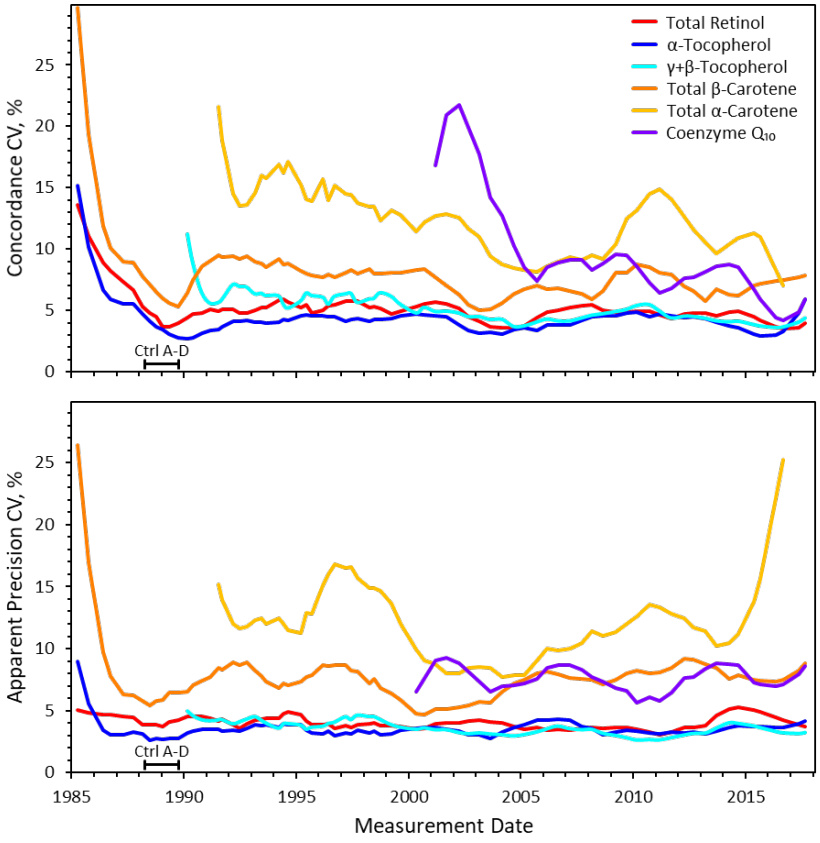
NIST Internal Report
NIST IR 7880-50

NIST Micronutrients Measurement Quality Assurance Program:

Performance History of the Fat-Soluble Vitamin-Related Studies



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September 2022

U.S. Department of Commerce
Gina M. Raimondo, Secretary

National Institute of Standards and Technology
Laurie E. Locascio, NIST Director and Under Secretary of Commerce for Standards and Technology

NIST IR 7880-50
September 2022

Publication History
Approved by the NIST Editorial Review Board on 2022-09-20

How to Cite this NIST Technical Series Publication
Duewer DL, Kline MC, May WE, Sharpless KE, Thomas JB (2022) NIST Micronutrients Measurement Quality Assurance Program: Performance History of the Fat-Soluble Vitamin-Related Studies. (National Institute of Standards and Technology, Gaithersburg, MD), NIST Internal Report (IR) NIST IR 7880-50.
https://doi.org/10.6028/NIST.IR.7880-50

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Abstract

From 1984 to 2017, the National Institute of Standards and Technology (NIST) Micronutrients Measurement Quality Assurance Program (MMQAP) coordinated 79 "Round Robin" (RR) interlaboratory studies designed to improve measurement comparability among laboratories measuring fat-soluble vitamins and carotenoids in human serum and plasma. The initial study had 22 participants; participation increased to 58 in 1997 and then declined in stages to 29 by 2017. A total of 138 academic, commercial, governmental, or non-governmental organizations actively participated in at least one RR; two laboratories participated in 77 of the 79 RRs. A total of 350 human serum or plasma samples were distributed in the RRs, typically three to five per RR. One hundred thirty one (131) of these samples were unique materials. While the initial RRs focused on just "retinol" (vitamin A), α-tocopherol (vitamin E), and "β-carotene" (provitamin A), over the life of the program 57 vitamin-related measurands were reported at least once. Fifteen (15) measurands were reported sufficiently often to enable analysis of measurement performance over time: total retinol, retinyl palmitate, α-tocopherol, γ- plus β-tocopherol, total β-carotene, *trans*-β-carotene, total *cis*-β-carotene, total α-carotene, total lycopene, *trans*-lycopene, total β-cryptoxanthin, total lutein, total zeaxanthin, total lutein plus zeaxanthin, and coenzyme Q_{10}. In addition to documenting the number and nature of the MMQAP's participants, measurands, materials, and reported measurements, this report explores the evolution of among-participant concordance and within-participant apparent precision as functions of calendar date documents and the relationships among results reported for materials delivered to participants both as liquid-frozen and lyophilized samples.

Keywords

Apparent Precision; Carotenoids; Coenzyme Q_{10}; Concordance; Human serum; Interlaboratory Measurement Reproducibility Functions; Liquid-Frozen Samples; Lyophilized Samples; Micronutrients Measurement Quality Assurance Program (MMQAP); SRM 968; Retinol; Robust Scale Estimators; Tocopherols.

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Acknowledgments

We thank our colleagues who over the years contributed to the Micronutrients Measurement Quality Assurance Program (MMQAP) studies and related materials by making measurements, analyzing results, preparing documentation, and helping deliver samples to the Round Robin participants: Carolyn Burdette, Neal Craft, Chris Christensen, Polly Ellerbe, Ken Gary, Lisa Gill, Bill MacCrehan, Sam Margolis, Isaac Mugenya, Reenie Parris, Karen Phinney, Robert Paule, Janet Redmond, Filmer Ruegg, Lane Sander, Robert Schaffer, Susannah Shiller, Susan Tai, Emil Schönberger, Lorna Sniegoski, Mark Vangel, Mike Welch, and James Yen. We especially thank the many participants in the MMQAP interlaboratory comparison studies for their questions, suggestions, interest, and patience.

1. Introduction

From its inception in 1984 until its end in 2017, the evolution of the National Institute of Standards and Technology (NIST) Micronutrients Measurement Quality Assurance Program (MMQAP) encompassed 79 interlaboratory studies (ILS) designed to promote improved measurement comparability for fat-soluble vitamins and vitamin-related compounds. These studies were termed "Round Robins" (RRs) followed by a sequential index expressed in Roman numerals (I to LXXXII), however it is more convenient to refer to them using the Arabic equivalents (1 to 82). The complete results from the individual studies are documented elsewhere [1- 48].

The MMQAP originated as a joint project of the National Bureau of Standards (NBS, now NIST) and the National Institutes of Health's National Cancer Institute (NCI). The project was designed to support and improve the analytical measurements of selected measurands with potential cancer chemopreventive activity [49,50]. In addition to the fat-soluble vitamin-related ILS, the project supported several ILS devoted to selenium and zinc measurements, more than 43 ILS devoted to ascorbic acid (vitamin C) [8-46], analytical method development [51- 66], workshops and tutorials [67], data analysis and visualization [68- 72], material characterization [73- 75], and creation of certified reference materials (CRMs) [76- 88].

NCI ended its financial sponsorship of the MMQAP in 1998. With financial support and encouragement from the US Centers for Disease Control and Prevention (CDC), NIST continued many of the components of the program as a service to the clinical and nutritional communities.

2. Participants

Table 1, Table 2, and Table 3 list the laboratories that submitted measurement results for at least one measurand in at least one MMQAP fat-soluble vitamin-related ILS. The few organizations that requested and received samples but did not report results are not included.

The RRs are identified by calendar year and number in the first and second rows. The "Code" column lists the participant identifier as listed in the NISTIR-7880 series of reports [1-48]. Participants are listed in order of first reported results. The numbers along each row beneath the header lines identify the number of measurands that the participant reported in the given RR. For participants who reported results for more than one analysis method, these numbers reflect the maximum number of measurands evaluated using any of the methods.

Table 1. Participation History, 1984 Through 1994.

	1984	1985	1985	1985	1986	1986	1987	1987	1988	1988	1988	1989	1989	1989	1990	1990	1990	1991	1991	1991	1992	1992	1992	1993	1993	1993	1994	1994	1994
Code	01	02	03	05	07	08	09	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
FSV-BD	2	3	2	3	3	2	2	2	2	2	2	2	3	3	3	3	2	2	2	3	2	2	2	2	2	2	2	2	2
FSV-BE	1	6	3	6	3	2		2	3	2	2	2	3	3	3	3	2	2	2	3	2	6	6	6	6	5	5	5	5
FSV-BF	3	6	3	6	3	3	3	3	3	3	3	3	4	4	6		5	5	5	7	5	6	6	6	6	6	6	6	6
FSV-BG	1	3	2	4	2	2	3	3	3	3	3	3	4	4	4				5	4	4	5	6	5	4	4			
FSV-BI	1	4	2	4	3	3	3	3	3	3	3	3	4	4	6	5	6	6	8	9	10	11	11	11	11	11	11	11	11
FSV-CO	2	6		6	2	3	3	3	3	3	3	3	4	4	4	3	3	3	3	4	3	3	3	3	3	3	11	11	12
FSV-CA	3	6	3	4	2	2	2		2	2	2	2	3	3	3	2	3	2	2	3	3	2	2	2	2	2	2	2	2
FSV-BY	1	4	2	4	2	2	2	2	2	3	3	3	4	3	6	6	6	6	6	8	11	9	9	9	9	11	11	11	11
FSV-CJ	1	4	2	3	3	3	3	3	3	3	3	3	3	4	4	3	3	3	7	8	7	7	7	7	7	8	7	6	
FSV-CL	2	6	3	6	3	3	3		3	3											9						7		7
FSV-CN	1	4	2	6	3	3		2	3	3	3	3	4	4	4	5													
FSV-DE	1	2	2	2	1	1	1	1	1	1	1	2	3	2	3	2	2	2	2	3	2								
FSV-DG	3	6	3	6	3	3	3	3	3	3	3	3	4	4	4	3	3	3	3	4									
FSV-DH	2	8	3	6	3	2	2	2	2				4	4	7	8	8	8	6	5									
FSV-DT	1	4	2	4	2	2	2	2	3	2	2	2	4	3	3		3												
FSV-DN	2	6	3	6	3	3	3	3	3	3	3	3		4		5	3	3											
FSV-DO	1	2	1	2	1	1	1	1	1	1	1	1		3		3	3			4									
FSV-EG	1	3	2	4	2	2	2	2	2	2	2																		
FSV-EP	2	4	2	4	2	2	2	2	2																				
FSV-ER	3	6	3	6	3	3	3	3																					
FSV-FO	2	6			2																								
FSV-GA	2																												
FSV-EU			2	4	3	3	3	2	2																				
FSV-BA				2		1	3	3	5	5	5	5	5	5	9	3	5	8	11	12	11	12	11	11	11	11	9	11	11
FSV-DC				4	2	2	2	2	2	2	2	2	3	3	3	3	2	5	4		6	4	4	2	4				
FSV-EO				4	2		2	1	4	2			3	3		2													
FSV-EN				2	2	2			2	2											3	3			3	3			
FSV-EW				6	3	3	3	3	3																				
FSV-DZ					2	3	2		2	2	2	2	3	3	3	2		2											
FSV-GC					2																								
FSV-BH						3		2	3	3	5	3	5	5	9	7	8	8	12	13	13	13	13	13	12	13	11	9	12
FSV-CK						3	3	2	5			3			9			6	10	11	10			8		8	8	8	8
FSV-ED						3	3	2	3	3	3	3	4	4		3			3										
FSV-BZ							2	1	2	2	2	2	3	3	2	1	1	1	1	2		1	2	2	6	6	6	6	6
FSV-BX							3	2	3	3			2							4	7		3	7	3		3		7
FSV-FI							1	1	1	1																			
FSV-FE									3	3		2	3																
FSV-CQ										1		3	4	4	7	3	3	3	3		3	3	3	3		3	3	3	3
FSV-CY										3	3	3	4	4	6	5	3	3	3	3	3	3	3	3	3	3	3	3	3
FSV-EF										2	2	2		3	4	3	3	3	3	4	3								
FSV-BL												2	2	3	3	3		2	2	3	2		2	2	2	2	2	2	2

	1984	1985	1985	1985	1986	1986	1987	1987	1988	1988	1988	1989	1989	1989	1990	1990	1990	1991	1991	1991	1992	1992	1992	1993	1993	1993	1994	1994	1994
Code	01	02	03	05	07	08	09	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
FSV-CM												2	3	3	2	1	1	1	1	2	1	1	1	1	1	1		1
FSV-DY												2	3	3	3	2		3	2	7	7	3	5	4					
FSV-FX												1	2																
FSV-CS													2	2		2					1								
FSV-FA													3	4	7	6	5												
FSV-FV														2		2													
FSV-BJ															6	5	6	6	7	8	6	7	7	7	7	7	7	7	7
FSV-BM															3	2	2	2	2	2	2			2	2	2	2	2	2
FSV-CV															4	5	5	5	6	6	6	6	6	5	6	6	6	4	5
FSV-DL															3	2	2	2	6	7	5	7	5	6			7	8	8
FSV-EB															4	3	3	3	3	4	3	3	3	3	3	3			
FSV-EV															3	2	2	2	2	2	2								
FSV-BK																2	2	2	2	2	2	2	2	2	2	2	2	2	2
FSV-CH																3	3	3	3	4	3	3	3	6	6	6	6	6	6
FSV-EJ																4		5	6	5	6	6	6	6		6			
FSV-EY																2	2	2	2	3	2								
FSV-FQ																3	4												
FSV-CP																		2	5	5	5	7	6	7	7	6	7	6	
FSV-DM																		2	3	4	3	3	3	3	3	3	3		
FSV-FL																		3	3	4									
FSV-FR																		3		3									
FSV-BN																			12	10	12	12	13	9	11	13	11	3	15
FSV-BS																			2	3	5		1		4		1	1	
FSV-BP																			6	7	6	5	5	5	6	6	6	6	6
FSV-CB																			2		2	2	2	2	2	7	7	7	7
FSV-CT																			5	6	5	1		5	5	6	8		4
FSV-CU																			6	5	6	6	6	6	6	6	6	6	6
FSV-CX																			5	4						7	8	9	9
FSV-DW																			5	1	7								
FSV-EA																			3	4	2			4		6	8	7	7
FSV-EI																			3	5	4			4		10			
FSV-FM																			3	4	3								
FSV-FU																			2	2									
FSV-FS																			3	4									
FSV-GB																				4									
FSV-BO																					3	7	7	6	7	7	7	7	7
FSV-DS																					3	3	3	3	3	3	3	3	3
FSV-EC																					3	3	3	3	3	3	3	3	3
FSV-BT																							3	10	13	15	14	14	15
FSV-BR																								1	1	1	1	1	
FSV-BQ																								3	3	3	3	3	3
FSV-CR																								2	2	2	2	2	2
FSV-DJ																								2	2	2	2	2	2
FSV-DX																								5	6	6	7	11	6
FSV-EK																								6	7	7	6	6	6
FSV-EX																								3	3	3	3	3	3
FSV-FF																								2	2	2	2		
FSV-DK																									2			2	2
FSV-FC																									4	4			
FSV-CG																										8	8	3	
FSV-DU																													3
FSV-FD																													3
NIST	3	4	3	3	3	3	5	3	5	5	4	6	4	5	7	6	8	6	10	11	12	6	12	15	16	16	15	16	12

Table 2. Participation History, 1995 Through 2005.

	1995	1995	1995	1996	1996	1996	1997	1997	1997	1998	1998	1998	1999	1999	2000	2000	2001	2001	2002	2002	2003	3003	2004	2004	2005	2005
Code	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58
FSV-BD	2	2	2	8	8	8	8	8	8	7	8	8	8	2	2	2	3	2	2		2	2	2	2	2	2
FSV-BE	4	4	4	4	4		4	3	2	4	4	4	4	4	4	5	4	4	4	5	6	5	5	5	5	5
FSV-BF			6	6		6	6	8	8	8	8	8	4	9	9	8	8	8	8	8	8	8	8	9	8	8
FSV-BG	6	6	6	6	7	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
FSV-BI	11	11	11	11	11	11	11	11	11	10	11	10	11	11	11	11	11	10	11	11	11	11	11	11	11	11
FSV-CO																										
FSV-CA	2		2	2	2	2	1	2	2																	
FSV-BY	11	11	11	15	15		15	15																		
FSV-CJ	6	7																								
FSV-CL	7					8	8	8	8	11	11	11	9	11	11	11	10	11	9	9	11					
FSV-CN	4	4	5	7	8		8	10	10	10	9			8	8	8										
FSV-DE																										
FSV-DG																										
FSV-DH													18	15												
FSV-DT																										
FSV-DN																										
FSV-DO																										
FSV-EG																										
FSV-EP																										
FSV-ER																										
FSV-FO																										
FSV-GA																										
FSV-EU																										
FSV-BA	11	11	10	11	11	12	11	11	10	11	11	15	15	15	15	15	15	15	15	15	15	15	17	16	16	16
FSV-DC																										
FSV-EO																										
FSV-EN																										
FSV-EW																										
FSV-DZ																										
FSV-GC																										
FSV-BH	11	12	11	13	13	13	12	12	14	12	13	13	12	13	13	15	13	9	13	12	12	12	11	11	12	12
FSV-CK	8	8	8	9	8	11	9	10	10	9	9			8		11		11								
FSV-ED																										
FSV-BZ		5	7	8	8	7	6	8	7	7	6	7	8	8	5											
FSV-BX	10			9	10	10	10	9			10	10	13	10	10	10	12	12	12	12	12	11	11	11	12	11
FSV-FI																										
FSV-FE																										
FSV-CQ		3	3	3	3	3	3	3	3	3	3															
FSV-CY	3	3	3																							
FSV-EF																										
FSV-BL		2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
FSV-CM	1	1	1	1	1	1	1	1	1	1	1	1														
FSV-DY																										
FSV-FX																										
FSV-CS				1	1	1	8	8	8	10	10	10	10	10	9	10					12	12	12	13	10	13
FSV-FA																										
FSV-FV																										
FSV-BJ	7	7	7	7	7	7	7	7	7	6	7	9	8	8	9	9	9	10	10	9	9	10	10	10	10	10
FSV-BM	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
FSV-CV	5	3	3										7	8	9	6	10	10	10							
FSV-DL	9	8					8																			
FSV-EB																										
FSV-EV																										
FSV-BK	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
FSV-CH	6	7	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7								
FSV-EJ	5																									
FSV-EY																										

	1995	1995	1995	1996	1996	1996	1997	1997	1997	1998	1998	1998	1999	1999	2000	2000	2001	2001	2002	2002	2003	3003	2004	2004	2005	2005
Code	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58
FSV-FQ																										
FSV-CP	8		7		7	7	7			7	4	7	7						2	2		7			7	
FSV-DM	3	6	6	6	6	6																				
FSV-FL																										
FSV-FR																										
FSV-BN	14	14	14	16	16	16	16	16	16	16	16	16	16	15	17	17	16	16	16	16	15	16	16	12	17	20
FSV-BS	4	7	7	8	8	8	8	6	4	7	7	9	7	7			10		9	6	7	7	7	9	9	9
FSV-BP	6	5	6	6	6	6	6	6	6	5		6	6	2	7	7	7	7	7	7	7	7	7	7	7	7
FSV-CB	6	2	2	2	2	2	2	2	2	9	9	8	9	9	8	9	9	9	9	9	9	9	9	9		
FSV-CT	3	4	4	4		4	3			8	7			8							6	6	6	6	6	6
FSV-CU	6	6	6	6	4	4	3	3	3	4	4	4	3		3	3										
FSV-CX	9	9	9	9	9	11	11	11	12	12	8	9	9	11	8	9		13								
FSV-DW										11	12	12							10	10	10		5	9	9	9
FSV-EA		7		5		8																				
FSV-EI					13	13	10	10	10																	
FSV-FM																										
FSV-FU																										
FSV-FS																										
FSV-GB																										
FSV-BO	7	6	7	7	7	7	7	7	7	7	9	9	9	11	11	11	9	9	9	9	10	9	12	9	9	9
FSV-DS		3	3	3	3	3	3																			
FSV-EC	3		3																							
FSV-BT	14	18	17	18	15	16	17		18		18	18	18	18		16	19		16	17	14	16		14		14
FSV-BR	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	3	3	3	3	3	3	3	3	3	3
FSV-BQ	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
FSV-CR	2	2	2	2	2	2	4	3	3	3	2	3	3	3	2	2	2	2	2	2	2					
FSV-DJ	2	2	2	2	2	2	2	2	2	2	2	1														
FSV-DX	7	6	6	5	5	5																				
FSV-EK	4	4	4	6																						
FSV-EX																										
FSV-FF																										
FSV-DK	2	5	4	5	6	6		8	8	8		6	6	6	6	6										
FSV-FC		5	5																							
FSV-CG				8			8		8				12	12	14	12	14	14	14	14	12	12	12	12	12	12
FSV-DU				3		3	3		3		3	3	3	3	3	3	5	4	4							
FSV-FD	3	3	5																							
FSV-BU	9	8	5	4	2	5	8	8	8	8	8	8	8	8	8	8	8	8	8	5	8	8	8	8	7	8
FSV-BV	8	6	7			7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
FSV-CD	9	9	9	10			9	9	9	10	10	10	10	10	9	9	10	10	9	9	9	9	9	9	10	10
FSV-DA	14	15	14	15	16	16	16	16	16		16	16			16	16					21	18	20	21	24	23
FSV-DB	3	3	3	6	6		6	6	6	6	6	6	6	6	6	6	6	6							8	8
FSV-DP	1	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1										
FSV-EH	12	10	13	14	12	14							15	15			17	16								
FSV-EL	1	1	1	1	1	1	1	1	1		1															
FSV-FP	6	6																								
FSV-BW				7	6	7	7	7	7	7	7	7	7	7	7	7	8	7	7	7	10	12	12	12	11	12
FSV-CF				2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	2	2	2
FSV-CC				2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3
FSV-FY					4																					
FSV-DR						3	3	3	3	3	3	3	3	3	3	3	3	3	3	3						
FSV-CE							3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
FSV-DQ							8	8	8						9	9	9	9	9	9						
FSV-EM							3	3	3	8	6		7	7	7	8										
FSV-FN							3	3	3																	
FSV-CI										3	3	3	4	4	4	4	4	4	10	10	11	11	11	10	11	11
FSV-DF										1	1	1	1	2	1	1	1	1	1	2	2	2	1	1	1	1
FSV-ES										10	9	10	10	10	10	10										
FSV-FG										2	2	2		2												
FSV-FH											1	1			2	2										

	1995	1995	1995	1996	1996	1996	1997	1997	1997	1998	1998	1998	1999	1999	2000	2000	2001	2001	2002	2002	2003	3003	2004	2004	2005	2005
Code	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58
FSV-DD													1	1			2	2	2	1	2			1	1	2
FSV-EQ													7	7	7	9	9	9	7	9						
FSV-CW															16	18	20	19	20	20	19		15	15	13	14
FSV-DI															10	10	11	10	11	11	11	11	10	10	10	12
FSV-FT															2	2										
FSV-FW															1	1										
FSV-FJ																5	5	5								
FSV-CZ																	4	4	4	4	4	4	4	4	4	4
FSV-FB																	14	14	13	10						
FSV-ET																			4	4	4	4	4	4	4	
FSV-DV																									2	2
NIST	15	16	14	16	16	15	14	17	7	11	12	14	13	13	15	16	19	20	19	19	18	17	19	10	13	8

Table 3. Participation History, 2006 Through 2017.

