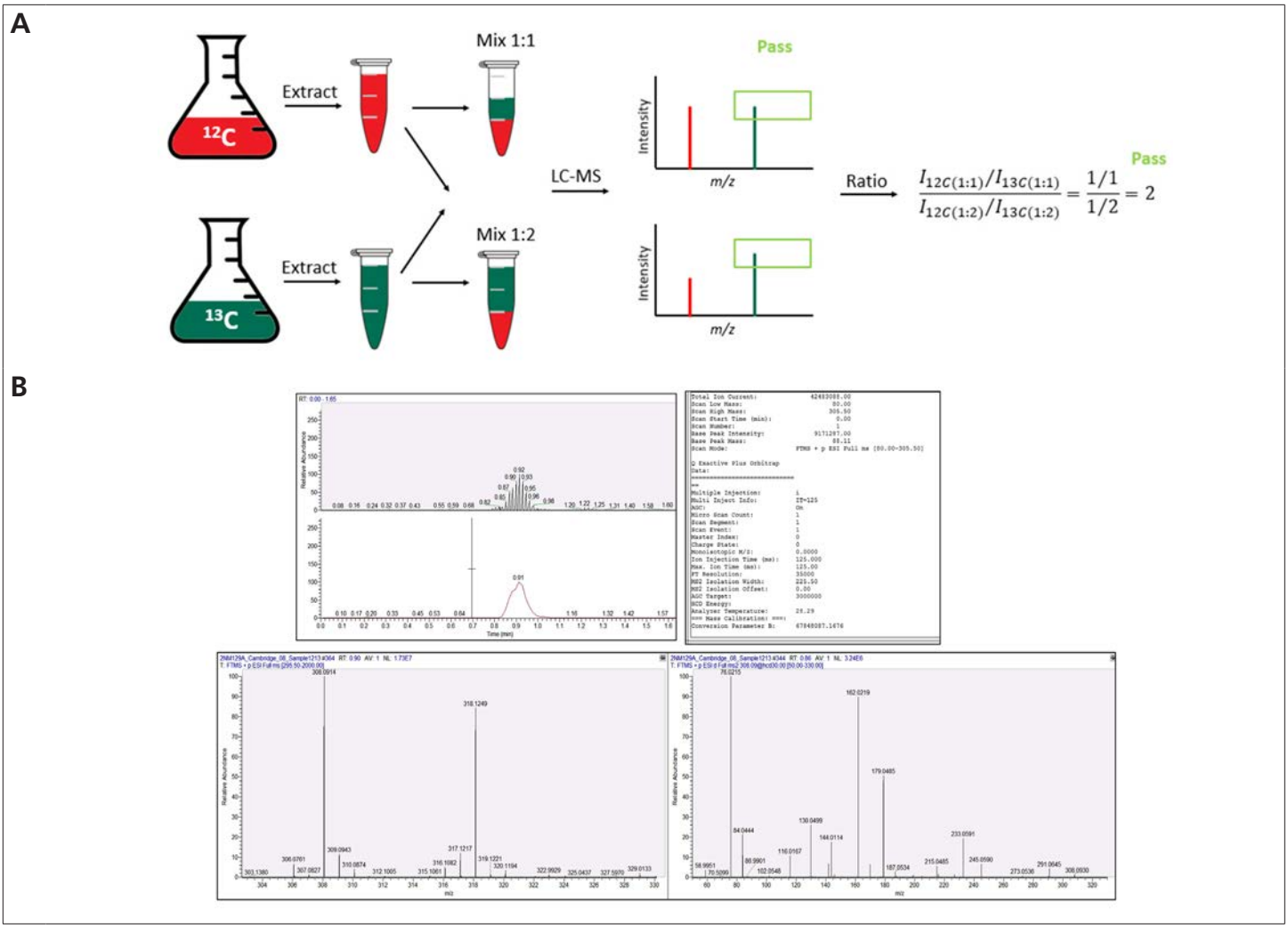

Figure. Credentialing benchmark approach for untargeted metabolomics. **A** Schematic of the credentialing workflow (abridged from **PMID: 25160088**) used to discriminate features of biological origin from contaminants and artifacts. The filtering criteria is based on feature ratios, with I being the intensity. **B** Credentialed metabolite measured on a Q Exactive Plus. Shown are the LC-MS details and spectra for glutathione ($C_{10}H_{17}N_3O_6S$). The M+0 in the MS survey scan is at *m/z* 308.0914, while the M+U is at 318.1249.