	2006	2006	2007	2007	2008	2008	2009	2009	2010	2010	2011	2011	2012	2012	2013	2013	2014	2014	2015	2015	2016	2016	2017	2017
Code	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
FSV-BD	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		3	2	5	2
FSV-BE	4	5	5	5	5	6	6	6	6	6	6	6	6	6	5	6	6	6	6	6	6	6	7	6
FSV-BF	8	8	8	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	2	2	2		
FSV-BG	12	12	12	12	12	12	10	10	10	10	10	10	10	10	9	10	10	10	10	10	10	10		
FSV-BI	11	9	11	10	10	11																		
FSV-CO															4	7	7	7	7	8	8	8		
FSV-CA																								
FSV-BY																								
FSV-CJ																								
FSV-CL																								
FSV-CN																								
FSV-DE																								
FSV-DG																								
FSV-DH																								
FSV-DT																								
FSV-DN																								
FSV-DO																								
FSV-EG																								
FSV-EP																								
FSV-ER																								
FSV-FO																								
FSV-GA																								
FSV-EU																								
FSV-BA	16	16	17	17	16	16	17	16	16	16	16	16	16	16	14	16	16	16	16	1	1	1	2	1
FSV-DC																								
FSV-EO																								
FSV-EN																								
FSV-EW																								
FSV-DZ																								
FSV-GC																								
FSV-BH	14	14	13	12	12	12	13	13	13	13	12	13			10		11	11	13	7	11	11	19	17
FSV-CK																								
FSV-ED																								
FSV-BZ																								
FSV-BX			13	12																				
FSV-FI																								
FSV-FE																								
FSV-CQ																								
FSV-CY																								

	2006	2006	2007	2007	2008	2008	2009	2009	2010	2010	2011	2011	2012	2012	2013	2013	2014	2014	2015	2015	2016	2016	2017	2017
Code	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
FSV-EF																								
FSV-BL	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
FSV-CM																								
FSV-DY																								
FSV-FX																								
FSV-CS	10	10	10	10																				
FSV-FA																								
FSV-FV																								
FSV-BJ	11	10	10	10	9	10	10	9	10	9	10	9	9	9	8	9	9	9	9	9	9	9	13	9
FSV-BM	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2
FSV-CV																								
FSV-DL																								
FSV-EB																								
FSV-EV																								
FSV-BK	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
FSV-CH																								
FSV-EJ																								
FSV-EY																								
FSV-FQ																								
FSV-CP	7	7					7																	
FSV-DM																								
FSV-FL																								
FSV-FR																								
FSV-BN	17	17	16	16	15	15	15	14	13	14	8	8	7	8	10	7	7	8	7	7	7	7	10	14
FSV-BS	7	9	10	10	8	8	12	8	11	11	13	13	11	13	10		10	15	14	13	14	13	16	10
FSV-BP	7	7		7	7	7	7	7	7	7	7	7	7		6									
FSV-CB																								
FSV-CT	6	6																						
FSV-CU																								
FSV-CX																								
FSV-DW																								
FSV-EA																								
FSV-EI																								
FSV-FM																								
FSV-FU																								
FSV-FS																								
FSV-GB																								
FSV-BO	9	10	12	12	11	12	10	10	12	12	11	11	11	11	10	11	11	10						
FSV-DS																								
FSV-EC																								
FSV-BT	14	14	15	12	13	14		17	16	14	16	14	14		11	16	16	15	15	15	15	15	21	15
FSV-BR	3	3	2	3	3	3	3	2	3	2	2	2	2	2	3	2	3	2	3	2	2	2	4	2
FSV-BQ	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2									
FSV-CR																								
FSV-DJ																								
FSV-DX																								
FSV-EK																								
FSV-EX																								
FSV-FF																								
FSV-DK																								
FSV-FC																								
FSV-CG	12	12	12	12	12	12	12	12	12		11	12	12	12	10	12	12	12	12	12	11	12	17	12
FSV-DU																								
FSV-FD																								
FSV-BU	8	8	8	8	8	8	8	8	8	10	10	10	9	9	7	8	8	8	10	10	8	8	12	8
FSV-BV	8	8	8	8	8	8	8	8	8	8	8	8	8	8	7	8	8	8	8	8	8	9		
FSV-CD		10			9	8	10	10	10	10	10	10	10		9		10	9	10	9	9	9	13	9
FSV-DA									20	20														
FSV-DB	8	8																						

	2006	2006	2007	2007	2008	2008	2009	2009	2010	2010	2011	2011	2012	2012	2013	2013	2014	2014	2015	2015	2016	2016	2017	2017
Code	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82
FSV-DP																								
FSV-EH																								
FSV-EL																								
FSV-FP																								
FSV-BW	12	12	10	12	12	12	12	9	12	12	12	8	10	8	7	8	8	8	8	8	7	9	10	7
FSV-CF	2	2	2	2	2	2	2	2	2	2									3	3	2	2	3	2
FSV-CC	3	3	3	3	3		3	3	3	3	3	3	3	3										
FSV-FY																								
FSV-DR																								
FSV-CE	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	6	4
FSV-DQ	10	9			9	9					9	9												
FSV-EM																								
FSV-FN																								
FSV-CI	11	11	13	12	12	11	11	10	11	11	11	11	11	11	10	11	11	11	11	11	11	6	9	6
FSV-DF	1	1	1	1																				
FSV-ES																								
FSV-FG																								
FSV-FH																								
FSV-DD			2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				
FSV-EQ																								
FSV-CW	14	14	14	14	13	13	13	13	11	10	10	11												
FSV-DI	12	12	13	13	12				9															
FSV-FT																								
FSV-FW																								
FSV-FJ																								
FSV-CZ	4	4	4		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
FSV-FB																								
FSV-ET																								
FSV-DV	2	3	2	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
FSV-EE			3	3	3	3	3	3	3	3	1	1	1	1	1	1	1	1	1	1	1	1	2	1
FSV-EZ					7		7		7		6		5		5		9		6			6		
FSV-FK											3	2	2	2	2	3	5	4	5	5	4	5		
FSV-FZ													3	3	5	5	6	6	4	4	4	4	6	4
FSV-GD																	9	9	9	9	9	9	13	9
FSV-GE																		3					7	4
FSV-GG																			2	2	1	1	3	4
FSV-GF																			1	1	2	2	3	2
FSV-GH																							5	3
FSV-GI																							12	7
FSV-GJ																							23	14
NIST	8			9	9	10	11	14	13				10											

2.1. Participation and Participant Characterization as Functions of Time

Panel A of Fig. 1 displays the number of active participants as a function of time. Potential factors influencing participation are discussed in Section 2.3.

Panel B displays the proportion of participants by their employment sector, categorized (when available) by the email domain of the primary contact (i.e., .com, .edu, .gov, and .org or their equivalents).

Panel C displays the proportion of participants located in the United States, Europe (including the United Kingdom), and the combination of Africa, Asia, Canada, Central America, and South America.

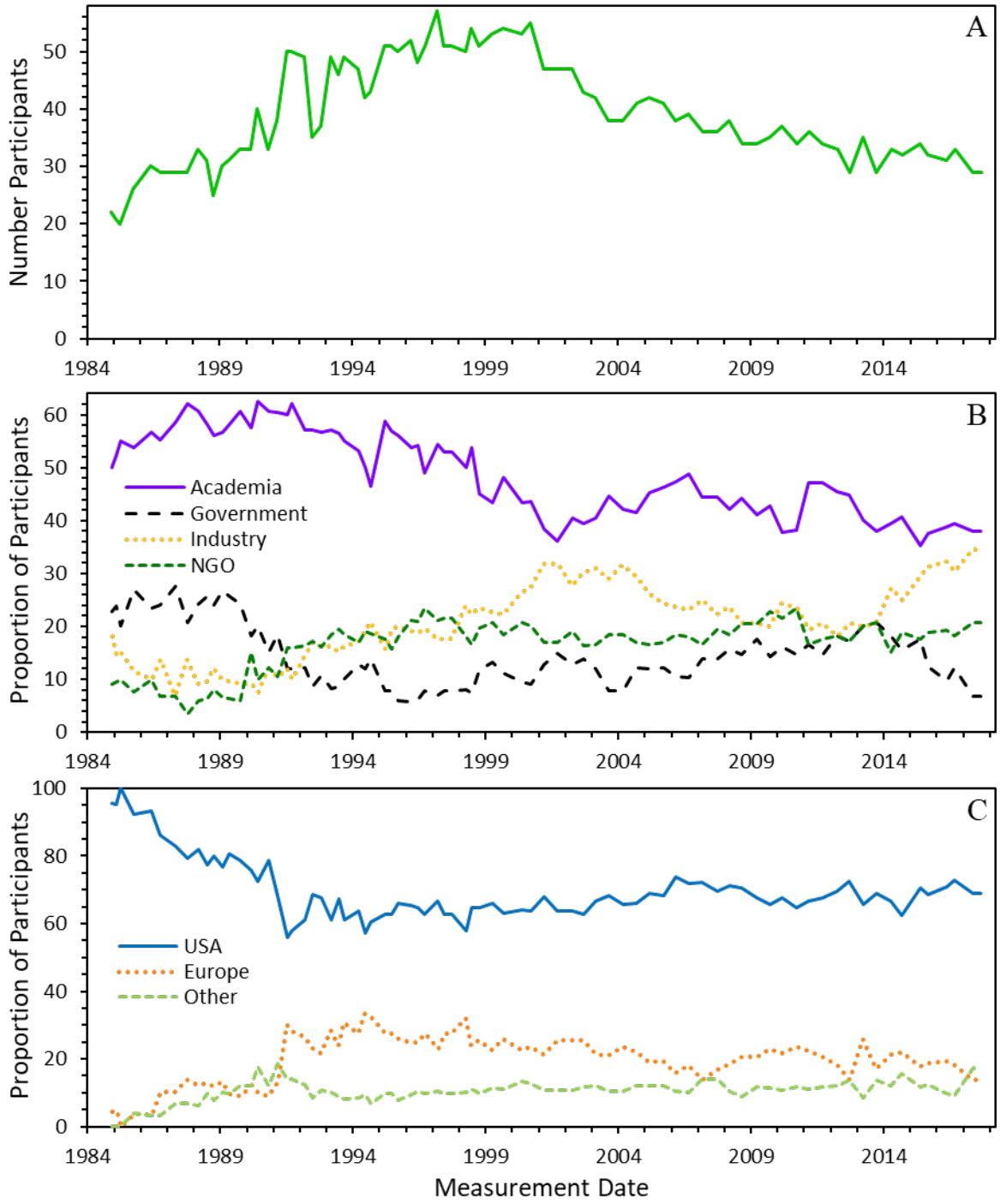


Fig. 1. Participation and Participant Characterization as Functions of Time

Panel A) The curve displays the number of active participants in the MMQAP interlaboratory studies. Panel B) The four curves display the proportion of participants from academia (solid blue), government (long dashed black), industry (dotted gold), and non-governmental organizations (dashed green). Panel C) the three curves indicate the proportion of participants located in the United States (solid blue), Europe including the United Kingdom (dotted orange), and the rest of the globe (dashed lime).

2.2. Participation Number and Frequency

The three panels of Fig. 2 summarize how often and how frequently participants reported results in the MMQAP studies.

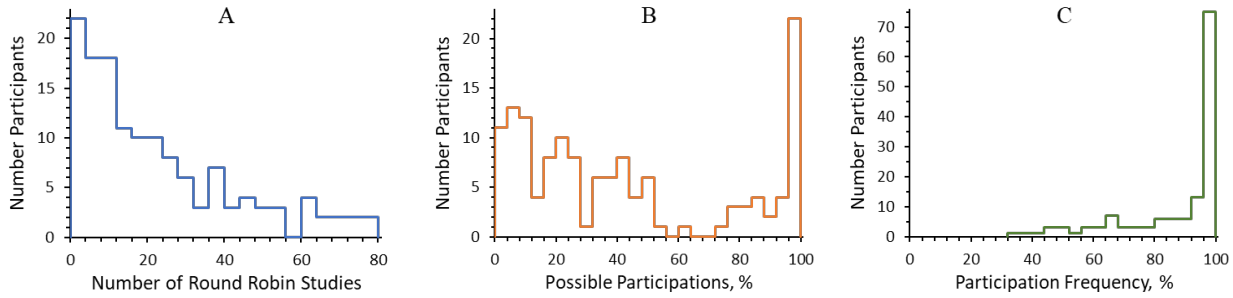


Fig. 2. Participation Number and Frequency

Panel A) The trace summarizes the number of participants that reported results as a function of the total number of Round Robin studies (RRs). For graphical clarity, the RRs are combined into sequential groups of four studies. Panel B) The trace summarizes the number of participants that reported results in the proportion of RRs available from the date of their initial participation. For graphical clarity, the proportions are combined into sequential groups of four percent. Panel C) The trace summarizes the proportion RRs in which results were reported from the initial to the final participation. For graphical clarity, the proportions are combined into sequential groups of four percent.

Panel A displays the number of active participants as a function of the 79 RRs. Laboratories most frequently reported results in fewer than five RRs, with a median number of 16 RRs. Two laboratories participated in 77 of the 79 RRs, both failing to report only during periods of equipment downtime.

Because laboratories began participating in the MMQAP studies at different times, Panel A does not fully reflect the longevity of participation. Panel B displays the number of active participants as a function of the proportion of RRs conducted from the date of their initial participation. Laboratories by far most frequently reported results in at least 96 % of their available RRs, with a median of 33 %. Note that this includes three laboratories that joined the MMQAP in its last year as well as the two laboratories that remained in the program throughout its lifetime.

Panel C displays the proportion of RRs that laboratories participated in from their first to their last RR. Laboratories most frequently reported results in at least 96 % of the RRs conducted during their participation interval, with a median participation frequency of 97 %. Note that this includes laboratories that only participated once as well as the two laboratories that remained in the program throughout its lifetime.

2.3. Factors Plausibly Influencing the Participation History

Some of the factors which may have influenced the number of participants in the MMQAP RRs are displayed in Fig. 3.

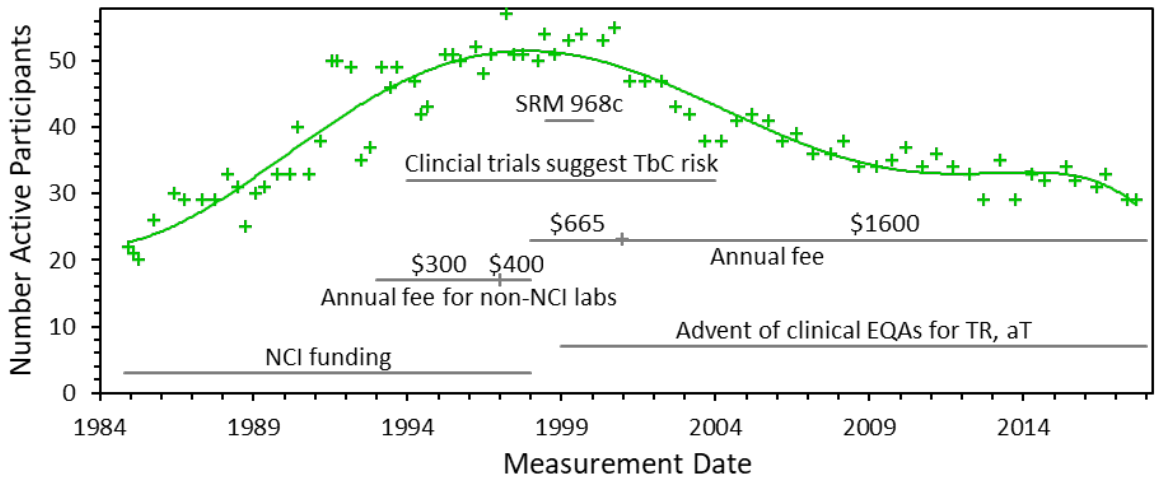


Fig. 3. Potential Influences on Participation

Symbols denote the number of active participants in the individual Round Robins (RRs). The smooth solid curve is an empirical high-order polynomial representing the general trend in participation over the MMQAP's 37 year lifetime. The horizontal line segments indicate events which may have influenced participation.

While driven by NCI's funding of the program, the fairly steady increase throughout the 1980s and early 1990s also likely reflects increased clinical interest in external quality assessment (EQA) programs following enactment of the Clinical Laboratory Improvement Amendments (CLIA) in 1988 in the USA.

The relative decline in European participation may reflect the increased regulatory rigor mandated by the European Union's 1998 adoption of the In Vitro Diagnostic Directive (IVDD) 98/79/EC, which became mandatory in 2003. At least one EQA provider had by that date established a formally accredited international program for the clinically important retinol (vitamin A) and α-tocopherol (vitamin E) measurements [89]. Other providers now support such programs, but they have not documented when they began [90]. In 2003, the CDC established the VITAL-EQA program for "predominantly less developed countries to assess and improve their ability to accurately and precisely measure serum retinol" [91].

While most laboratories located outside of the US had from the beginning been assessed a fee to cover shipping, only in 1993 were US laboratories outside of NCI's grantee pool assessed a fee of $300 per year. In 1997 this was raised to $400 per year. In 1998 NCI terminated support for studies involving the measurands addressed by the MMQAP. In 1999 the participation fee for all US-based participants was $665 per year and the number of RRs per year reduced from three to two. The fee was raised to $1600 per year in 2001 and stayed at that level until the program's end. Fees for non-US laboratories mirrored these values, plus a sizable surcharge to defray the expense of international shipping of serum samples on dry ice.

Clinical trials conducted in the early 1990s suggested that β-carotene and other antioxidant supplementation "may actually have harmful as well as beneficial effects" [92]. By 2004, meta-analysis of an increasing body of clinical trial data strongly supported the conclusion that supplementation with β-carotene, α-tocopherol, ascorbic acid, and other antioxidants has adverse outcomes for some populations without providing significant cancer chemopreventive benefit [93- 98].

Following certification of Standard Reference Material (SRM) 968c Fat-Soluble Vitamins, Carotenoids, and Cholesterol in Human Serum [80] in 1999, NIST sought to maintain but not expand participation in the MMQAP. While user fees defrayed direct costs, the number of ILS per year was reduced from three to two to conserve staff hours and minimize the need to produce new sample materials. Rather than diluting the MMQAP's focus on retinol, tocopherols, and carotenoids, from 2010 to 2017 NIST and the National Institutes of Health Office of Dietary Supplements (NIH ODS) established two additional programs: 1) Vitamin D Metabolites Quality Assurance Program (VitDQAP) to assess vitamin D-related measurements [99,100] and 2) Fatty Acids in Human Serum and Plasma Quality Assurance Program (FAQAP) to assess measurements of 24 fatty acids [101]. From 2017 to 2021, NIST and NIH ODS used the Health Assessment Measurements Quality Assurance Program (HAMQAP) to support nutritionally relevant measurements in dietary intake as well as human metabolism [102]. Beginning in 2022, NIST is supporting the measurement needs of the clinical community with the Clinical Measurements Quality Assurance Program (ClinQAP) [103].

2.4. Influence of the SRM 968 Reference Materials

Results from the MMQAP studies were used to help assign values to the measurand concentrations in the seven members of the SRM 968 [76-88] family of CRMs. As shown in Fig. 4, the 1992 peak in participation corresponds to RRs in which the candidate SRM 968a materials were distributed as unknowns. The large number of results for this and the next two members of the SRM 968 family improved the number and quality of the assigned values. Given the relatively large number of measurands reported per participant, the fall in the number of participants after 2000 had little impact on the certification processes of the latter three SRMs.

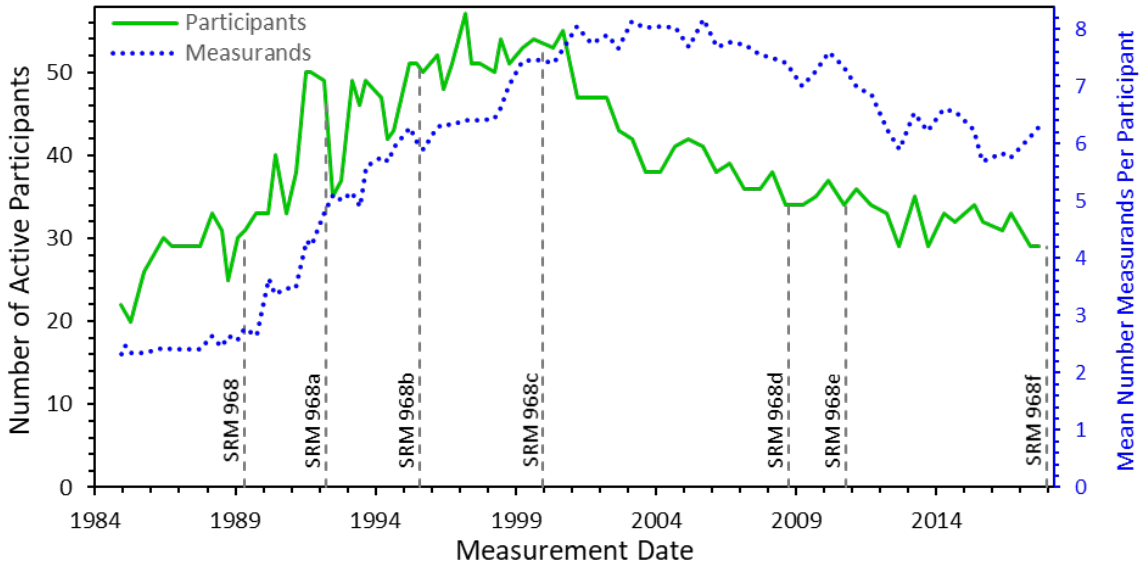


Fig. 4. Certification Dates for the SRM 968 Family of Reference Materials

The solid green curve, plotted against the left-hand vertical axis, displays the number of active participants in the MMQAP interlaboratory studies as a function of calendar date. The dashed vertical lines connect the curve to the certification date, with a label that identifies the SRM. The materials that became the SRMs were distributed as unknowns starting one to two years before the certification date. The dotted blue curve, plotted against the right-hand axis, displays the mean number of measurands reported per participant.

While the statistical methods used to assign values and their 95 % expanded uncertainties to measurand concentrations in the SRM 968 family evolved over time, the MMQAP consensus results typically had about equal weight with NIST-determined results in assigning certified values. What are now termed “non-certified” values were often assigned using just MMQAP consensus values.

2.4.1. Sales History

As shown in Fig. 5, nearly 7600 units of the SRM 968 family of CRMs have been purchased since the onset of accessible sales information in mid-1990.

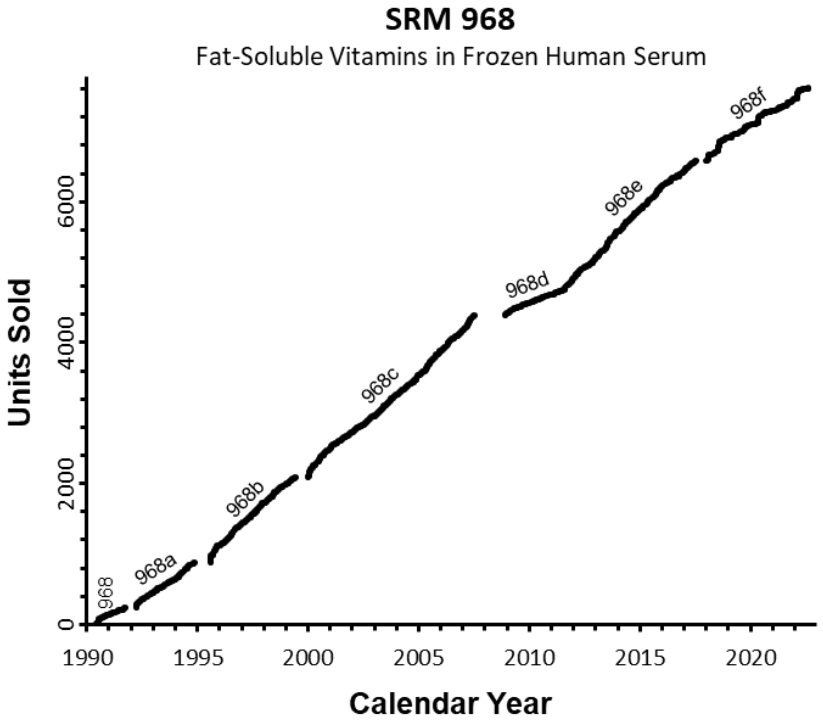


Fig. 5. SRM 968 Sales History, 1990 through 2022

The number of units purchased per year peaked at over 400 about eight years after participation in the MMQAP began to decline, suggesting the continued existence of a large measurement community interested in the clinical and/or nutritional role of fat-soluble vitamin-related measurands. The sharp decline of sales with SRM 968d does not reflect a sudden lack of community interest but rather a production failure that was remedied only with the issuance of SRM 968e. While sales sharply declined after the MMQAP ended in late 2017, post-Covid-19 sales of the most recent member of the family, SRM 968f, are again exceeding 300 units per year.

As shown in Fig. 6, a large and generally increasing proportion of purchasers of the SRM 968 family of CRMs are located in the USA. Unlike the proportion of MMQAP participants (Fig. 1, panel C), the proportion of European purchasers has generally declined with time. The proportion of purchasers in other areas (particularly Asia) has recently increased.

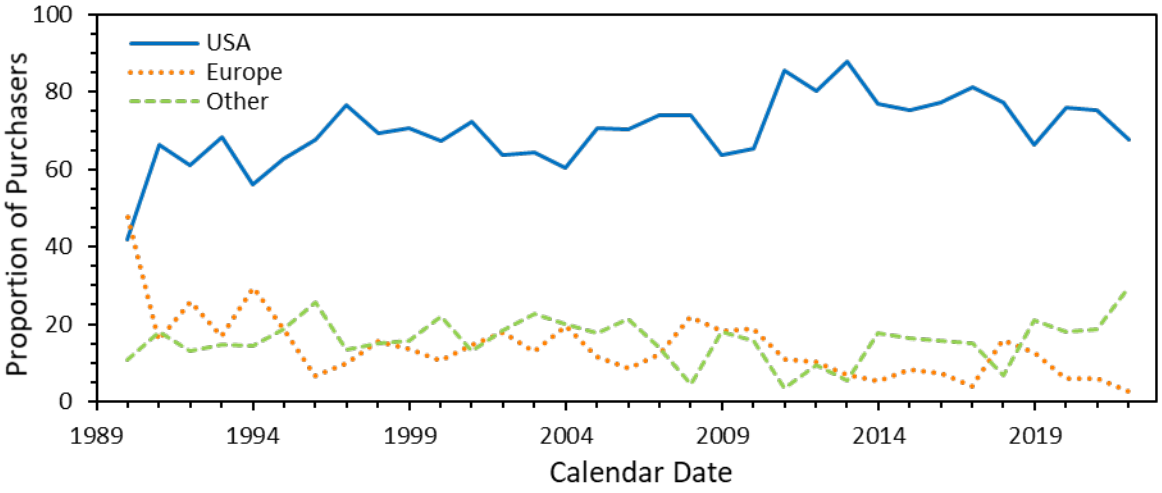


Fig. 6. Proportions of SRM 968 Sales by Purchaser Location

The three curves indicate the proportion of the SRM 968 family of certified reference materials located in the United States (solid blue), Europe including the United Kingdom (dotted orange), and the rest of the globe (dashed lime).

3. Measurands

A measurand is "the quantity intended to be measured" [104], not necessarily what is actually measured. Here, the measurands are the concentration of selected fat-soluble vitamin-related analytes in human serum or plasma. Many of these measurands are composite concentrations of chemically distinct species (e.g., "total retinol" includes the *trans*- and all of the *cis*-retinol isomers). None of the MMQAP participants reported results for specific optical isomers.

Table 4 lists the fifteen measurands that were reported on average six or more times per RR, enabling summarization of the MMQAP community's measurement performance. In addition to the measurand name and short description, a short code name is provided.

Table 4. The Fifteen Most Frequently Reported Measurands.

Measurand	Code [a]	Description	RRs [b]	Values [c]	Ratio [d]	Year [e]
Total Retinol	TR	all retinol isomers	79	2908	36.8	1984
Retinyl Palmitate	RP		65	647	10.0	1990
α-Tocopherol	aT		79	2772	35.1	1984
γ+β-Tocopherol	gbT	γ-tocopherol and β-tocopherol	68	1277	18.8	1985
Total β-Carotene	TbC	all β-carotene isomers	79	2128	26.9	1984
Trans-β-Carotene	t-bC		71	627	8.8	1988
Total *cis*-β-Carotene	c-bT	all cis-β-carotene isomers	69	439	6.4	1988
Total α-Carotene	TaC	all α-carotene isomers	65	1306	20.1	1984
Total Lycopene	TLy	all lycopene isomers	65	1297	20.0	1990
Trans-Lycopene	t-Ly		59	409	6.9	1991
Total β-Cryptoxanthin	TbX	all β-cryptoxanthin isomers	61	1113	18.2	1991
Total Lutein	TLu	all lutein isomers	61	676	11.1	1991
Total Zeaxanthin	TZ	all zeaxanthin isomers	61	549	9.0	1991
Total Lutein+Zeaxanthin	TLZ	all lutein and zeaxanthin isomers	61	1061	17.4	1991
Coenzyme Q_{10}	Q_{10}	both ubiquinone redox states	48	289	6.0	1995

a Code used to represent measurand in this document when full description is inconvenient due to length.

b Total number of RRs in which the measurand was reported at least once.

c Total number of values for the measurand reported in all 79 RRs.

d Ratio of total values to total RRs. The minimum average number of values per RR for all of the measurands in this Table was at least 6.

d Year that the measurand was first reported in an MMQAP RR.

Table 5 lists all other measurands reported by participants in one or more RR. These measurands were typically reported only once by a single laboratory (e.g., didehydroretinol), by many laboratories in many RRs but only for samples with particularly high analyte concentrations (e.g., δ-Tocopherol), regularly but by only one participant (e.g., phytoene and phytofluene), or in many RRs for many samples but by fewer than five participants (e.g., *trans*-retinol). None of these measurands were reported sufficiently often, by a sufficient number of participants, and for a sufficient diversity of samples to support meaningful statistical summary.

Table 5. Infrequently Reported Measurands.

Measurand	Description	RRs [a]	Values [b]	Ratio [c]	Year [d]
trans-Retinol		33	158	4.8	1999
Retinyl Stearate		7	7	1.0	2003
Didehydroretinol		1	1	1.0	2003
β-Tocopherol		4	4	1.0	2015
γ-Tocopherol		1	1	1.0	2016
δ-Tocopherol		51	237	4.6	1994
9-*Cis*-β-Carotene		4	5	1.3	1994
13-*Cis*-β-Carotene		5	6	1.2	1994
Trans-α-Carotene		15	29	1.9	1995
Total ζ-Carotene		1	1	1.0	2014
Total Carotene	Sum of all carotenes	2	5	2.5	1985
Phytoene		29	31	1.1	1998
Phytofluene		30	32	1.1	1996
9-*Cis*-Lycopene		3	3	1.0	1999
13-*Cis*-Lycopene		3	3	1.0	1999
15-*Cis*-Lycopene		3	3	1.0	1999
Dihydro-Lycopene		1	1	1.0	1994
26-Cyclolycopene-15-diol		1	1	1.0	2006
Trans-β-Cryptoxanthin		1	1	1.0	1993
3-*Cis*-β-Cryptoxanthin		1	1	1.0	1999
Total *Cis*-β-Cryptoxanthin		7	7	1.0	1997
Total α-Cryptoxanthin		49	192	3.9	1995
Total Cryptoxanthin		3	5	1.7	1999
Total Canthaxanthin		1	1	1.0	1996
Total Astaxanthin		1	1	1.0	2017
Trans-Lutein		14	17	1.2	1993
Trans-Anhydrolutein		3	3	1.0	1997
Total Anhydrolutein		2	2	1.0	1999
3'-Dehydro-Lutein		2	2	1.0	2000
Trans-Zeaxanthin		4	4	1.0	1993
Trans-Lutein+Zeaxanthin		3	3	1.0	1993
Total *Cis*-Lutein+Zeaxanthin		1	1	1.0	2001
Cis-Lutein+Zeaxanthin		6	6	1.0	1993
Total Carotenoids		12	13	1.1	1994
25-Hydroxyvitamin D	25-Hydroxyvitamin D_2 and D_3	32	68	2.1	2000
25-Hydroxyvitamin D_2		2	2	1.0	2000
25-Hydroxyvitamin D_3		3	3	1.0	2000
Vitamin D_3		2	2	1.0	2015
24,25-$(OH)_2$-D_3		1	1	1.0	2017
Phylloquinone (K_1)		36	90	2.5	2000
Ubiquinol		17	25	1.5	2003
Ubiquinone		17	24	1.4	2003

a Total number of RRs in which the measurand was reported at least once.

b Total number of values for the measurand reported in all 79 RRs.

c Ratio of total values to total RRs.

d Year that the measurand was first reported in an MMQAP RR.

Occasionally participants reported results for the constituents of a "total" measurand but did not explicitly report the combined values (for example, when both *trans*- and *cis*-β-carotene were reported but not total β-carotene). When this occurred, a combined result was calculated as the sum of the constituents and was added to the participant's report. In addition to total β-carotene, this happened when total lutein and total zeaxanthin were individually reported but not total lutein plus zeaxanthin, when ubiquinone and ubiquinol were individually reported but not coenzyme Q_{10}, and when 25-hydroxyvitamin D_2 and D_3 were reported but not 25-hydroxyvitamin D (however, all but one of the 25-hydroxyvitamin D results that were reported apparently were produced using methods that did not differentiate between the D_2 and D_3 forms.) The γ+β-tocopherol measurand results never needed to be augmented in this manner because the chromatographic columns typically used do not resolve these two tocopherols.

Most measurand values that are the sum of the values for separately reported constituents were calculated and reported by the participants themselves. The RR summary reports [1-48] list NIST-calculated combined results in *italic* font.

4. Materials

Table 6 lists all materials distributed in any MMQAP RR, along with the year the materials were packaged, terse descriptions, what if anything they were used for outside of RR unknowns, and the sample codes of the materials when used as RR unknowns.

Table 6. MMQAP Materials and Sample Identification Codes.

ID	Year	Description[a]	Name[b]	1[c]	2[c]	3[c]	4[c]	5[c]	6[c]	7[c]	8[c]	9[c]
5s	1984	Ethanolic solution of R, aT, bC		5s								
6s	1984	Ethanolic solution of R, aT, bC		6s								
7s	1984	Ethanolic solution of R, aT, bC		7s								
8s	1984	Hexane solution of R, aT, bC		8s								
9s	1984	Hexane solution of R, aT, bC		9s								
10s	1984	Hexane solution of R, aT, bC		10s								
18s	1985	Ethanolic solution of R, aT, bC		18s								
19s	1985	Ethanolic solution of R, aT, bC		19s								
6	1985	Lq serum with R, aT, bC in serum #8		6								
7	1985	Lq serum with R, aT, bC in serum #8		7								
8	1985	Lq stripped		8								
9	1985	Lq stripped, augmented with R, aT, bC		9								
19	1985	Lq citrated plasma (nutritional R, ascorbic acid)		19								
20	1985	Lq citrated plasma with ascorbic acid, dithiothreitol		20								
21	1985	Lq citrated plasma (nutritional bC)		21	32							
31	1986	Lq serum		31								
33	1986	Ly serum, 1.2 mL water, paired with 44		33								
34	1986	Lq serum, paired with 35		34								
35	1986	Ly serum, 1.2 mL water, paired with 34		35								
44	1986	Lq serum, paired with 33		44								
50	1986	Ly serum, 1.2 mL water then 1 mL		50	75							
51	1986	Ly serum, 1.2 mL water, then 1 mL		51	76							
52	1986	Ly serum with R, aT, 1.2 mL water, then 1 mL		52	73							
62	1987	Ly serum, 1.2 mL water, then 1 mL		62	97	115						
63	1987	Ly serum, 1.2 mL water, then 1 mL		63	72	116						
64	1987	Ly serum, 1.2 mL water, then 1 mL		64	99	117						
65	1987	Ly serum, 1.2 mL water, then 1 mL		65	74	118						
66	1987	Ly serum, 1.2 mL water, then 1 mL		66	96	119						
77	1987	Ly serum	Control D	77	91	164						
78	1987	Ly serum	Control A	78	163	252						
79	1987	Ly serum		79	110							
80	1987	Ly serum	Control C	80	144							
81	1987	Ly serum	Control B	81	94	112	208					
90	1988	Ly serum		90	109							
92	1988	Ly serum		92	95	98						

ID	Year	Description[a]	Name[b]	1[c]	2[c]	3[c]	4[c]	5[c]	6[c]	7[c]	8[c]	9[c]
93	1987	Ly serum		93	111	289						
100	1988	Ly serum	SRM 968-L	100								
101	1988	Ly serum (nutritional bC)	SRM 968-M	101								
102	1988	Ly serum with R, aT (nutritional bC)	SRM 968-H	102								
120	1989	Ly serum		120	147	206						
121	1989	Ly serum		121	145	187						
122	1989	Ly serum		122	141	165						
130	1989	Ly serum		130	142	186						
131	1989	Ly serum		131	146	166						
132	1989	Ly serum		132	162							
133	1989	Ly serum		133	140	188						
134	1989	Lq heparin plasma (glycyrrhetinic acid study)		401	413							
135	1989	Lq heparin plasma (glycyrrhetinic acid study)		393								
136	1989	Lq serum (glycyrrhetinic acid study) fibrin clots		417								
138	1990	Lq serum (nutritional bC)		138	168	190						
139	1990	Lq serum		139	169	189						
148	1991	Ly serum with aT	SRM 968a-L	148	167							
149	1991	Ly serum with aT (nutritional bC)	SRM 968a-M	149	159	173						
150	1991	Ly serum with R, aT (nutritional bC)	SRM 968a-H	150	161	177						
155	1991	Ly serum		155	174							
156	1991	Ly serum		156	175							
157	1991	Ly serum		157	160							
170	1991	Ly serum		170	172	215						
171	1991	Ly serum		171	176	257						
181	1992	Ly serum with RP		181	222	243	283					
182	1992	Ly serum		182	185	216	253					
183	1992	Ly serum		183	196							
184	1992	Ly serum		184	319	327	407					
191	1994	Ly serum with (too high) R		191	213							
192	1994	Ly serum		192	199	218	250	278				
193	1994	Ly serum with c-R		193	254	255	269	281				
194	1994	Ly serum		194	217							
195	1994	Ly serum, 1+1 of #198 and stripped		195	214	244	328	347	402			
197	1994	Ly serum, 1+3 of #198 and stripped		197	211	245	310	320				
198	1994	Ly serum with R, RP, aT, gT		198	212	246	311	321				
200	1994	Ly serum with R, RP, aT, gT (nutritional bC)	SRM 968b-L	200	207	235						
201	1994	Ly serum with R, RP, aT, gT (nutritional bC)	SRM 968b-M	201	209	234						
202	1994	Ly serum with R, RP, aT, gT (nutritional bC)	SRM 968b-H	202	210	227						
203	1995	Ly serum with R, RP, aT, gT, dT, bC, aC, Ly		203	273	294						
204	1995	Ly serum, 1+2 of #203 and stripped		204								
205	1995	Ly serum, 1+1 of #203 and stripped		205								
219	1996	Ly serum with gT, dT, bC (Roche beadlets)		219								
220	1996	Ly serum with dT, aC, Ly		220								
221	1996	Ly serum with aT, RP		221								
223	1996	Ly serum with RP		223	225	228	272					
224	1996	Ly serum with R, RP, aT, gT, bC, aC, Ly, bX, Lu, Z		224	392	397						
229	1996	Ly serum with RP, gT, dT, Ly, Lu		229								
230	1996	Ly serum with R, RP, aT, gT, aC, Ly, bX, Z		230								
231	1996	Ly serum with 1+9 RP, carotenoids in HDL/LDL		231	412							
232	1996	Ly serum with 1+1 RP, carotenoids in HDL/LDL		232								
233	1996	Ly serum with 9+1 RP, carotenoids in HDL/LDL		233								
236	1997	Ly serum with 1+9 carotenoids in HDL/LDL		236								
237	1997	Ly serum with 1+1 carotenoids in HDL/LDL		237								
239	1997	Ly serum (plasticizer peaks from storage bottles)		239								
240	1997	Ly serum, 1+1 of #241, #242		240	431							
241	1997	Ly serum (#239) with RP, gT, dT, bC, aC, Ly, Z		241	334							
242	1997	Ly serum (#239) with R, RP, aT, dT, bC, aC, bX, Lu		242	251							
247	1998	Ly serum, 1+1 of #248, #249		247	317	352						
248	1998	Ly serum with R, gT	SRM 968c-I	248	258	263	280	304	318			
249	1998	Ly serum with aT, dT	SRM 968c-II	249	256	264	284	299	309			
259	1999	Lq serum, paired with #261		259								
260	1999	Lq serum, paired with #262		260								
261	1999	Ly serum, paired with #259		261								
262	1999	Ly serum, paired with #260		262								
265	1999	Ly serum, paired with #268		265								
266	1999	Ly serum, paired with #271		266	277	282	295	305				
267	1999	Lq serum, paired with #270		267	274	368	380	388				
268	1999	Lq serum, paired with #265		268								
270	1999	Ly serum, paired with #267		270	276	367	377	387				

ID	Year	Description[a]	Name[b]	1[c]	2[c]	3[c]	4[c]	5[c]	6[c]	7[c]	8[c]	9[c]
271	1999	Lq serum, paired with #266		271	275	279	296	308	394a			
285	2002	Lq serum, #288 with t-R		285	297	306						
286	2002	Lq serum, #288 with c-R		286	298	307						
287	2002	Lq hemolyzed serum		287	303							
288	2002	Lq serum		288	293	302						
290	2002	Ly serum, paired with #292		290	300	312	322	333	348	362		
291	2002	Lq serum		291								
292	2002	Lq serum, paired with #290		292	301	313	323	332	349	366		
314	2005	Lq serum		314								
315	2005	Lq serum, 77+110 of #314,#316		315	335	378						
316	2005	Lq serum		316	336	381						
324	2006	Lq serum (nutritional aC)		324								
325	2006	Lq serum, 25+35 #324,#326		325								
326	2006	Lq serum		326	331	338	339					
329	2006	Lq serum (nutritional aC)		329	337							
330	2006	Lq serum, 30+32 of #329, #326		330								
340	2006	Lq plasma	SRM 1950	340	350	437						
341	2007	Lq serum	SRM 968d	341	344	351	361	372	419	422		
353	2008	Lq serum, 105+25 of native and bC-augmented stripped		353	371	394b						
354	2008	Lq serum, 120+10 of native and bC-augmented stripped		354	370							
355	2008	Lq serum, 126+4 of native and bC-augmented stripped		355	369							
356	2008	Lq serum, 222+125 of #248, #249		356	360	376	391	435				
357	2009	Lq serum	SRM 968e-I	357	365	375	389	398	403	427	432	
358	2009	Lq serum	SRM 968e-II	358	364	374	386	399	408	416	426	440
359	2009	Lq serum	SRM 968e-III	359	363	373	379	400	405	429	436	
382	2011	Lq serum (nutritional carotene)		382	395	421	441					
383	2011	Lq serum		383	390	409	414					
384	2011	Lq serum		384	410	418						
385	2011	Lq serum, 310+260 of #383, #384		385	396	411	424					
404	2013	Lq serum with R, RP, βT		404	420							
406	2013	Lq serum with c-R, gT		406	415							
423	2012	Lq serum	SRM 972a-2	423								
425	2013	Lq serum	VitDQAP-I	425								
428	2015	Lq serum	SRM 968f-I	428	433	438						
430	2015	Lq serum	SRM 968f-II	430	434	439						

a

HDL/LDL	mixture of high- and low-density lipoproteins used to deliver carotenoid spikes
Lq serum	liquid-frozen material
Ly serum	lyophilized material
native	unmodified serum
nutritional X	increased concentration of X achieved by supplementing donors' diets
paired with	same serum, packaged at same time, with a portion lyophilized and remainder frozen
stripped	commercially obtained deproteinated, delipidized human serum with very low concentrations of vitamin-related compounds
with X	increased concentration of X achieved by spiking. A variety of spiking approaches were used for the carotenoids. Spiked analytes are identified by measurand code.
x+y of X, Y	mixture of X and Y serum pools in the ratio of x volumes of X and y volumes of Y
1.2 mL water then 1 mL	Lyophilized samples originally distributed with instructions to reconstitute with 1.2 mL water. In subsequent distributions they were to be reconstituted with 1.0 mL water

b identity of the material.

c sample code used in the n^{th} distribution of the material.