Example References

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Companion unlabeled standard mixes and kits may be available; please inquire.

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PeptiQuant™ Plus Assay Kits

Researchers in academia and life science industries continue to implement a bottom-up MS-based workflow for protein biomarker screening. Biomarker verification/validation requires absolute quantification of surrogate peptides in a sample matrix, a requirement that is best achieved using well-characterized stable isotope-labeled standards. To ensure robust quantitative measurements, QC checks should be routinely performed. CIL offers a collection of PeptiQuant Assay Kits (from MRM Proteomics Inc.) for QC and biomarker assessment using bottom-up LC-MS/MS methodologies. The QC kits are designed to evaluate the performance of an LC-MS platform, either alone or in combination with a human plasma proteomics workflow (see corresponding flyer for panel details). The biomarker assessment kits (BAKs) are intended to help researchers screen target panels of candidate protein disease biomarkers in human or mouse plasma samples (see corresponding flyer for panel details). The current platform-specific offerings for each kit type are listed in the overview below.

MRM Proteomics
mrmproteomics.com

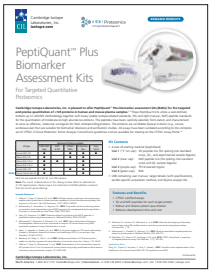
Overview

QC Kits

Catalog No.	Description	Kit Contents	No. of Peptides	Unit Size	Optimized Instrument
LCMSP-QC	PeptiQuant Plus Human Plasma Daily QC Kit	• $^{13}C/^{15}N$-labeled peptide mix • USB (e.g., user manual, acquisition and analysis files)	35	10, 20, or 50 injections	• 6490/6495 QqQ • QTRAP® 6500 • Q Exactive™ Plus
WFPK	PeptiQuant Plus Human Plasma Workflow QC Kit	• $^{13}C/^{15}N$-labeled peptide mix • unlabeled peptide mix • trypsin • BSA • human plasma • USB (e.g., user manual, acquisition and analysis files)	35	1 or 2 runs	• 6490/6495 QqQ • QTRAP 6500 • Q Exactive Plus

Biomarker Assessment Kits (BAKs)

Catalog No.	Description	Kit Contents	No. of Quant. Proteins	Unit Size	Optimized Instrument
Human					
BAK-125	PeptiQuant Plus Human Plasma Proteomics Kit	• $^{13}C/^{15}N$-labeled peptide mix • unlabeled peptide mix • trypsin • BSA • USB (e.g., user manual, acquisition and analysis files)	125	20, 50, or 100 samples	• 6490/6495 QqQ • QTRAP 6500 • Q Exactive Plus • Xevo TQ-XS
BAK-270	Expanded PeptiQuant Plus Human Plasma Proteomics Kit	• $^{13}C/^{15}N$-labeled peptide mix • unlabeled peptide mix • trypsin • BSA • USB (e.g., user manual, acquisition and analysis files)	270	20, 50, or 100 samples	• 6490/6495 QqQ • QTRAP 6500 • Q Exactive Plus
BAK-CNCR50	DiseaseQuant Human Tissue Cancer Pathway Proteomics Kit	• $^{13}C/^{15}N$-labeled peptide mix • unlabeled peptide mix • trypsin • BSA • USB (e.g., user manual, acquisition and analysis files)	50	50 or 100 samples	• 6490/6495 QqQ • Q Exactive Plus
Mouse					
M-BAK-125*	PeptiQuant Plus Mouse Plasma Proteomics Kit	• $^{13}C/^{15}N$-labeled peptide mix • unlabeled peptide mix • trypsin • BSA • USB (e.g., user manual, acquisition and analysis files)	125	20, 50, or 100 samples	• 6490/6495 QqQ • QTRAP 6500 • Q Exactive Plus • 6545 Q-TOF