The numeric sample identification (ID) codes used to identify materials prepared for MMQAP studies are mostly derived from the label used in the material's first RR distribution as an unknown. The values increase with the material's preparation date but are not strictly sequential. Some codes were pre-allocated but never used, some materials were used only in NIST's method development studies, and some materials were determined to be too unstable and/or heterogenous for use as unknowns.

The samples 5s to 19s used in the first two RRs were gravimetrically prepared calibration solutions. For several years, some of these ethanol-based solutions were provided to new

participants; the first serum-based materials were then provided only after calibration issues had been explored.

A set of four lyophilized materials (ID 77, 78, 80, and 81) were prepared and characterized in 1988 and then for two years provided to participants for use as control materials (labeled A through D) with instructions not to proceed with the analysis of the RR unknown samples until results for the controls agreed with their consensus value assignments.

Seventeen of the materials (100, 101, 102, 148, 149, 150, 200, 201, 202, 248, 249, 341, 357, 358, 359, 428, and 430) were prepared as components of the 968 family of SRMs. Materials 340 (SRM 1950 [105]), 423 (SRM 972a-2 [106]), and 425 (VitDQAP-I [107]) were not prepared for the MMQAP but were matrices of human plasma or serum and were graciously made available for distribution as MMQAP unknowns.

5. Measurements

The MMQAP studies provide [number of RRs (79)] × [number of unknowns per RR (2 to 5)] × [number of measurands per unknown (3 to 22)]= 4419 single-distribution datasets ranging in size (i.e., number of quantitative results) from 2 to 54. An additional 1182 datasets, ranging in size from 2 to 266, combine results for one material that was distributed more than once. Together, 5601 datasets are available for analysis. Usefully summarizing these results requires use of appropriate statistical estimators.

Participants in interlaboratory studies are typically expected to have different measurement competences, ranging from expert to novice. With its fairly stable participant population, most results reported for a given MMQAP sample are expected to cluster around a well-defined consensus location (center point), $\bar{x}$, with a characteristic measurement scale (dispersion about the location, generally reported as the standard deviation, (SD)). Given that results are generated by individual analysts rather than "laboratories," even well-established organizations sometimes report "bad" results. To avoid explicitly identifying outlier results and yet provide reliable statistics, in all but the earliest studies robust estimators were used to estimate consensus values [108,109].

Because of its simplicity and well-defined performance properties, consensus locations were estimated as medians. While more sophisticated estimators exist [110], the familiar median is appropriate to the purposes of this retrospective analysis.

As the MMQAP evolved, the SDs were estimated using either the interquartile range (IQR, the central 50 % of a set of results) or the adjusted median absolute deviation from the median (MAD_E) [110,111]. Wanting to use a consistent and reliable scale estimator in this retrospective analysis, MAD_E values were compared with those from the recently advocated Q_n estimator [112, 113]. While much less familiar and more computationally complex than the MAD_E, the Q_n has much better statistical efficiency when applied to data sampled from normally distributed (i.e., Gaussian) populations in the limit of very large datasets. However, the relative performance of these scale estimators is not well documented for relatively small datasets.

5.1. Comparison of MAD_E and Q_n Estimators of Measurement Scale

The MAD_E and Q_n are equally robust, with 50 % breakdown points ("the proportion of incorrect observations (e.g., arbitrarily large observations) an estimator can handle before giving an incorrect (e.g., arbitrarily large) result" [109]). If they a) provide equally accurate estimates of the standard deviation for normally distributed populations and b) if the MMQAP datasets are distributed as lightly contaminated (a minority of values from some other population mixed in with the majority) normal populations, the Q_n/MAD_E ratios are expected to cluster about unity. Fig. 7 displays the results of the comparison as a function of dataset size, *n,* from 2 to 100.

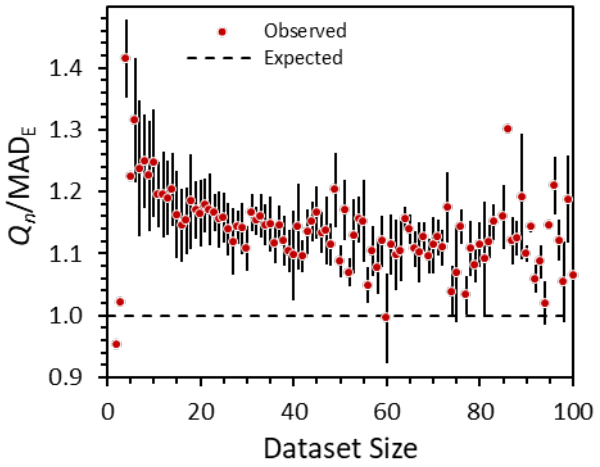


Fig. 7. Observed Q_n/MAD_E Ratios as a Function of Dataset Size.

Dots represent the mean of the Q_n/MAD_E ratios for all datasets of a given sample size; bars represent standard uncertainties of the means. The dashed horizontal line indicates the expected ratio for normally distributed datasets.

The Q_n/MAD_E ratios for datasets of size of $n = 2$ and $n = 3$ are essentially constant regardless of the magnitudes of the two or three values summarized. The ratios have a reasonably well-defined trend with dataset size for $n \geq 4$; however, the ratios do not cluster about unity but exponentially decline from a high of about 1.4 to an asymptote of about 1.13 by $n \approx 30$. The greater than unity ratio requires that the Q_n estimates are consistently somewhat larger than those provided by the MAD_E. However, this does not necessarily imply that the Q_n provides more accurate estimates.

The MAD_E and Q_n are "tuned" to provide unbiased estimates of the SD of data drawn from normally distributed populations. The estimators are readily rescaled to provide unbiased estimates of dispersion parameters for other distributions, once the nature of the distribution is known. The relative behavior of the "tuned-to-normal" estimators may help to characterize distribution aspects of the observed data.

To this end, Monte Carlo sampling was used to characterize the behavior of the MAD_E and Q_n estimators for datasets drawn from several well-defined statistical distributions. The mean values of the MAD_E and Q_n estimates and the Q_n/MAD_E ratio for four distributions centered on zero and having unit standard deviation, zero skew (symmetry), and very different kurtosis ("tailedness") are displayed in Fig. 8.

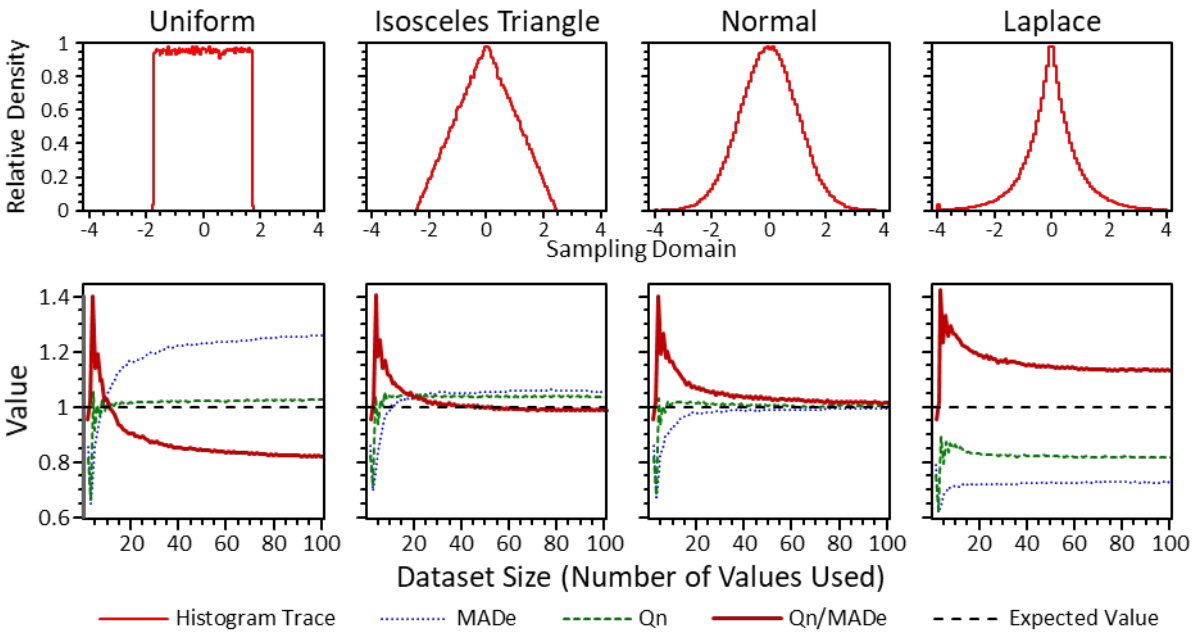


Fig. 8. MAD_E and Q_n Estimates as Functions of Dataset Size for Symmetric Distributions.

The panels in the upper row depict the shape of the distributions as histogram traces, each normalized to have unit height. Each trace summarizes the results of 576 000 independent random draws from the chosen distribution: uniform (rectangular), isosceles triangle, normal (Gaussian), or Laplace (double exponential). The panels in the lower row depict the performance of the MAD_E and Q_n robust estimators for datasets drawn from the distributions as functions of sample size. Each point along the curves are means of 1089 independent random samplings of the given dataset size, n. The dotted blue curve depicts the mean of the MAD_E values, the dashed green curve depicts the mean of the Q_n values, and the solid auburn curve depicts the mean of the Q_n /MAD_E ratios. The dashed horizontal line indicates the theory-based SD for the distribution.

The two estimators perform very differently with uniformly distributed datasets, with the Q_n providing accurate values for datasets of size $n \geq 10$ while the MAD_E overestimates by 20 % and more for datasets of size $n \geq 20$. Both estimators only slightly overestimate the SD for triangularly distributed data. The Q_n approaches the theory-derived SD for smaller n and is consistently if slightly less biased than the MAD_E. As expected, both estimators perform well for normally distributed data; however, like the triangularly distributed data, the Q_n approaches the expected SD at smaller n. Both estimators consistently underestimate the theory-based SD for samples drawn from the thick-tailed Laplace distribution.

The $\{n, Q_n/MAD_E\}$ curves in all four distributions have the same basic shape, but only the curve for the Laplace distribution has an asymptote that is compatible with that of the MMQAP ratios shown in Fig. 7. This suggests that the Q_n may provide somewhat less biased estimates than the MAD_E when applied to datasets sampled from thick-tailed distributions.

Results for four distributions that combine a normally distributed population contaminated with 20 % of various uniform populations are displayed in Fig. 9. This model has been advocated as producing "normal-ish" mixture populations with realistically thick tails [114], representing situations where the majority of results are from well calibrated measurement processes that are in reasonable statistical control (i.e., a normal distribution) but a minority are from processes that are poorly calibrated and/or not in proper control (collectively represented as a uniform distribution).

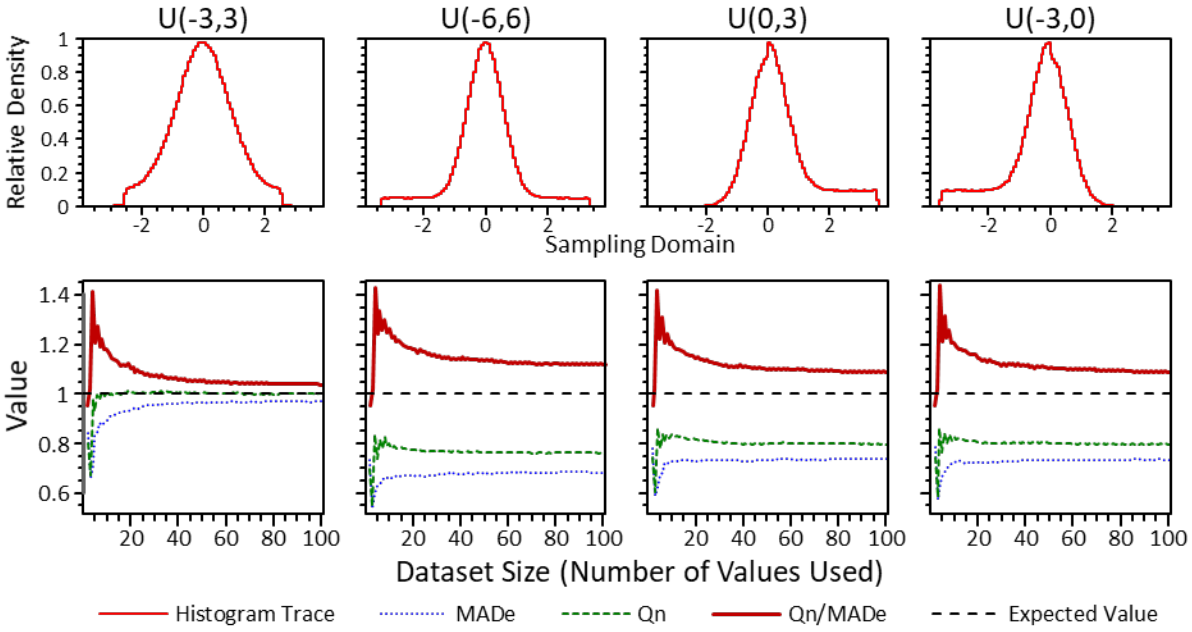


Fig. 9. MAD_E and Q_n Estimates as Functions of Dataset Size for Thick-Tailed Distributions.

The four exemplar distributions are 80 % drawn from a normal distribution having zero mean and unit standard deviation (SD) mixed with 20 % contamination drawn from uniform distributions having differing limits. After generation, all of the mixture populations were empirically scaled to have a combined SD of 1. The contamination in the left-most panel, U(-3,3), was generated between -3 and 3 SD from the mean of the majority population; that of the panel labeled U(-6,6) between -6 and 6 SD. The contamination in panel U(0,3) was generated between 0 and 3 SD from the mean of the majority population; that in panel U(-3,0) between -3 and 0 SD. The graphical format is described in Fig. 8.

The $\{n, Q_n/MAD_E\}$ curves have the characteristic shape with asymptotes that are functions of the breadth and position of the contaminating uniform distribution but not of the skew direction. In addition to the position and breadth of contamination, the asymptote is also a strong function of the proportion of contamination (data not shown).

As shown in Fig. 10, the $\{n, Q_n/MAD_E\}$ curves for these mixture distributions are qualitatively similar to the observed MMQAP ratios. While these mixture distributions are not uniquely appropriate (other thick-tailed distributions perform similarly, data not shown), they provide a plausible model for the MMQAP data.

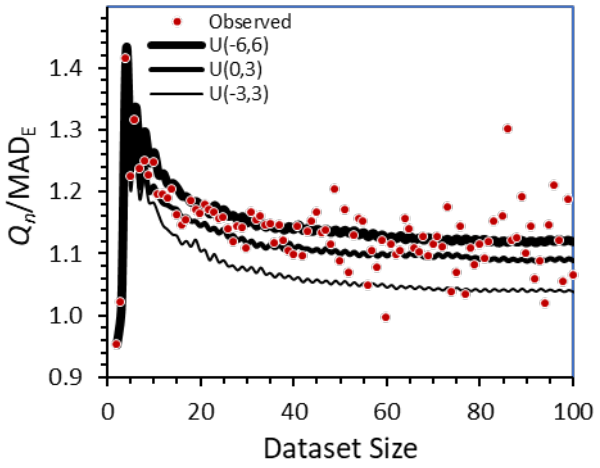


Fig. 10. Observed and Empirical Q_n/MAD_E Ratios as Functions of Dataset Size.

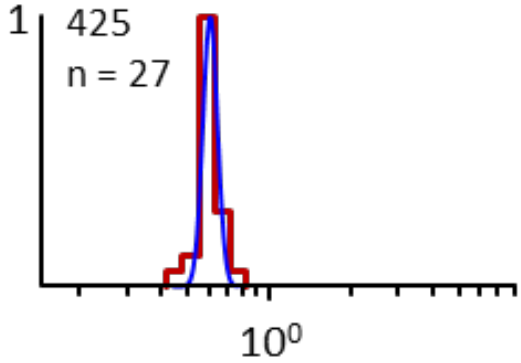
The red dots depict the mean values of the observed Q_n/MAD_E ratios, with error bars suppressed for graphical clarity. The empirical $\{n, Q_n/MAD_E\}$ curves are those of the mixture distributions examined in Fig. 9.

While not necessarily accurately estimating the SD of the exemplar distributions displayed in Fig. 8 and Fig. 9, the Q_n is at least as accurate as the MAD_E and is consistently better for thick-tailed distributions. Therefore, the Q_n has been used as the distribution scale estimator in the following analyses.

5.2. Empirical Distributions

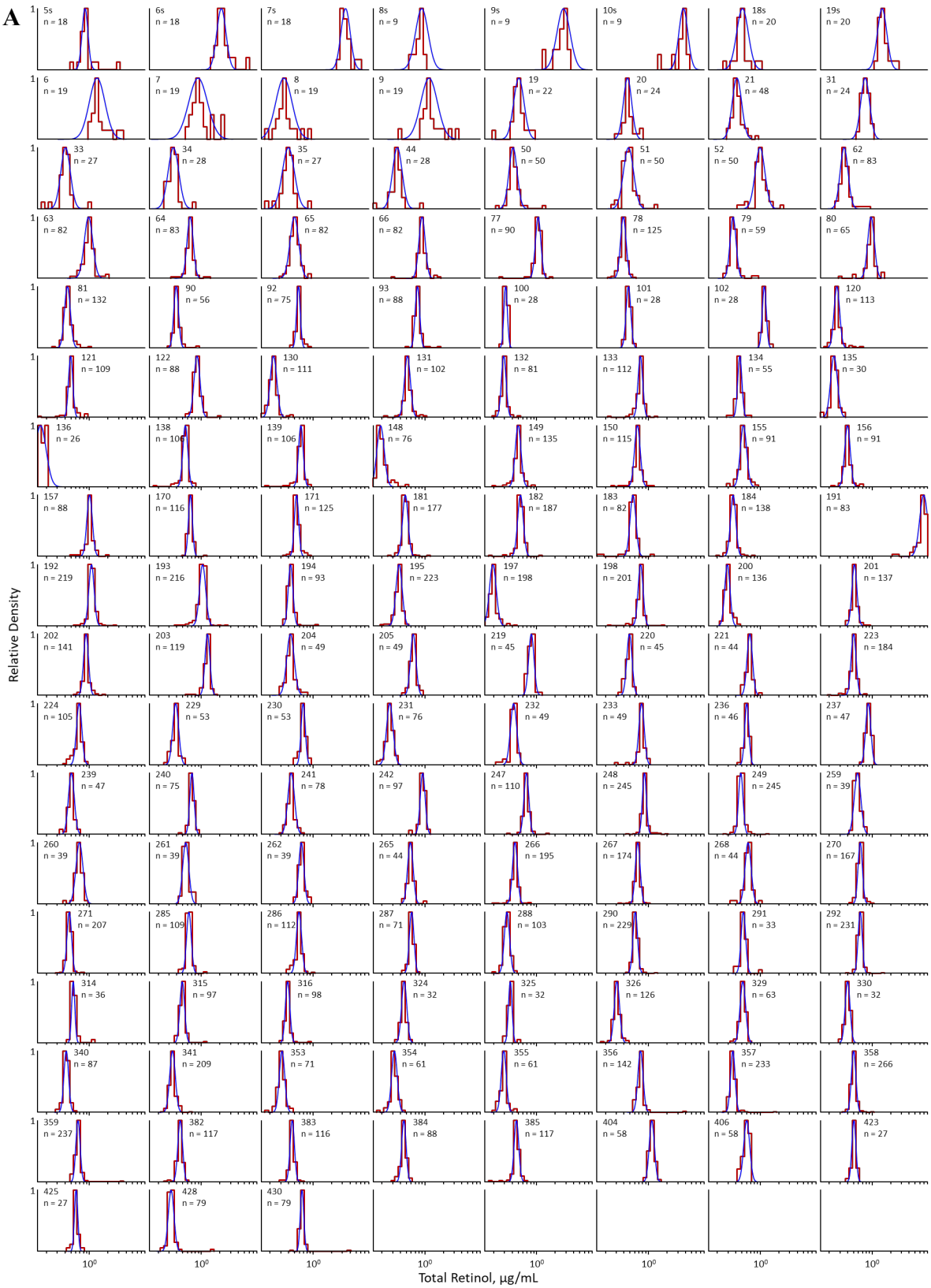
The measurement results in all the MMQAP fat-soluble vitamin-related RRs are provided elsewhere [1-48]. The 15 panels, A to O, of Fig. 11 display empirical measurement distributions for all the materials distributed as MMQAP unknowns. Each of these panels is an 8 column by 18 row multi-plot for one of the fifteen most commonly reported measurands (Table 4).

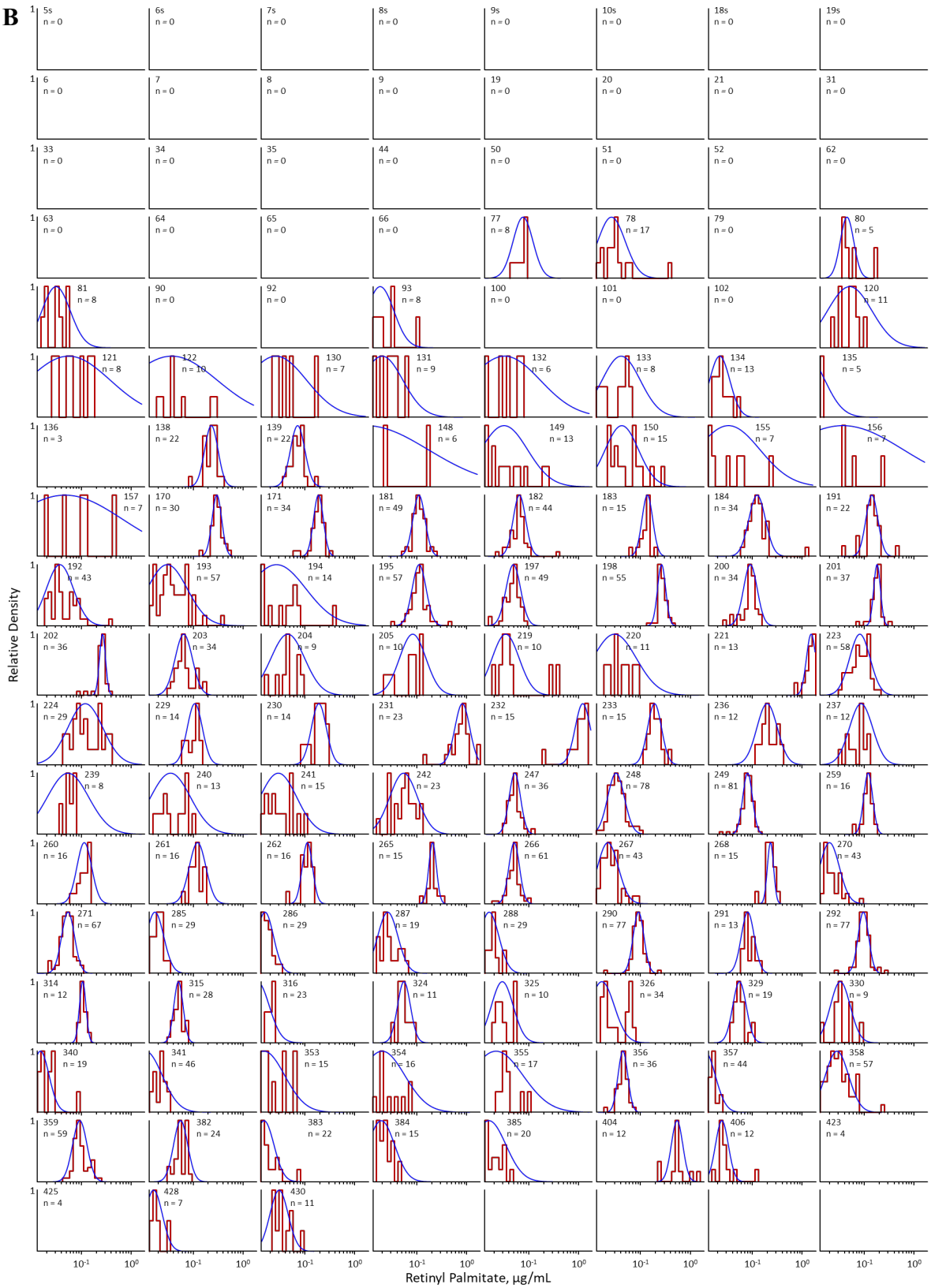
The x-axis of each segment in a given panel spans the same µg/mL concentration range, from the smallest to the largest reported value for any of the materials. The y-axis of each segment spans the same relative density range, from 0 (no density) to 1 (maximum density). The following illustrates (in a much enlarged format) the information presented in each segment of each panel.



The thick red histogram trace (the jagged envelope of a histogram without vertical lines bounding each bin) displays the empirical distribution of the decadic logarithm ($\log_{10}$) of the available quantitative results. The logarithmic transformation is necessary to accommodate the range of the concentration values. Each of the histogram bins spans $1/30^{th}$ of the $\log_{10}$-transformed concentration range. The thinner blue smooth curve displays a normal $N(\bar{x}, s^2)$ distribution, where $\bar{x}$ is estimated as the median and s as the Q_n of the $\log_{10}$-transformed values. The material ID and number of results available to characterize the distribution are displayed at the top of each segment, either to the left or to the right of the distributions.

The x-axis of each segment is displayed with the usual $\log_{10}$ tic-marks. The tics for the integer powers of 10 {0.01, 0.1, 1, and 10} are labeled {10^{-2}, 10^{-1}, 10^{0}, and 10^{1}}. While tics are provided for every segment, labels are provided only at the bottom row of each panel. The y-axis scale is indicated only for the segments in the left-most column of each panel.


A
Relative Density
Total Retinol, µg/mL
10⁰


B
Relative Density
Retinyl Palmitate, µg/mL
5s n = 0
6s n = 0
7s n = 0
8s n = 0
9s n = 0
10s n = 0
18s n = 0
19s n = 0
6 n = 0
7 n = 0
8 n = 0
9 n = 0
19 n = 0
20 n = 0
21 n = 0
31 n = 0
33 n = 0
34 n = 0
35 n = 0
44 n = 0
50 n = 0
51 n = 0
52 n = 0
62 n = 0
63 n = 0
64 n = 0
65 n = 0
66 n = 0
77 n = 8
78 n = 17
79 n = 0
80 n = 5
81 n = 8
90 n = 0
92 n = 0
93 n = 8
100 n = 0
101 n = 0
102 n = 0
120 n = 11
121 n = 8
122 n = 10
130 n = 7
131 n = 9
132 n = 6
133 n = 8
134 n = 13
135 n = 5
136 n = 3
138 n = 22
139 n = 22
148 n = 6
149 n = 13
150 n = 15
155 n = 7
156 n = 7
157 n = 7
170 n = 30
171 n = 34
181 n = 49
182 n = 44
183 n = 15
184 n = 34
191 n = 22
192 n = 43
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201 n = 37
202 n = 36
203 n = 34
204 n = 9
205 n = 10
219 n = 10
220 n = 11
221 n = 13
223 n = 58
224 n = 29
229 n = 14
230 n = 14
231 n = 23
232 n = 15
233 n = 15
236 n = 12
237 n = 12
239 n = 8
240 n = 13
241 n = 15
242 n = 23
247 n = 36
248 n = 78
249 n = 81
259 n = 16
260 n = 16
261 n = 16
262 n = 16
265 n = 15
266 n = 61
267 n = 43
268 n = 15
270 n = 43
271 n = 67
285 n = 29
286 n = 29
287 n = 19
288 n = 29
290 n = 77
291 n = 13
292 n = 77
314 n = 12
315 n = 28
316 n = 23
324 n = 11
325 n = 10
326 n = 34
329 n = 19
330 n = 9
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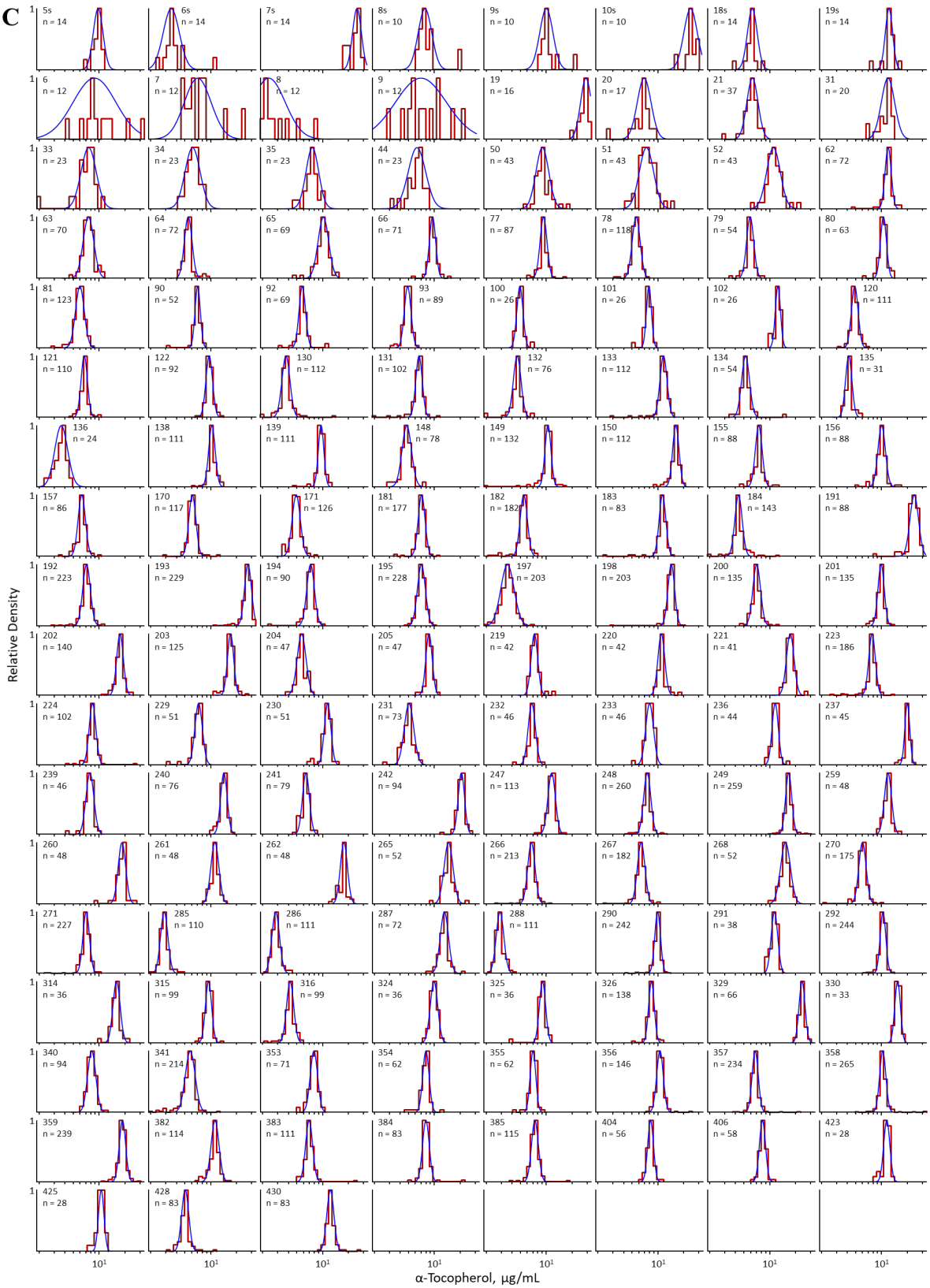
356 n = 36
357 n = 44
358 n = 57
359 n = 59
382 n = 24
383 n = 22
384 n = 15
385 n = 20
404 n = 12
406 n = 12
423 n = 4
425 n = 4
428 n = 7
430 n = 11


C
Relative Density
α-Tocopherol, µg/mL
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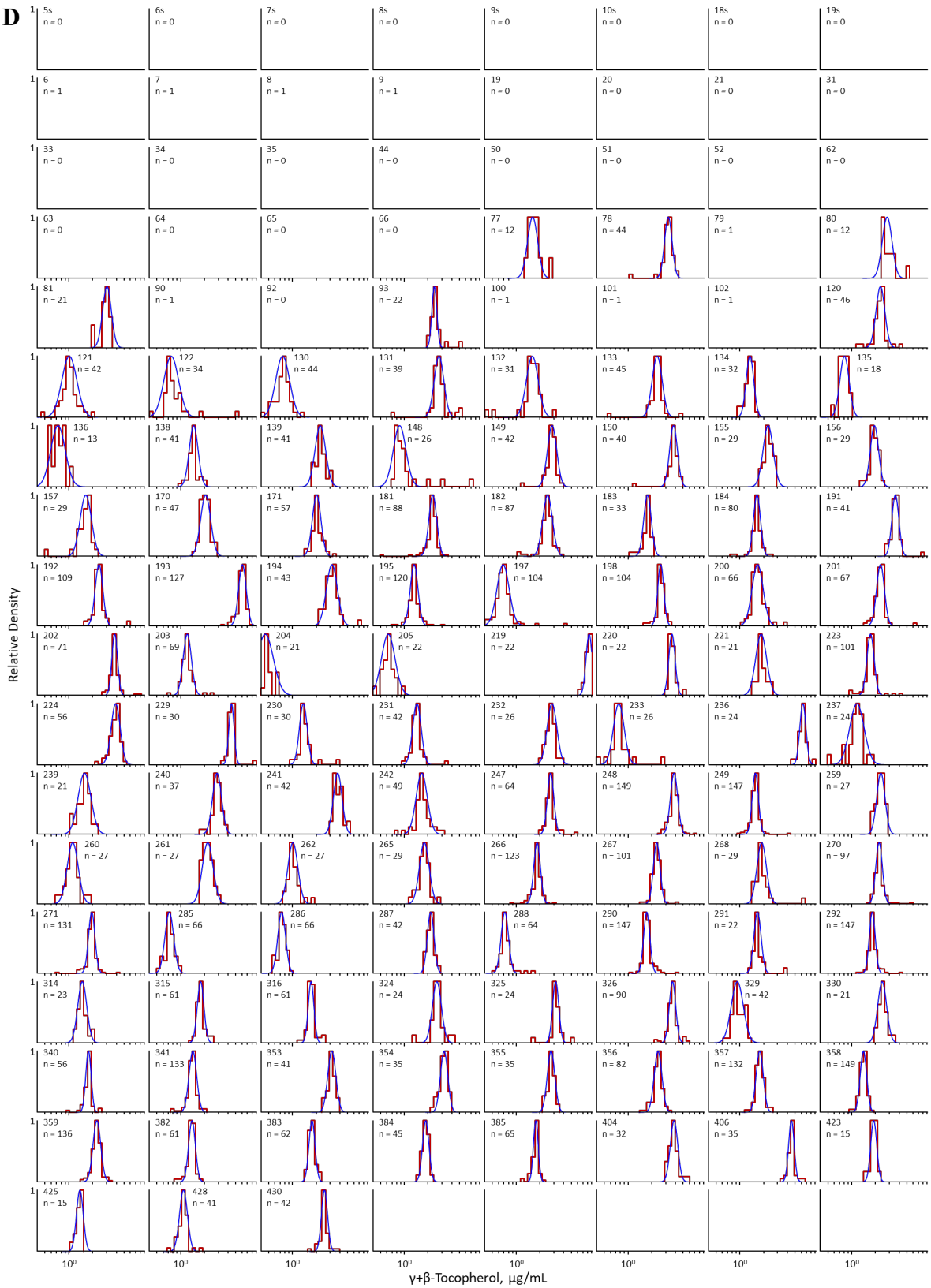
7s n = 14
8s n = 10
9s n = 10
10s n = 10
18s n = 14
19s n = 14
6 n = 12
7 n = 12
8 n = 12
9 n = 12
19 n = 16
20 n = 17
21 n = 37
31 n = 20
33 n = 23
34 n = 23
35 n = 23
44 n = 23
50 n = 43
51 n = 43
52 n = 43
62 n = 72
63 n = 70
64 n = 72
65 n = 69
66 n = 71
77 n = 87
78 n = 118
79 n = 54
80 n = 63
81 n = 123
90 n = 52
92 n = 69
93 n = 89
100 n = 26
101 n = 26
102 n = 26
120 n = 111
121 n = 110
122 n = 92
130 n = 112
131 n = 102
132 n = 76
133 n = 112
134 n = 54
135 n = 31
136 n = 24
138 n = 111
139 n = 111
148 n = 78
149 n = 132
150 n = 112
155 n = 88
156 n = 88
157 n = 86
170 n = 117
171 n = 126
181 n = 177
182 n = 182
183 n = 83
184 n = 143
191 n = 88
192 n = 223
193 n = 229
194 n = 90
195 n = 228
197 n = 203
198 n = 203
200 n = 135
201 n = 135
202 n = 140
203 n = 125
204 n = 47
205 n = 47
219 n = 42
220 n = 42
221 n = 41
223 n = 186
224 n = 102
229 n = 51
230 n = 51
231 n = 73
232 n = 46
233 n = 46
236 n = 44
237 n = 45
239 n = 46
240 n = 76
241 n = 79
242 n = 94
247 n = 113
248 n = 260
249 n = 259
259 n = 48
260 n = 48
261 n = 48
262 n = 48
265 n = 52
266 n = 213
267 n = 182
268 n = 52
270 n = 175
271 n = 227
285 n = 110
286 n = 111
287 n = 72
288 n = 111
290 n = 242
291 n = 38
292 n = 244
314 n = 36
315 n = 99
316 n = 99
324 n = 36
325 n = 36
326 n = 138
329 n = 66
330 n = 33
340 n = 94
341 n = 214
353 n = 71
354 n = 62
355 n = 62
356 n = 146
357 n = 234
358 n = 265
359 n = 239
382 n = 114
383 n = 111
384 n = 83
385 n = 115
404 n = 56
406 n = 58
423 n = 28
425 n = 28
428 n = 83
430 n = 83
10¹


D
Relative Density
γ+β-Tocopherol, µg/mL
5s n = 0
6s n = 0
7s n = 0
8s n = 0
9s n = 0
10s n = 0
18s n = 0
19s n = 0
6 n = 1
7 n = 1
8 n = 1
9 n = 1
19 n = 0
20 n = 0
21 n = 0
31 n = 0
33 n = 0
34 n = 0
35 n = 0
44 n = 0
50 n = 0
51 n = 0
52 n = 0
62 n = 0
63 n = 0
64 n = 0
65 n = 0
66 n = 0
77 n = 12
78 n = 44
79 n = 1
80 n = 12
81 n = 21
90 n = 1
92 n = 0
93 n = 22
100 n = 1
101 n = 1
102 n = 1
120 n = 46
121 n = 42
122 n = 34
130 n = 44
131 n = 39
132 n = 31
133 n = 45
134 n = 32
135 n = 18
136 n = 13
138 n = 41
139 n = 41
148 n = 26
149 n = 42
150 n = 40
155 n = 29
156 n = 29
157 n = 29
170 n = 47
171 n = 57
181 n = 88
182 n = 87
183 n = 33
184 n = 80
191 n = 41
192 n = 109
193 n = 127
194 n = 43
195 n = 120
197 n = 104
198 n = 104
200 n = 66
201 n = 67
202 n = 71
203 n = 69
204 n = 21
205 n = 22
219 n = 22
220 n = 22
221 n = 21
223 n = 101
224 n = 56
229 n = 30
230 n = 30
231 n = 42
232 n = 26
233 n = 26
236 n = 24
237 n = 24
239 n = 21
240 n = 37
241 n = 42
242 n = 49
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249 n = 147
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261 n = 27
262 n = 27
265 n = 29
266 n = 123
267 n = 101
268 n = 29
270 n = 97
271 n = 131
285 n = 66
286 n = 66
287 n = 42
288 n = 64
290 n = 147
291 n = 22
292 n = 147
314 n = 23
315 n = 61
316 n = 61
324 n = 24
325 n = 24
326 n = 90
329 n = 42
330 n = 21
340 n = 56
341 n = 133
353 n = 41
354 n = 35
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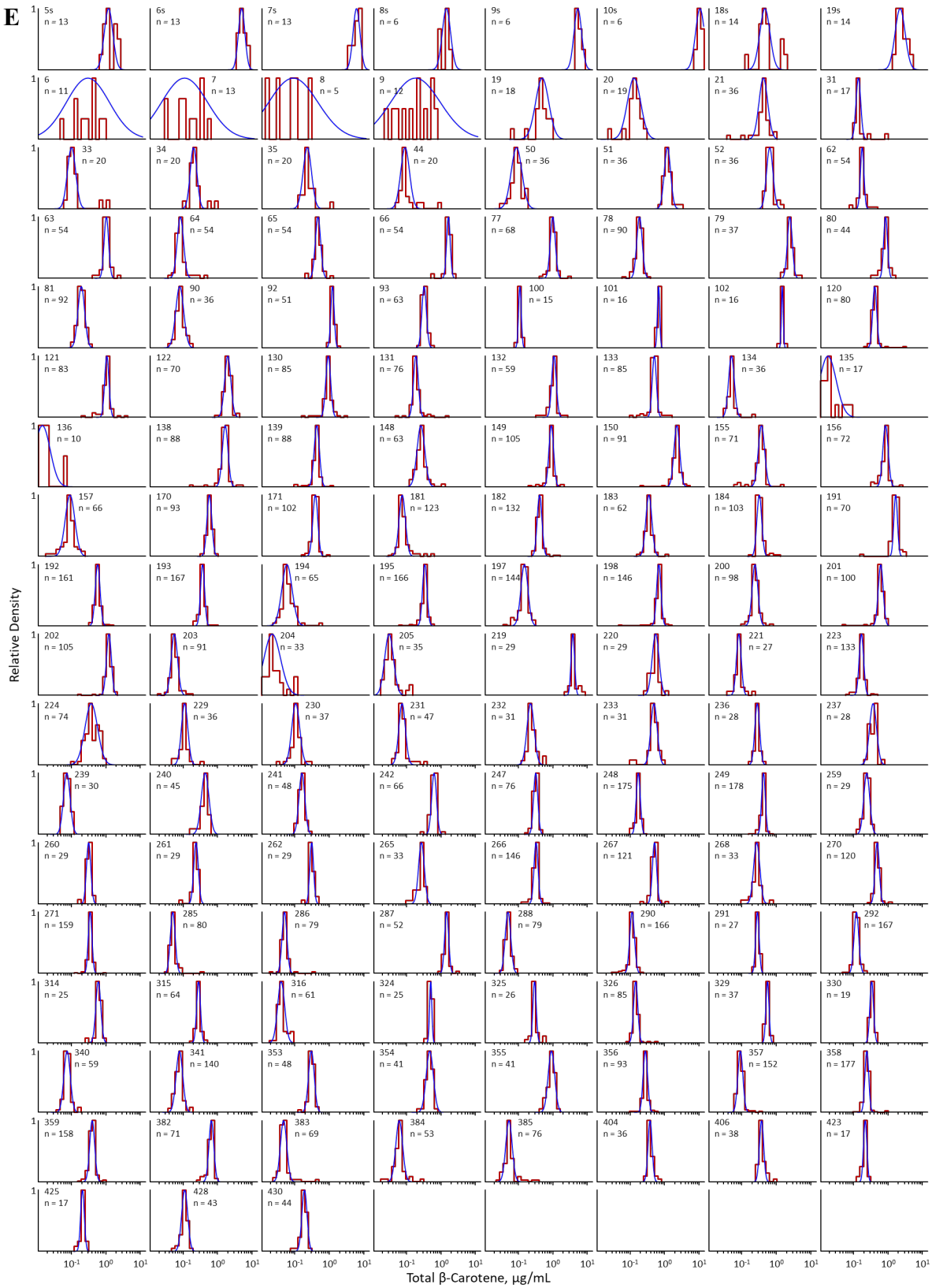
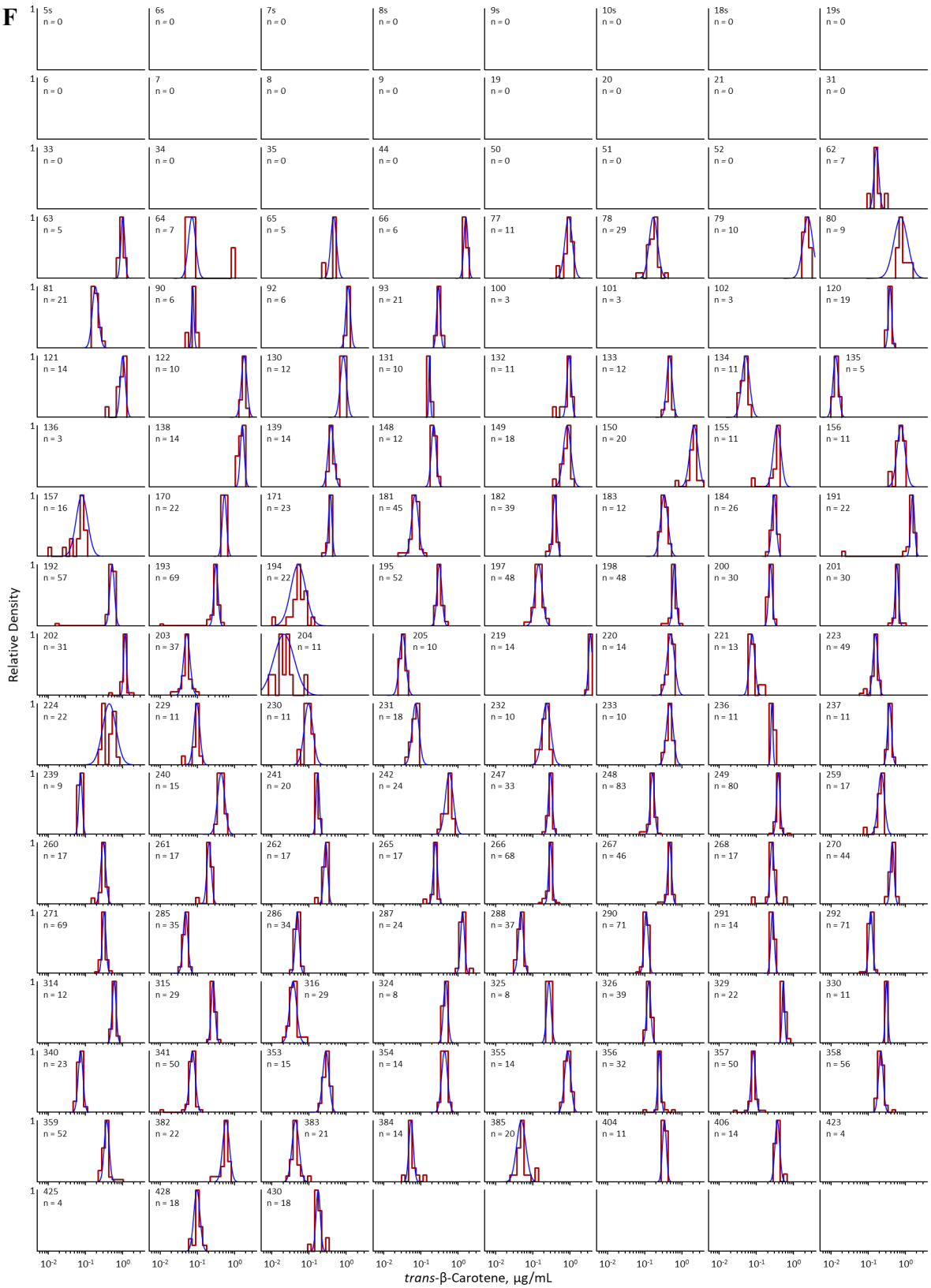
358 n = 149
359 n = 136
382 n = 61
383 n = 62
384 n = 45
385 n = 65
404 n = 32
406 n = 35
423 n = 15
425 n = 15
428 n = 41
430 n = 42