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**Alternate sets of 125 target proteins are available (see PeptiQuant Plus BAK flyer for details).*

PeptiQuant is a trademark of MRM Proteomics Inc.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Usage Specifications

Before reconstitution (for peptide mixes):	
Storage	-80°C
Recommended retest	6 months from date of manufacture

Note: The dried-down trypsin and BSA materials supplied with the BAKs are not stable at room temperature and must be stored at 4°C. Trypsin is to be prepared immediately prior to use and stored on ice until then.

Example Results

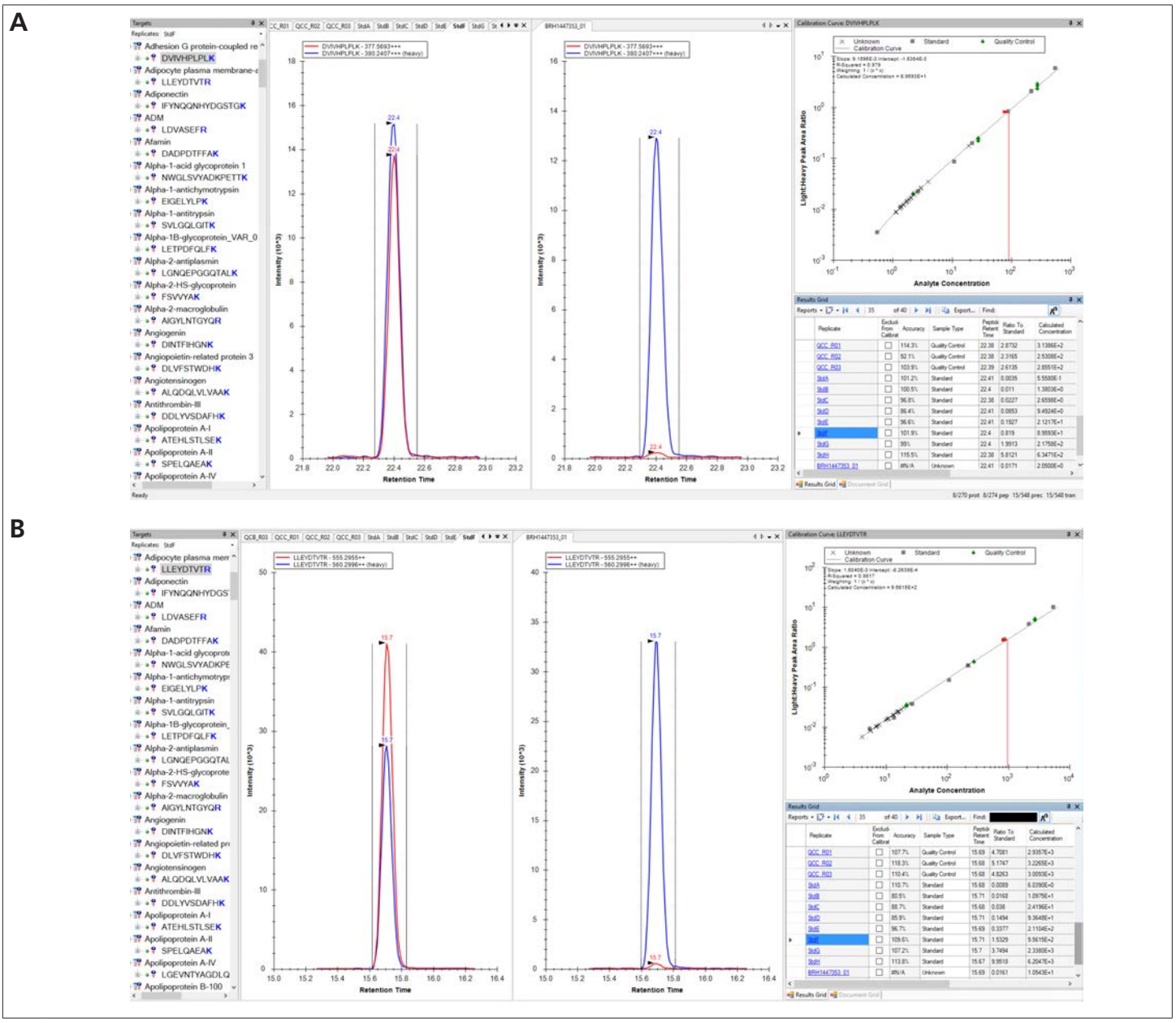

Figure. Bottom-up LC-MRM/MS data for two representative, low abundance targets from a PeptiQuant Plus BAK-270 analysis. Illustrated are Skyline screenshots for peptide DVIVHPLPLK (from Adhesion G protein-coupled receptor F5, gene ADGRF5, UniProtKB Q8IZF2) in **A** and peptide LLEYDTVTR (from Adipocyte plasma membrane-associated protein, gene APMAP, UniProtKB Q9HDC9) in **B**. The tabs refer to the monitored panel, two example XICs (for curve calibrant level F and a pooled human plasma sample analysis), the standard curve (with calibrant levels marked with gray squares, QC samples with green diamonds, experimental sample with red arrow), and the results grid. The protein concentration in the pooled human plasma sample was determined to be 321.2 ng/mL for ADGRF5 and 439.9 ng/mL for APMAP. Results courtesy of MRM Proteomics.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Example References

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Application Note

Percy, A.J.; Trouvé, R.; Lehmann, S.; Hirtz, C. Vialaret, J. **2021**. Translation and implementation of the PeptiQuant™ Plus Human Plasma BAK-270. (CIL application note #50)

"The PeptiQuant Plus Platform Performance Kit has proven to be a vital component of our everyday quality assurance that enables us to deliver high-quality targeted proteomics data in an accurate and timely manner. This kit has a 'dilute and shoot' operation and comes with vendor-specific LC-MRM/MS parameters and a Skyline analysis file for quick input and results output. Altogether, the performance kit is an excellent means to rapidly assess LC-MS performance that should become a routine staple in a proteomic user's toolbox."