E
Relative Density
Total β-Carotene, µg/mL

F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8s n = 0
9s n = 0
10s n = 0
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19s n = 0
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62 n = 7
63 n = 5
64 n = 7
65 n = 5
66 n = 6
77 n = 11
78 n = 29
79 n = 10
80 n = 9
81 n = 21
90 n = 6
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93 n = 21
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101 n = 3
102 n = 3
120 n = 19
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122 n = 10
130 n = 12
131 n = 10
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138 n = 14
139 n = 14
148 n = 12
149 n = 18
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155 n = 11
156 n = 11
157 n = 16
170 n = 22
171 n = 23
181 n = 45
182 n = 39
183 n = 12
184 n = 26
191 n = 22
192 n = 57
193 n = 69
194 n = 22
195 n = 52
197 n = 48
198 n = 48
200 n = 30
201 n = 30
202 n = 31
203 n = 37
204 n = 11
205 n = 10
219 n = 14
220 n = 14
221 n = 13
223 n = 49
224 n = 22
229 n = 11
230 n = 11
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237 n = 11
239 n = 9
240 n = 15
241 n = 20
242 n = 24
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248 n = 83
249 n = 80
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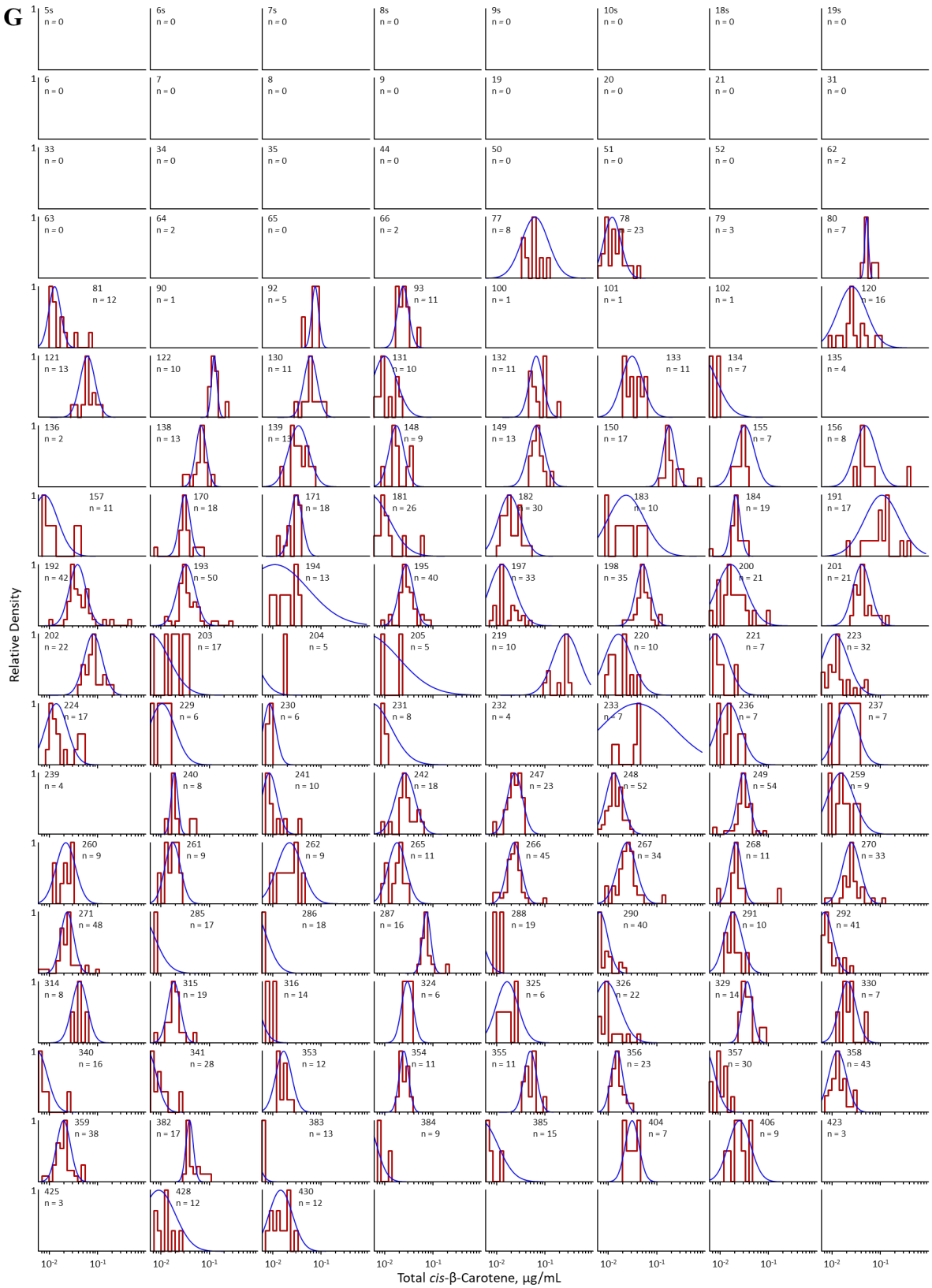
265 n = 17
266 n = 68
267 n = 46
268 n = 17
270 n = 44
271 n = 69
285 n = 35
286 n = 34
287 n = 24
288 n = 37
290 n = 71
291 n = 14
292 n = 71
314 n = 12
315 n = 29
316 n = 29
324 n = 8
325 n = 8
326 n = 39
329 n = 22
330 n = 11
340 n = 23
341 n = 50
353 n = 15
354 n = 14
355 n = 14
356 n = 32
357 n = 50
358 n = 56
359 n = 52
382 n = 22
383 n = 21
384 n = 14
385 n = 20
404 n = 11
406 n = 14
423 n = 4
425 n = 4
428 n = 18
430 n = 18
Relative Density
trans-β-Carotene, µg/mL


G
Relative Density
Total cis-β-Carotene, µg/mL
5s n = 0
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9s n = 0
10s n = 0
18s n = 0
19s n = 0
6 n = 0
7 n = 0
8 n = 0
9 n = 0
19 n = 0
20 n = 0
21 n = 0
31 n = 0
33 n = 0
34 n = 0
35 n = 0
44 n = 0
50 n = 0
51 n = 0
52 n = 0
62 n = 2
63 n = 0
64 n = 2
65 n = 0
66 n = 2
77 n = 8
78 n = 23
79 n = 3
80 n = 7
81 n = 12
90 n = 1
92 n = 5
93 n = 11
100 n = 1
101 n = 1
102 n = 1
120 n = 16
121 n = 13
122 n = 10
130 n = 11
131 n = 10
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133 n = 11
134 n = 7
135 n = 4
136 n = 2
138 n = 13
139 n = 13
148 n = 9
149 n = 13
150 n = 17
155 n = 7
156 n = 8
157 n = 11
170 n = 18
171 n = 18
181 n = 26
182 n = 30
183 n = 10
184 n = 19
191 n = 17
192 n = 42
193 n = 50
194 n = 13
195 n = 40
197 n = 33
198 n = 35
200 n = 21
201 n = 21
202 n = 22
203 n = 17
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205 n = 5
219 n = 10
220 n = 10
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223 n = 32
224 n = 17
229 n = 6
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249 n = 54
259 n = 9
260 n = 9
261 n = 9
262 n = 9
265 n = 11
266 n = 45
267 n = 34
268 n = 11
270 n = 33
271 n = 48
285 n = 17
286 n = 18
287 n = 16
288 n = 19
290 n = 40
291 n = 10
292 n = 41
314 n = 8
315 n = 19
316 n = 14
324 n = 6
325 n = 6
326 n = 22
329 n = 14
330 n = 7
340 n = 16
341 n = 28
353 n = 12
354 n = 11
355 n = 11
356 n = 23
357 n = 30
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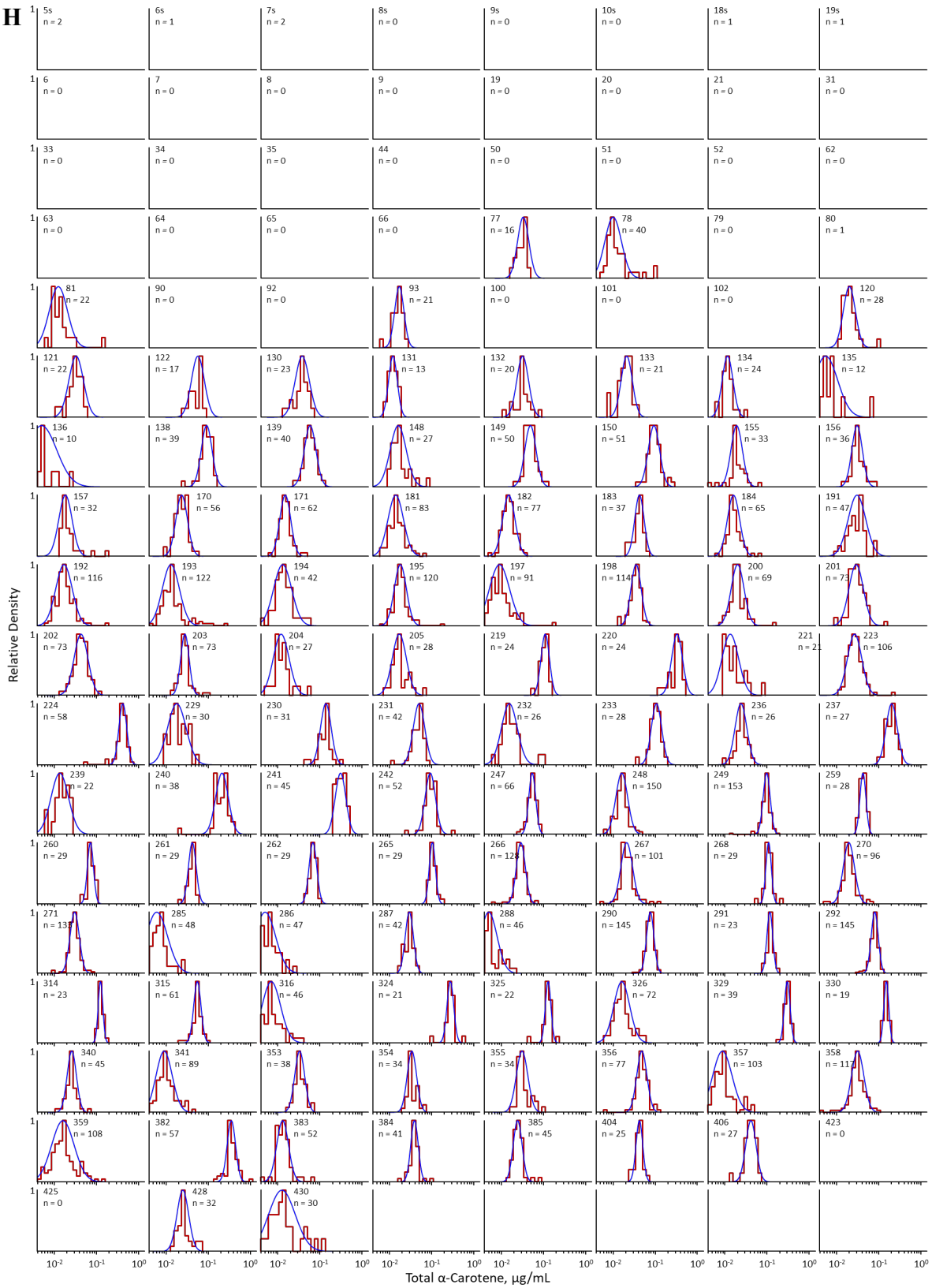
359 n = 38
382 n = 17
383 n = 13
384 n = 9
385 n = 15
404 n = 7
406 n = 9
423 n = 3
425 n = 3
428 n = 12
430 n = 12


H
Relative Density
Total α-Carotene, µg/mL
5s n = 2
6s n = 1
7s n = 2
8s n = 0
9s n = 0
10s n = 0
18s n = 1
19s n = 1
6 n = 0
7 n = 0
8 n = 0
9 n = 0
19 n = 0
20 n = 0
21 n = 0
31 n = 0
33 n = 0
34 n = 0
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64 n = 0
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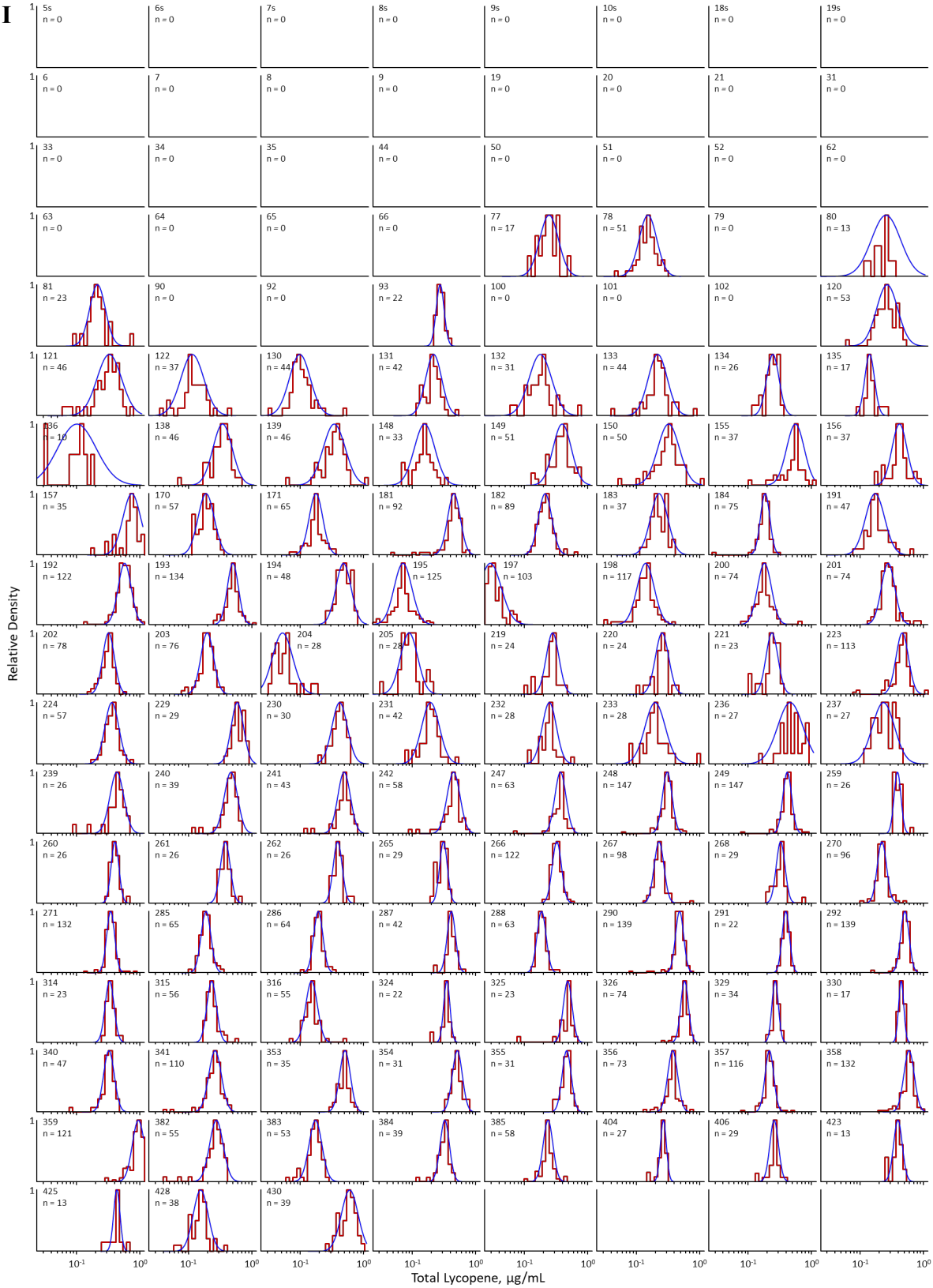
77 n = 16
78 n = 40
79 n = 0
80 n = 1
81 n = 22
90 n = 0
92 n = 0
93 n = 21
100 n = 0
101 n = 0
102 n = 0
120 n = 28
121 n = 22
122 n = 17
130 n = 23
131 n = 13
132 n = 20
133 n = 21
134 n = 24
135 n = 12
136 n = 10
138 n = 39
139 n = 40
148 n = 27
149 n = 50
150 n = 51
155 n = 33
156 n = 36
157 n = 32
170 n = 56
171 n = 62
181 n = 83
182 n = 77
183 n = 37
184 n = 65
191 n = 47
192 n = 116
193 n = 122
194 n = 42
195 n = 120
197 n = 91
198 n = 114
200 n = 69
201 n = 73
202 n = 73
203 n = 73
204 n = 27
205 n = 28
219 n = 24
220 n = 24
221 n = 22
223 n = 106
224 n = 58
229 n = 30
230 n = 31
231 n = 42
232 n = 26
233 n = 28
236 n = 26
237 n = 27
239 n = 22
240 n = 38
241 n = 45
242 n = 52
247 n = 66
248 n = 150
249 n = 153
259 n = 28
260 n = 29
261 n = 29
262 n = 29
265 n = 29
266 n = 128
267 n = 101
268 n = 29
270 n = 96
271 n = 138
285 n = 48
286 n = 47
287 n = 42
288 n = 46
290 n = 145
291 n = 23
292 n = 145
314 n = 23
315 n = 61
316 n = 46
324 n = 21
325 n = 22
326 n = 72
329 n = 39
330 n = 19
340 n = 45
341 n = 89
353 n = 38
354 n = 34
355 n = 34
356 n = 77
357 n = 103
358 n = 117
359 n = 108
382 n = 57
383 n = 52
384 n = 41
385 n = 45
404 n = 25
406 n = 27
423 n = 0
425 n = 0
428 n = 32
430 n = 30