– Tasso Miliotis, PhD
Associate Principal Scientist at AstraZeneca Gothenburg (Sweden)

"PeptiQuant Plus Assay Kits contain all the essential materials, including the standards and methods, for performing absolute protein quantification by LC-MRM/MS in a standardized way. The standard protocol helped us reduce the assay development time, while improve the reproducibility and precision of multiplex protein quantification. In addition to the biomarker assessment kits, the quality control kits enable the instrument performance and assay reproducibility to be monitored and assessed, which ultimately provided us confidence in the reliability of the quantification results."

– Elaine Wong, PhD
Scientific Officer at Queen Mary Hospital, Fu Lam (Hong Kong)

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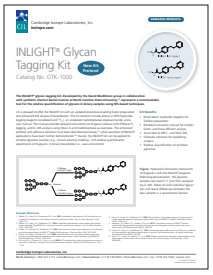
INLIGHT® Glycan Tagging Kit



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Glycans participate in a large number of cellular, molecular, and biological processes and are implicated in a number of diseases (e.g., Alzheimer's, cancer). To aid the identification and relative quantification of glycans by LC-MS, CIL offers the innovative INLIGHT® (Individuality Normalization when Labeling with Isotopic Glycan Hydrazide Tag) glycan-tagging kit. This kit employs both natural (NAT – $^{12}C_6$) and stable isotope-labeled (SIL – $^{13}C_6$) phenyl 2-GPN reagents in the hydrazide derivatization of free *N*-glycans. While this tagging strategy was developed for *N*-glycans, it has also been adapted to sample analysis of *O*-glycan and heparin oligomer profiles. The INLIGHT kit contains five vials of NAT reagent and five vials of SIL reagent, which in total provides sufficient tagging for approximately 125 relative quantification experiments. The user manual provides step-by-step instructions for executing the modified INLIGHT strategy using maltoheptaose and fetuin A as examples. Data processing and analysis of derivatized glycans can be facilitated in GlycoHunter or Skyline.