I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7s n = 0
8s n = 0
9s n = 0
10s n = 0
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19s n = 0
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7 n = 0
8 n = 0
9 n = 0
19 n = 0
20 n = 0
21 n = 0
31 n = 0
33 n = 0
34 n = 0
35 n = 0
44 n = 0
50 n = 0
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52 n = 0
62 n = 0
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65 n = 0
66 n = 0
77 n = 17
78 n = 51
79 n = 0
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92 n = 0
93 n = 22
100 n = 0
101 n = 0
102 n = 0
120 n = 53
121 n = 46
122 n = 37
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156 n = 37
157 n = 35
170 n = 57
171 n = 65
181 n = 92
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183 n = 37
184 n = 75
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192 n = 122
193 n = 134
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195 n = 125
197 n = 103
198 n = 117
200 n = 74
201 n = 74
202 n = 78
203 n = 76
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205 n = 28
219 n = 24
220 n = 24
221 n = 23
223 n = 113
224 n = 57
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230 n = 30
231 n = 42
232 n = 28
233 n = 28
236 n = 27
237 n = 27
239 n = 26
240 n = 39
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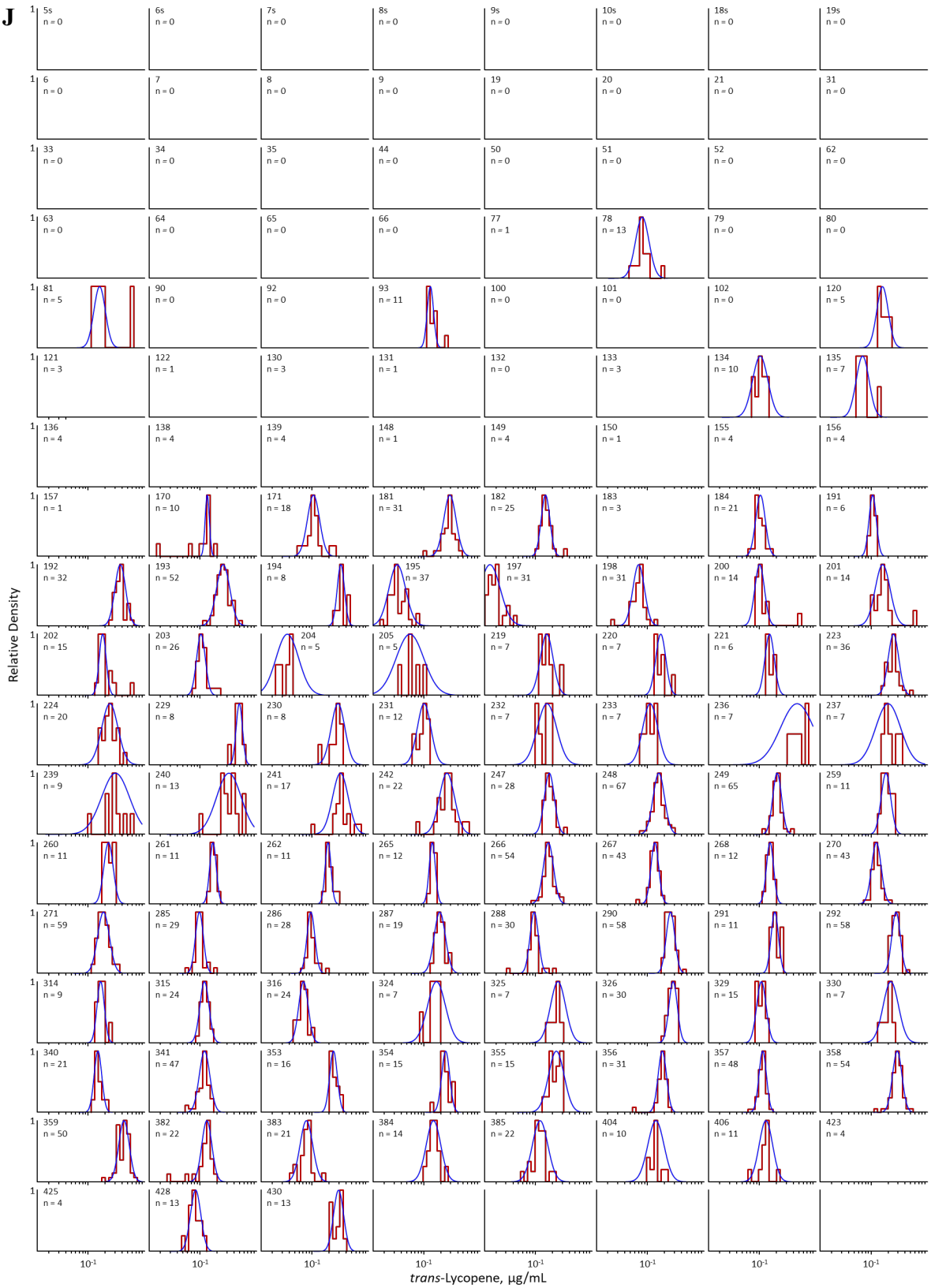
268 n = 29
270 n = 96
271 n = 132
285 n = 65
286 n = 64
287 n = 42
288 n = 63
290 n = 139
291 n = 22
292 n = 139
314 n = 23
315 n = 56
316 n = 55
324 n = 22
325 n = 23
326 n = 74
329 n = 34
330 n = 17
340 n = 47
341 n = 110
353 n = 35
354 n = 31
355 n = 31
356 n = 73
357 n = 116
358 n = 132
359 n = 121
382 n = 55
383 n = 53
384 n = 39
385 n = 58
404 n = 27
406 n = 29
423 n = 13
425 n = 13
428 n = 38
430 n = 39
Relative Density
Total Lycopene, µg/mL


J
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8s n = 0
9s n = 0
10s n = 0
18s n = 0
19s n = 0
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19 n = 0
20 n = 0
21 n = 0
31 n = 0
33 n = 0
34 n = 0
35 n = 0
44 n = 0
50 n = 0
51 n = 0
52 n = 0
62 n = 0
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64 n = 0
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79 n = 0
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92 n = 0
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192 n = 32
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197 n = 31
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385 n = 22
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428 n = 13
430 n = 13
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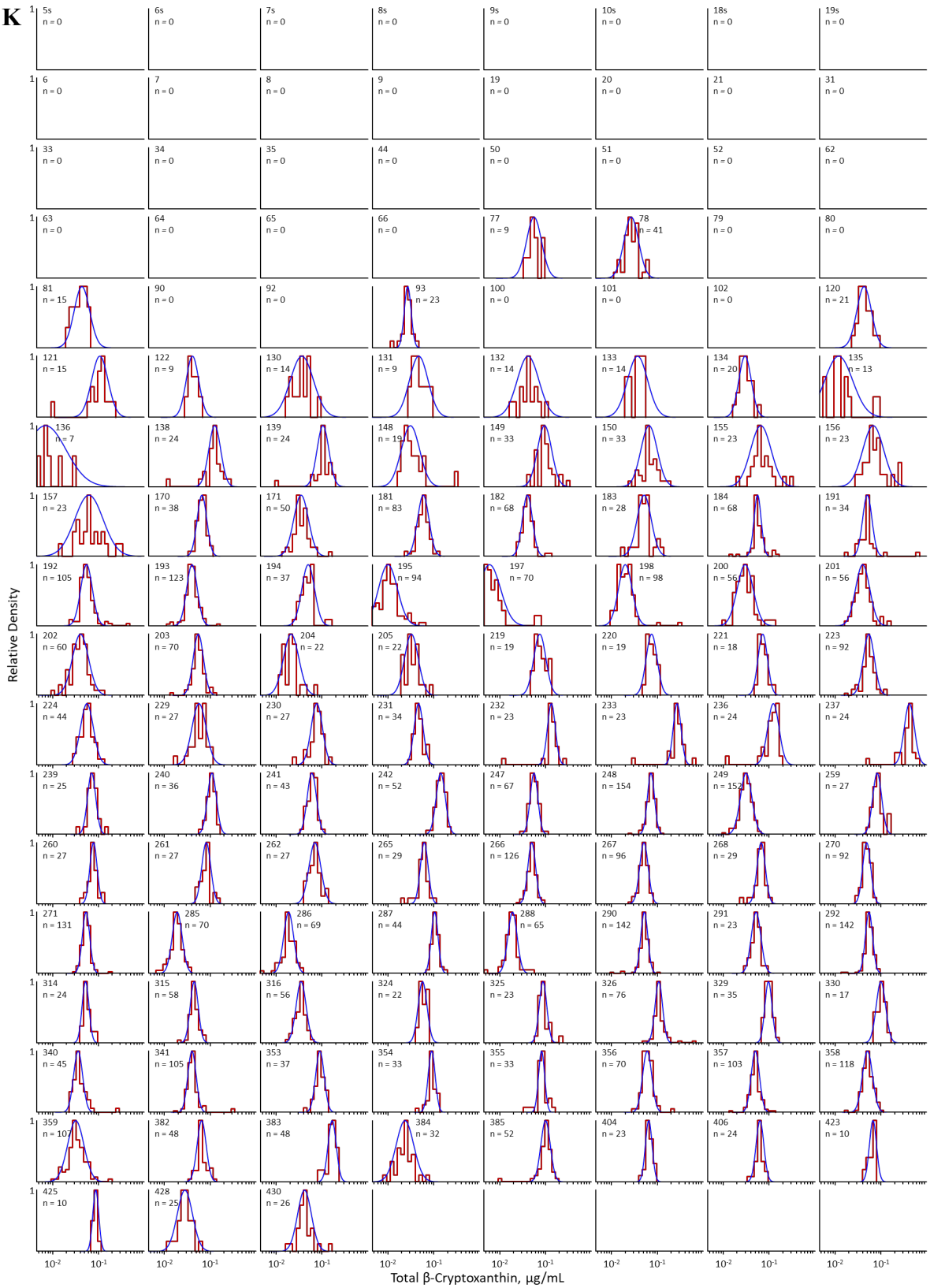
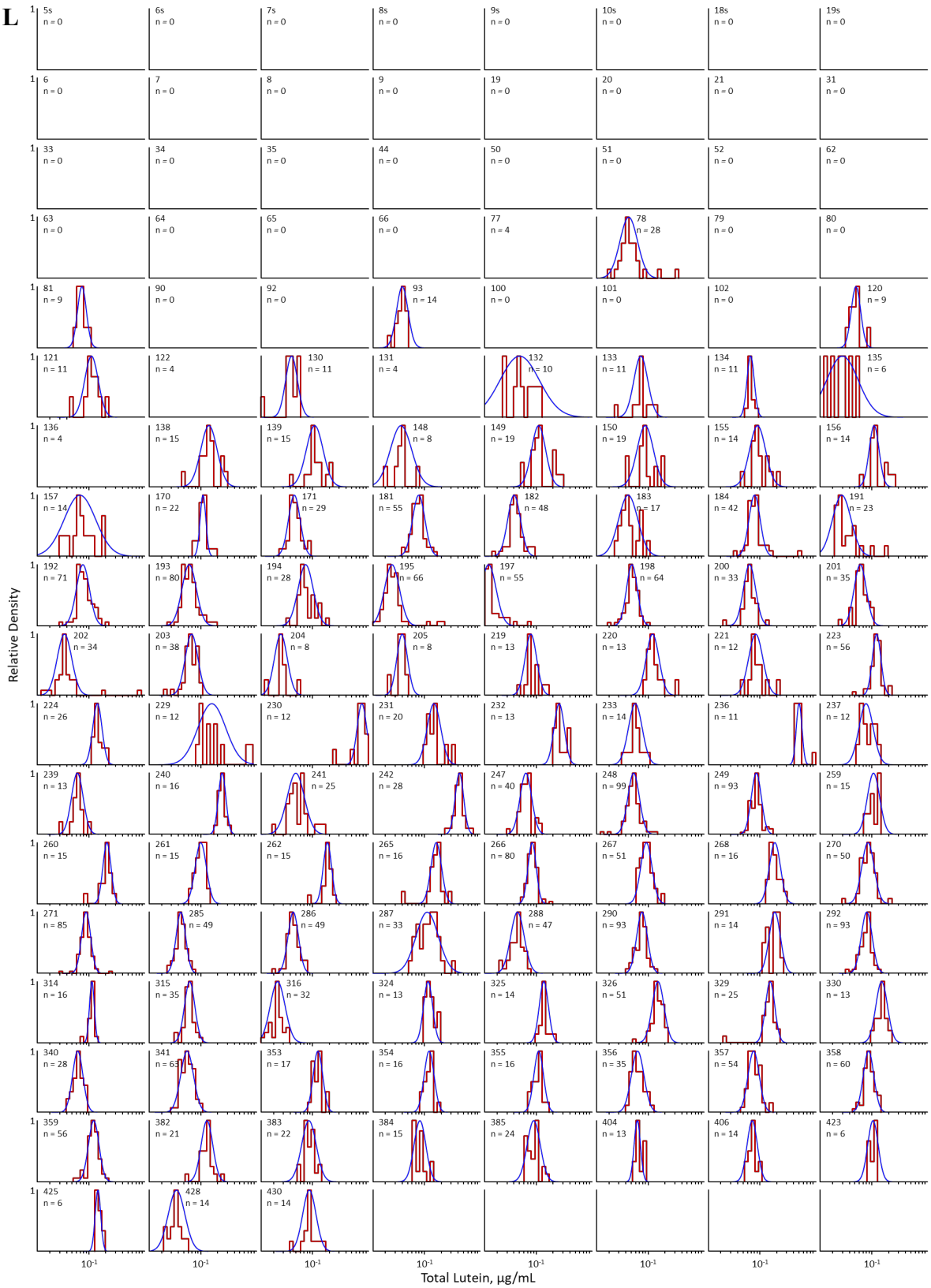
10^{-1}
Relative Density
trans-Lycopene, µg/mL


K
Relative Density
Total β-Cryptoxanthin, µg/mL

L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425 n = 6
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430 n = 14
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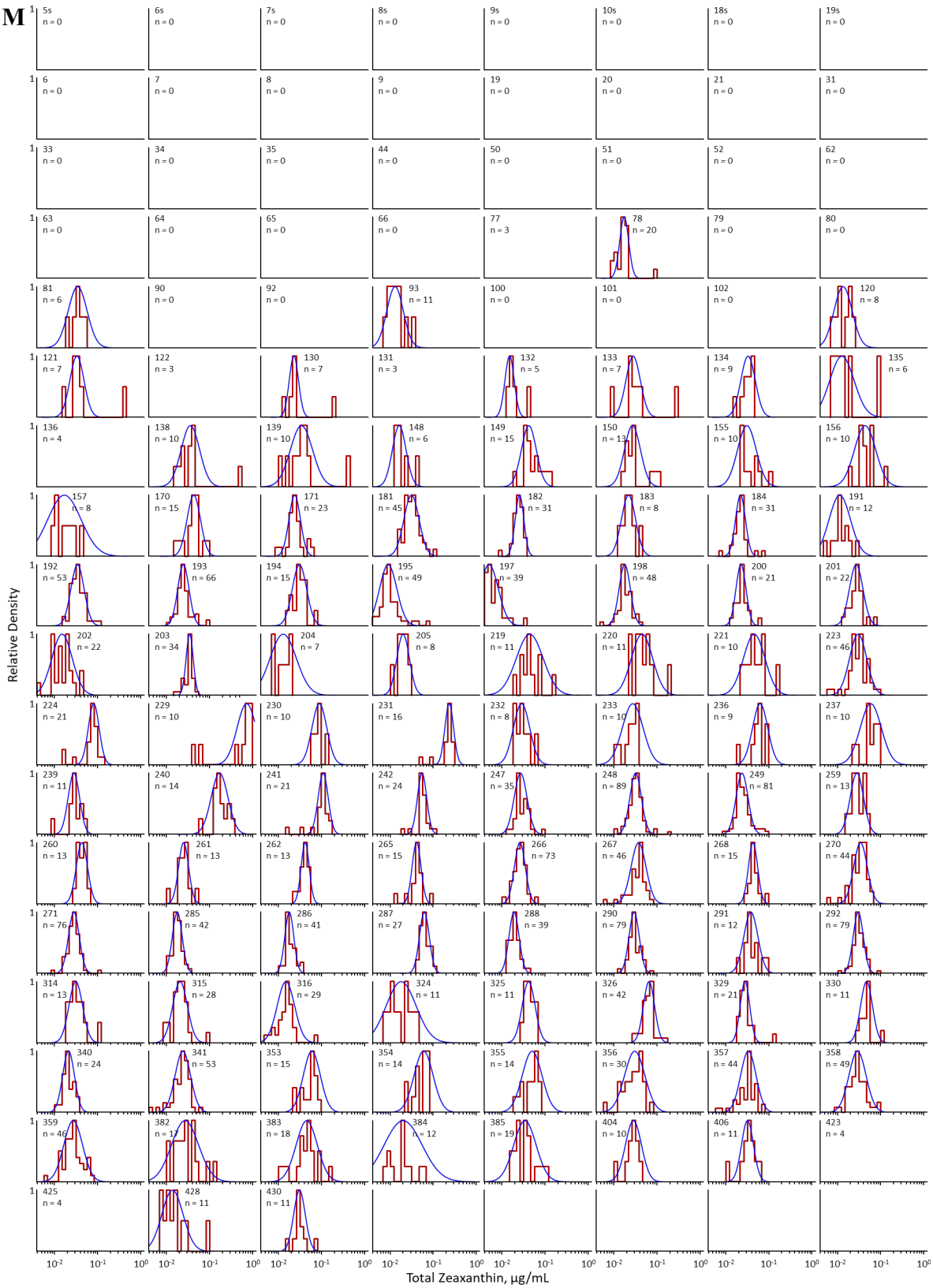
10^{-1}
Relative Density
Total Lutein, µg/mL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384 n = 12
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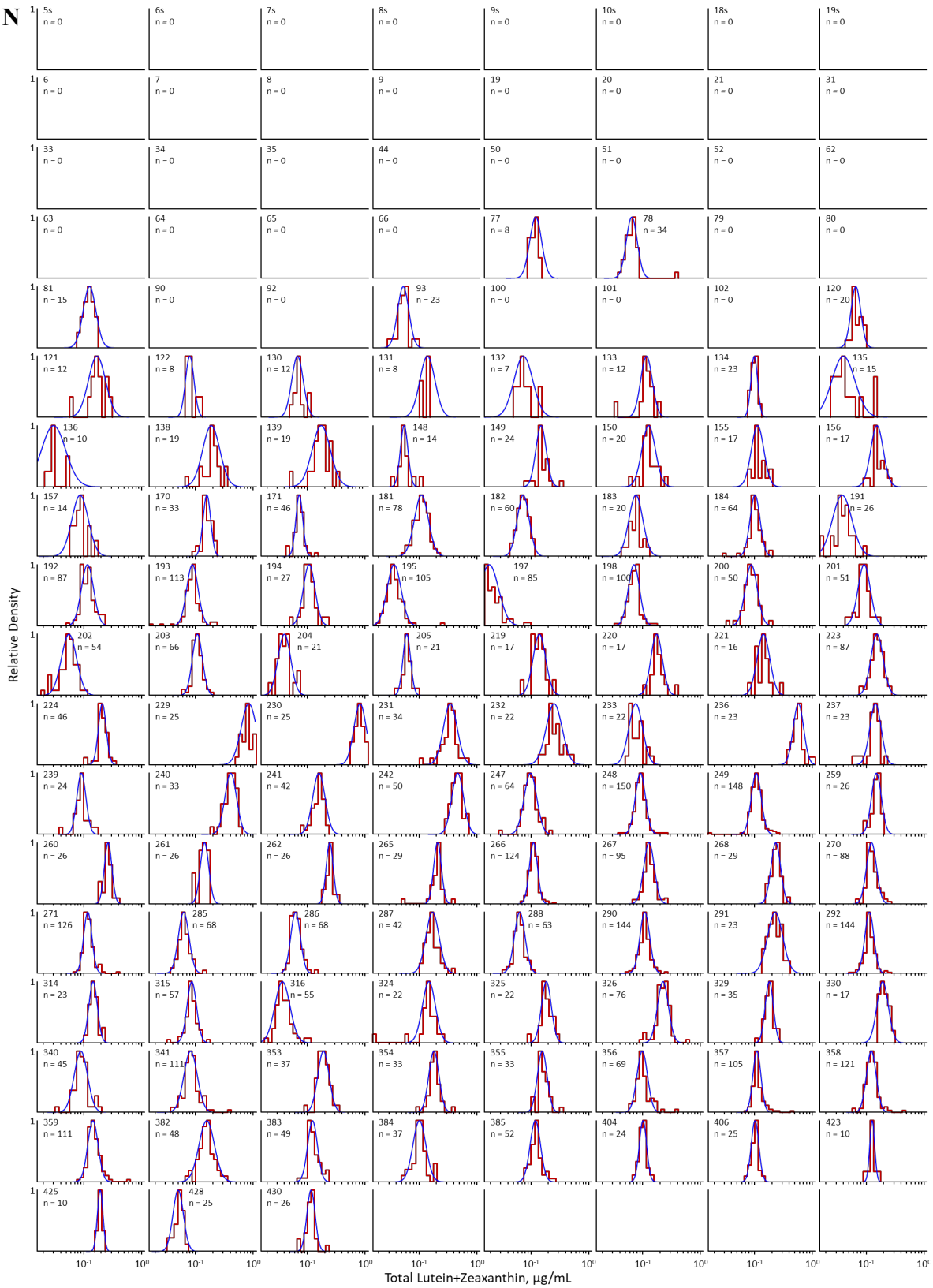
406 n = 11
423 n = 4
425 n = 4
428 n = 11
430 n = 11
Relative Density
Total Zeaxanthin, µg/mL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382 n = 48
383 n = 49
384 n = 37
385 n = 52
404 n = 24
406 n = 25
423 n = 10
425 n = 10
428 n = 25
430 n = 26
Relative Density
Total Lutein+Zeaxanthin, µg/mL