Overview

Catalog No.	Description	Kit Contents
GTK-1000	INLIGHT® Glycan Tagging Kit	• Light phenyl 2-GPN INLIGHT reagent (5 × 0.25 mg) • Heavy phenyl 2-GPN INLIGHT reagent ($^{13}C_6$; 5 × 0.25 mg) • Unlabeled maltoheptaose (5 × 10 µg)

Usage Specifications

Criteria	Recommendation
No. of Uses	25 per vial
Before reconstitution:	
Storage	ambient temperature; protect from light and moisture
Recommended retest	5 years from date of manufacture

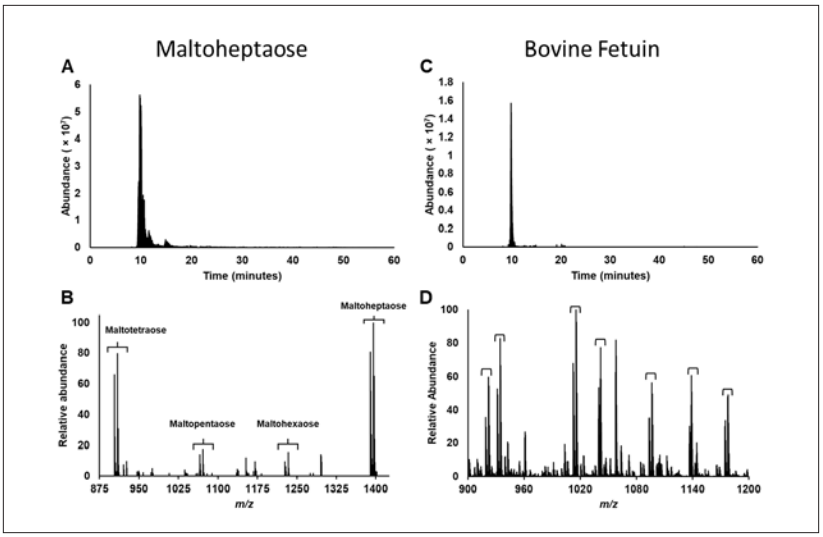

Figure. LC-MS examples of INLIGHT derivatized maltoheptaose and *N*-linked glycans from bovine fetuin.

A. Extracted ion chromatogram of $[NAT + H]^+$ maltoheptaose.

B. Mass spectrum at 10 minutes illustrating NAT and SIL derivatized maltoheptaose, maltohexaose, maltopentaose, and maltotetraose.

C. Extracted ion chromatogram of a fetuin-based glycan at *m/z* 1012.3980 corresponding to $[NAT + 2H + (Fuc)_1(Gal)_2(GlcNAc)_4(Man)_3]^{2+}$.

D. Average mass spectrum of a fetuin analysis showing the NAT and SIL derivatized *N*-linked glycan pairs in the LC window 8-11 min.

Example References

Butler, K.E.; Kalmar, J.G.; Muddiman, D.C.; et al. **2022**. Utilizing liquid chromatography, ion mobility spectrometry, and mass spectrometry to assess INLIGHT™ derivatized N-linked glycans in biological samples. *Anal Bioanal Chem, 414(1),* 623-637.

Kalmar, J.G.; Garrard, K.P.; Muddiman, D.C. **2021**. GlycoHunter: An open-source software for the detection and relative quantification of INLIGHT®-labeled *N*-linked glycans. *J Proteome Res, 20(4)*, 1855-1863.

Kalmar, J.G.; Butler, K.E; Baker, E.S.; et al. **2020**. Enhanced protocol for quantitative *N*-linked glycomics analysis using Individuality Normalization when Labeling with Isotopic Glycan Hydrazide Tags (INLIGHT).® *Anal Bioanal Chem, 412(27),* 7569-7579.

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Hecht, E.S.; Scholl, E.H.; Walker, S.H.; et al. **2015**. Relative quantification and higher-order modeling of the plasma glycan cancer burden ratio in ovarian cancer case-control samples. *J Proteome Res, 14(10),* 4394-4401.

Chemical purity (CP) is 98% or greater, unless otherwise indicated.

For research use only. Not for use in diagnostic procedures.

Q&As

Listed below are a series of general Q&As for CIL's mixes and kits. Product-specific FAQs can be located at isotope.com/applications/ under their corresponding product application page (e.g., Metabolic Research → Metabolomics Mixtures and Kits → QReSS Kits).

What are the advantages of selecting an off-the-shelf mix vs. a collection of individual isotope standards for self-mixing?

The MSK/NSK products are formulated to exacting standards following detailed batch records developed from over 20 years of formulation experience. Following production, randomly selected vials are analyzed to ensure both accuracy and consistency. The astute attention and process control generates exceptional vial-to-vial and lot-to-lot reproducibility. This high reproducibility return is one of the merits of utilizing CIL prepared mixes. Additional advantages are:

- reduced development time and cost;
- enhanced data quality;
- ease of user implementation; and
- improved confidence in analytical results.

The majority of the mixes are ^{13}C- and/or ^{15}N-labeled. What are the advantages of ^{13}C/^{15}N-labeling vs. D-labeled in MS measurements?

The nature of the stable isotope can potentially impact the preanalytical (e.g., storage and handling) and analytical (e.g., sample preparation and processing) phases of an experiment. In comparison to D labels, ^{13}C/^{15}N labels can have:

- improved isotope stability;
- negligible isotope scrambling issues;
- conserved chromatographic elution (relative to its unlabeled standard); and
- heightened analytical reliability.

In cases where D-labeled compounds were selected, the D-label is located at nonexchangeable positions and was stability tested for preservation as well as product application. For further background, please refer to our technical note that describes the benefits of ^{13}C vs. D standards in MS-based studies.

How often should QC measurements be performed, and what mixes are most suitable?

Prior to first use, QCs should be conducted several times in succession prior to sample analysis to establish baseline performance and intervention limits. Once established, QCs should be performed routinely (i.e., before, during, and after sample analysis) to monitor the effectiveness of the analytical method and instrument platform over time. While all of CIL's mixes could be used in these types of operations, the ones ideally suited for these type of measurements are the metabolomic QC kits (see **MSK-QC-KIT** and **MSK-QReSS-KIT**) and the proteomic QC kits (see **PeptiQuant Plus** daily and workflow QC kits).

In a targeted quantitative application, how many MRM transitions should be monitored per analyte?

Ideally, a minimum of two MRM transitions per compound (be it metabolite or peptide) should be targeted. This will allow for a quantifier and qualifier(s) assignment, with the ion ratios serving as an additional metric for performance qualification. Nonetheless, this may not be possible for all analytes given the compound's fragmentation chemistry, the employed MS/MS parameters, and the mode of operation utilized. Empirical experiments with isotope-labeled standards should therefore be first performed to optimize the MS/MS parameters prior to conducting the quantitative study with precious experimental samples.

Can custom mixes or add-on vials be formulated?

Yes, we have the ability to customize. We would first review feasibility and then provide a quotation on your specific mix. To start this process, please provide the necessary details on this **custom mix request form** or contact your local sales representative.

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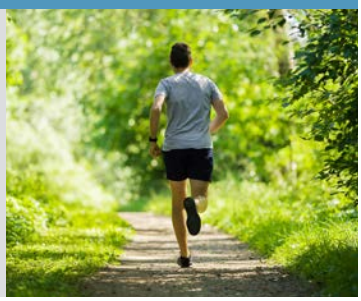
Please visit isotope.com for a complete list of isotope-labeled compounds.

Research products are distributed and sold worldwide via our extensive network.
CIL's distributor listing is available at isotope.com.

To request a quotation or place an order:
North America: 1.978.749.8000 | 1.800.322.1174 | cilsales@isotope.com
International: +1.978.749.8000 | intlsales@isotope.com
Fax: 1.978.749.2768 | isotope.com



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