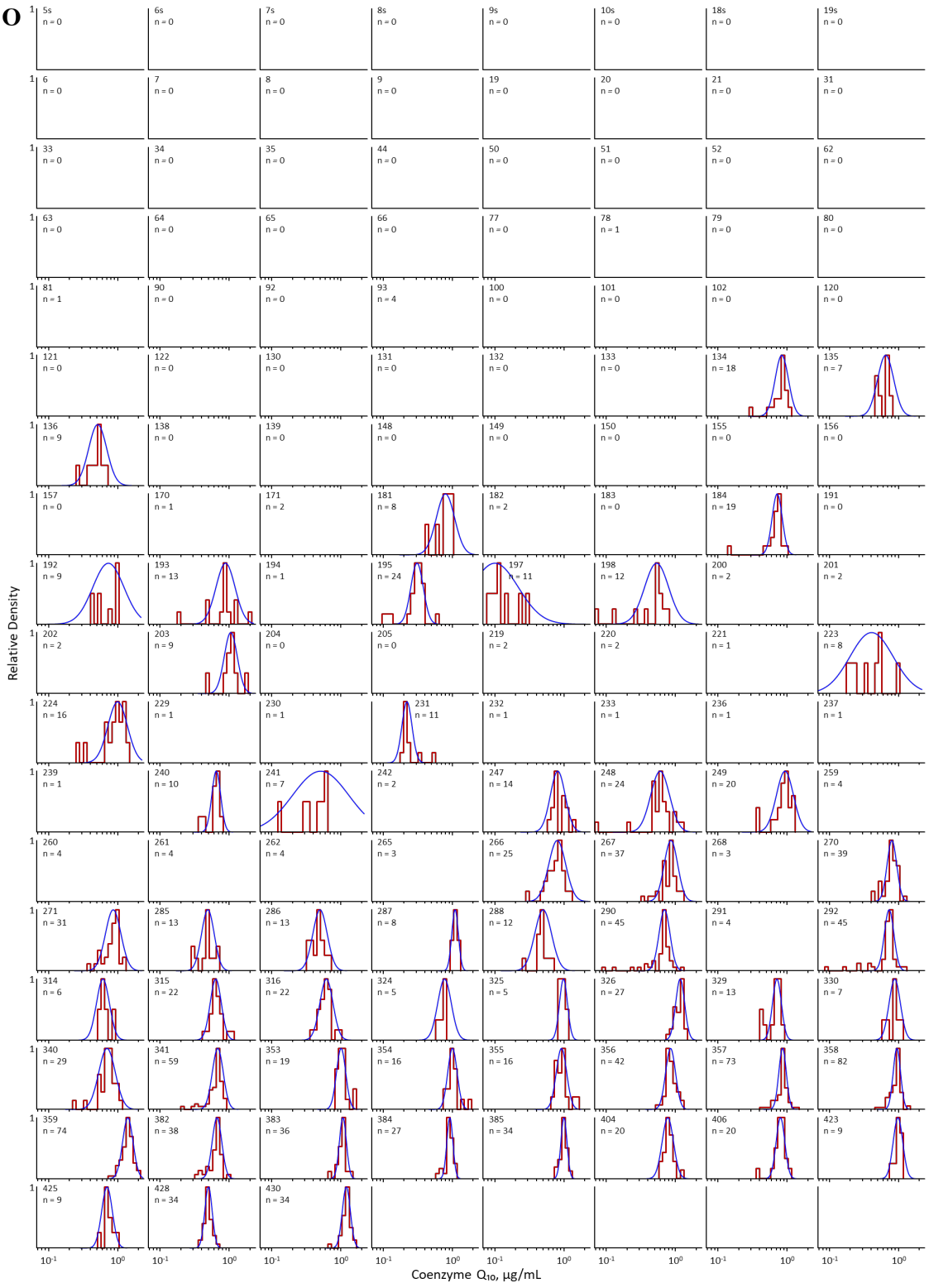


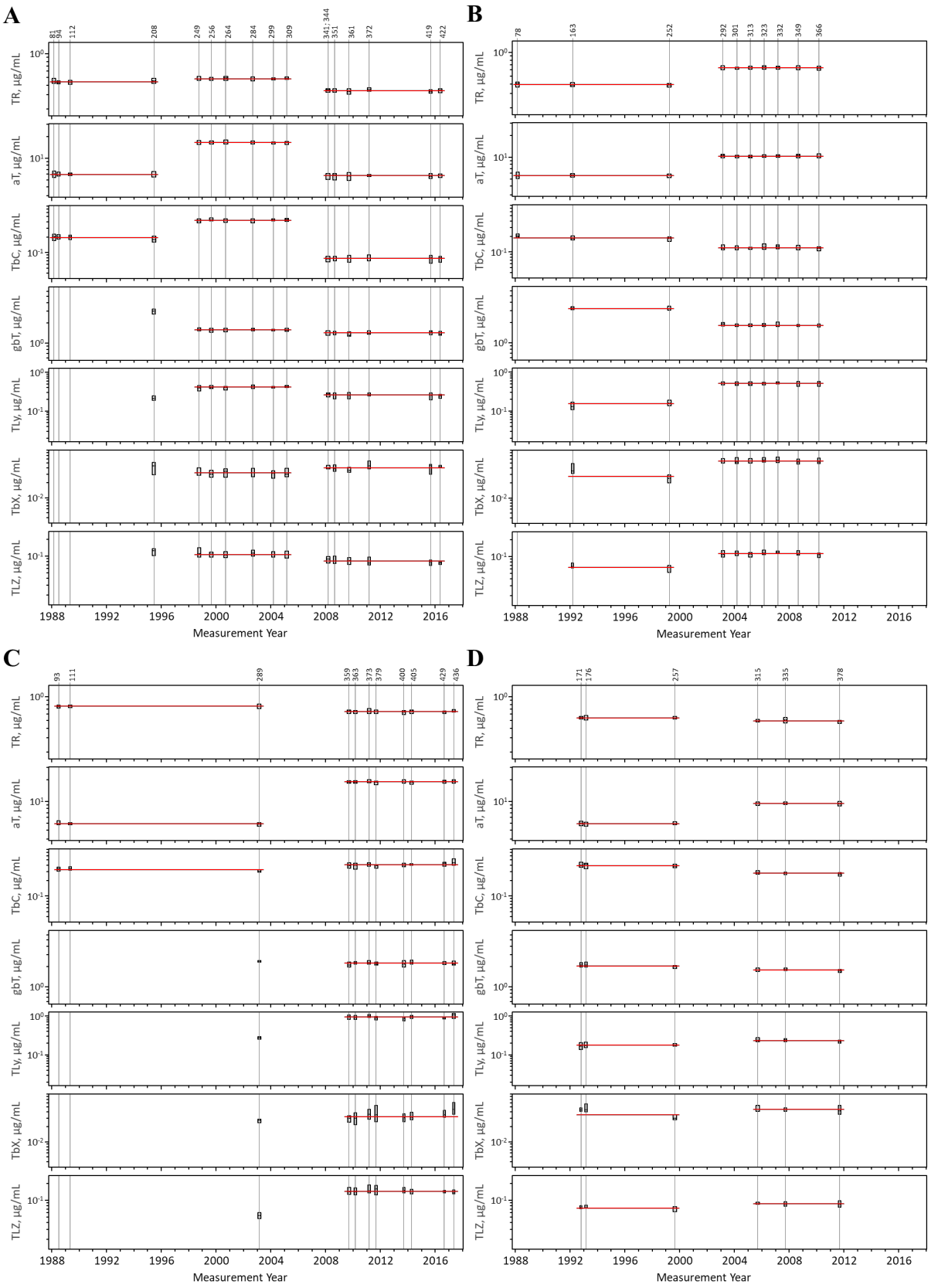
Fig. 11. Summary Distributions for the Most Frequently Reported Measurands.

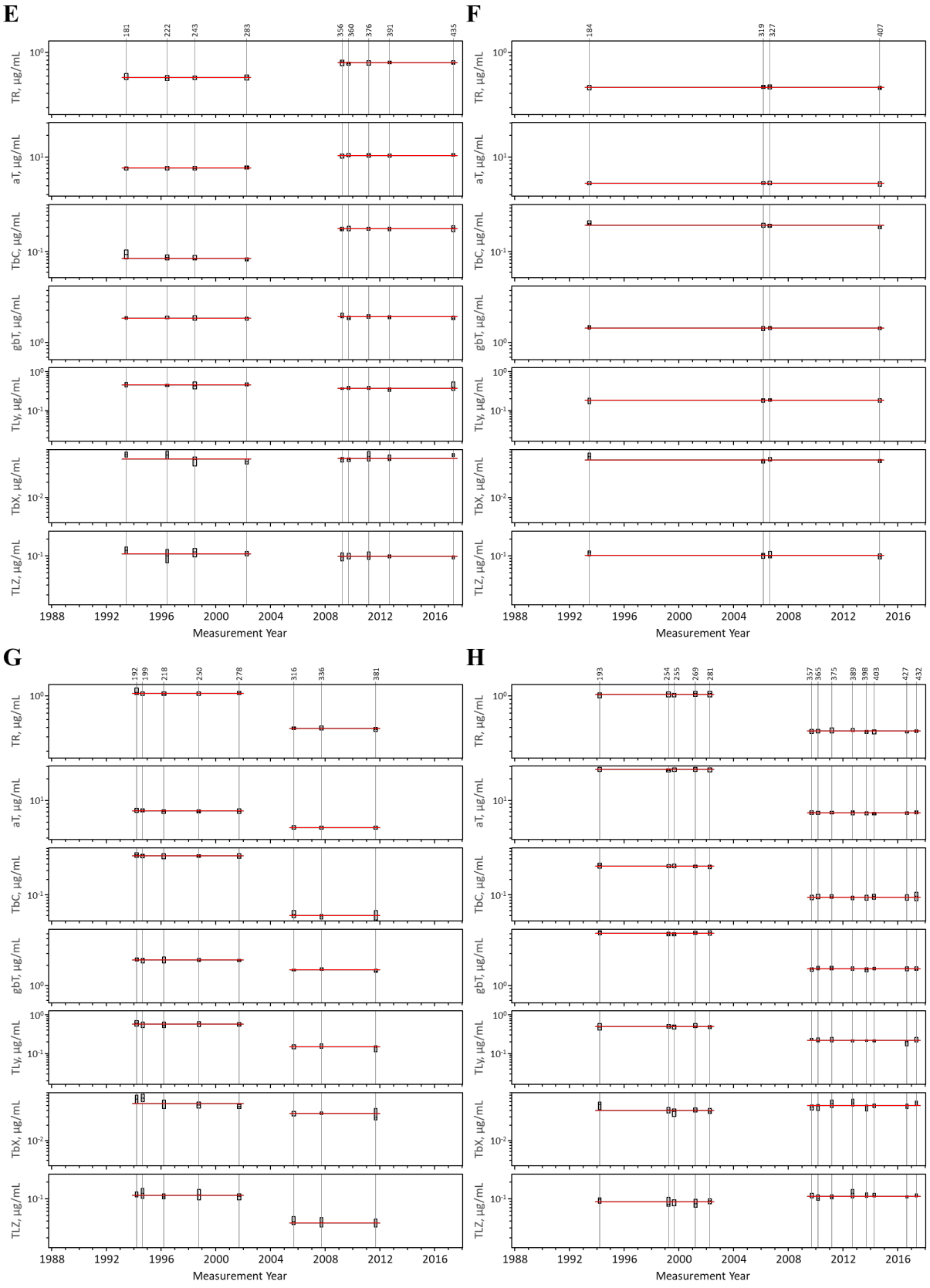
The thick red histogram trace displays the empirical distribution of the decadic logarithm ($\log_{10}$) of the reported results. The thin blue smooth curve displays a best-fit normal distribution. The material ID and number of results available to characterize the distribution are displayed to the left or to the right of the distributions.

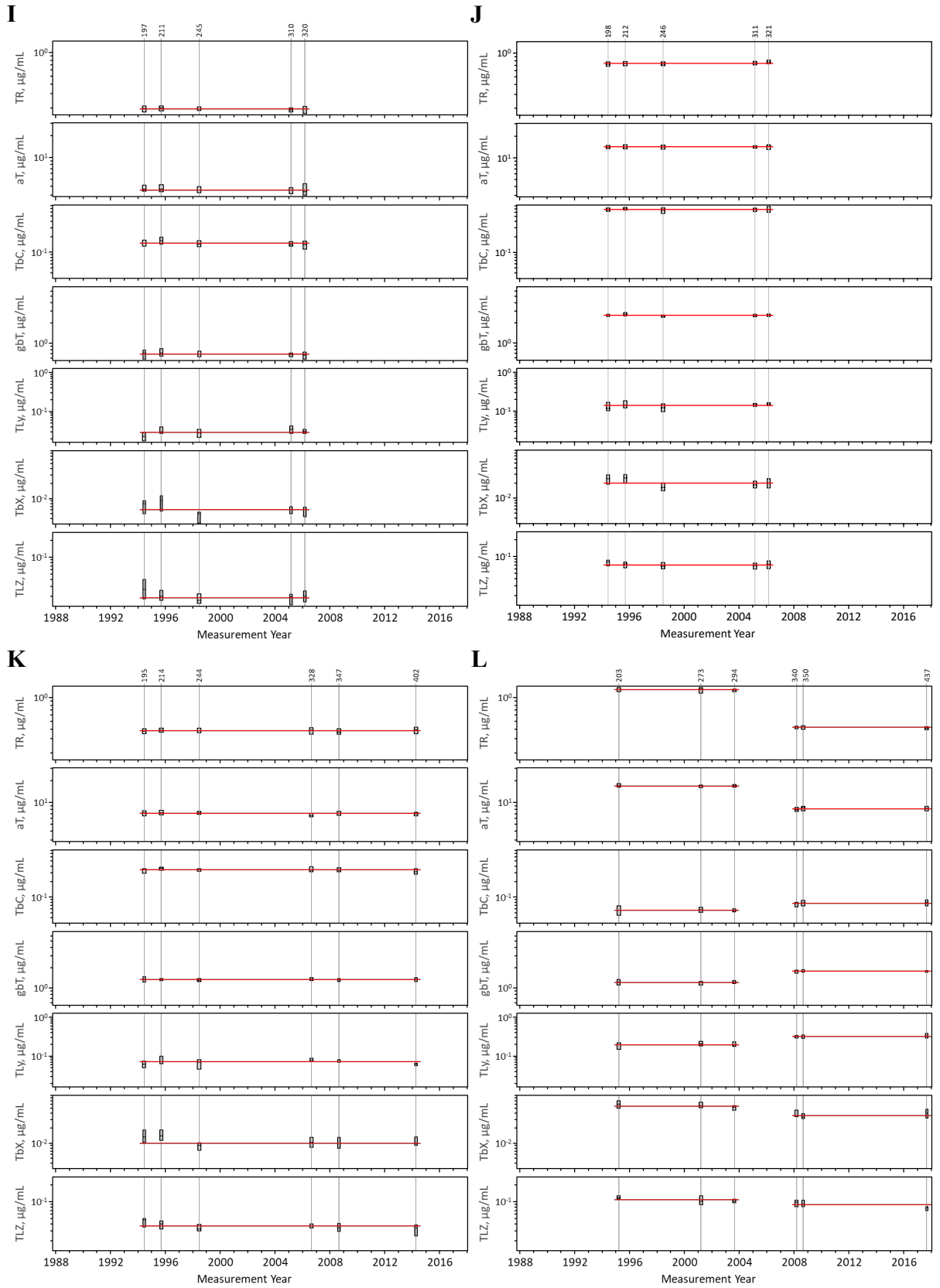
5.3. Measurand Stability Assessed From Multiple Distributions

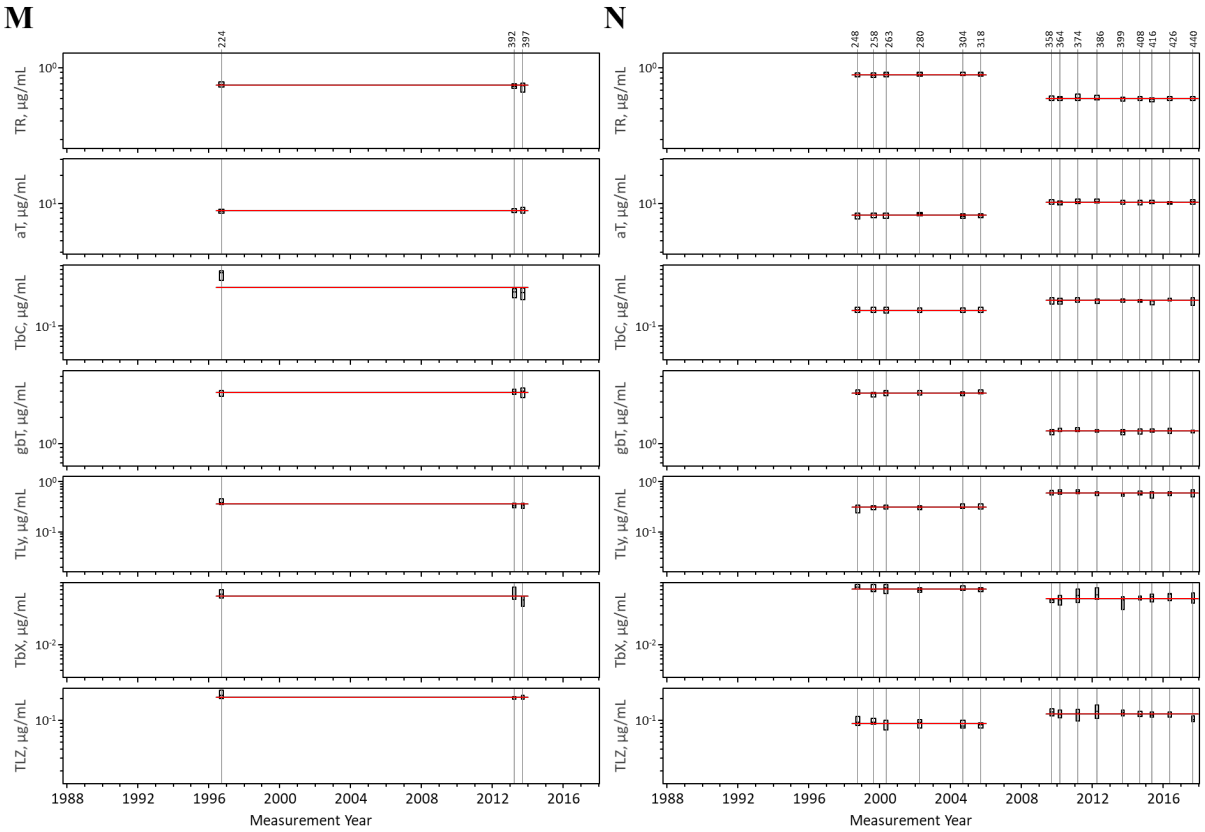
The 17 panels, A to Q, of Fig. 12 summarize results for the 27 materials distributed in at least 3 MMQAP RRs. Each panel displays results for the seven most often reported measurands: TR, aT, TbC, gbT, Tly, TbX, and TLZ. The x-axis (horizontal) of each segment spans from 1988 through 2017; the y-axis (vertical) spans the $\log_{10}$(concentration) range of the measurand over all 27 materials. Each panel displays results from one to three materials, the number of materials set by when the materials were distributed, the need to avoid overlapping intervals, and the desire to minimize the number of panels.

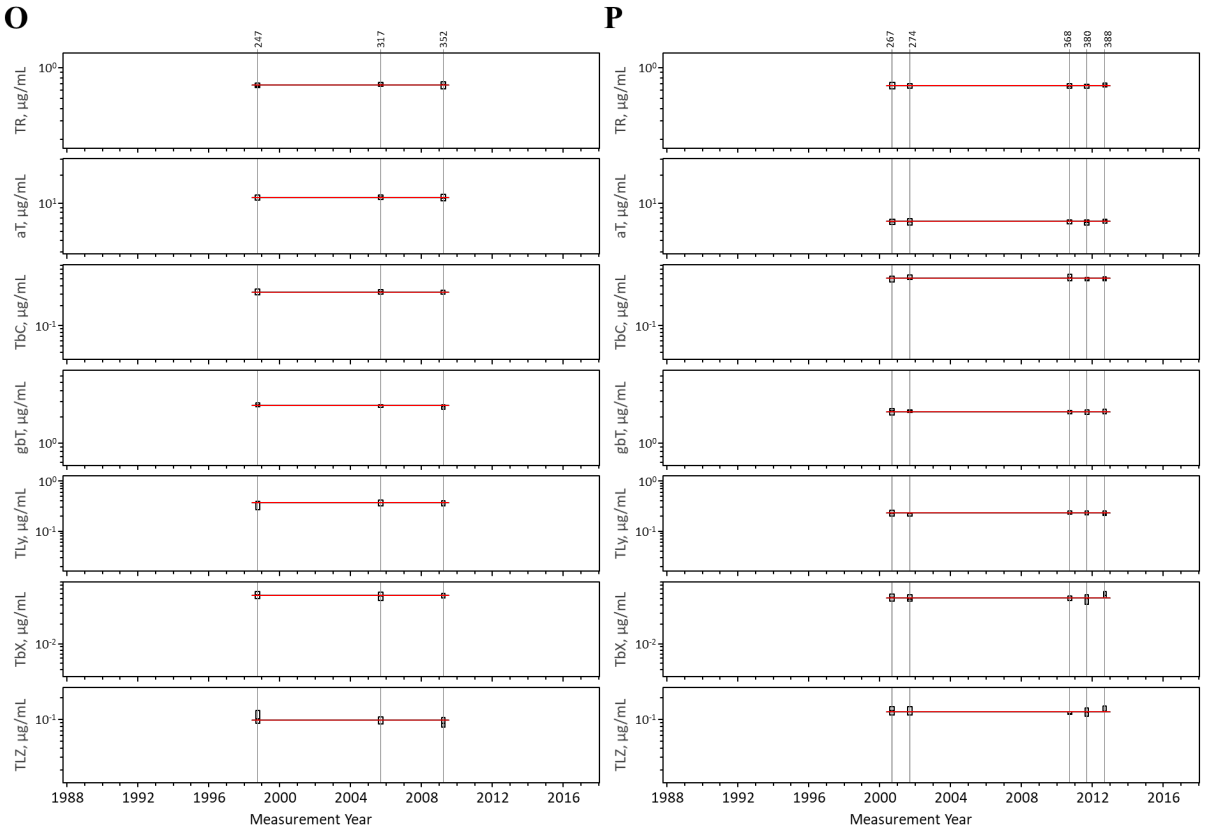
Little to no evidence of significant changes in concentration was observed over time for any of the 27 materials for any of the 7 measurands. While the pre-1996 results for TbX and TLZ are typically greater than those following, the trend holding across materials suggests that the higher values for these measurands result from calibration and/or definition issues rather than sample degradation.


A
B
C
D
TR, µg/mL
aT, µg/mL
TbC, µg/mL
gbT, µg/mL
TLy, µg/mL
TbX, µg/mL
TLZ, µg/mL
Measurement Year
1988
1992
1996
2000
2004
2008
2012
2016


E
F
G
H
TR, µg/mL
aT, µg/mL
TbC, µg/mL
gbT, µg/mL
TLy, µg/mL
TbX, µg/mL
TLZ, µg/mL
Measurement Year
1988
1992
1996
2000
2004
2008
2012
2016


I
J
K
L
TR, µg/mL
aT, µg/mL
TbC, µg/mL
gbT, µg/mL
TLy, µg/mL
TbX, µg/mL
TLZ, µg/mL
Measurement Year
1988
1992
1996
2000
2004
2008
2012
2016


M
224
392
397
N
248
258
263
280
304
318
358
364
374
386
399
408
416
426
440
TR, µg/mL
aT, µg/mL
TbC, µg/mL
gbT, µg/mL
TLy, µg/mL
TbX, µg/mL
TLZ, µg/mL
1988
1992
1996
2000
2004
2008
2012
2016
Measurement Year


O
247
317
352
P
267
274
368
380
388
TR, µg/mL
aT, µg/mL
TbC, µg/mL
gbT, µg/mL
TLy, µg/mL
TbX, µg/mL
TLZ, µg/mL
1988
1992
1996
2000
2004
2008
2012
2016
Measurement Year

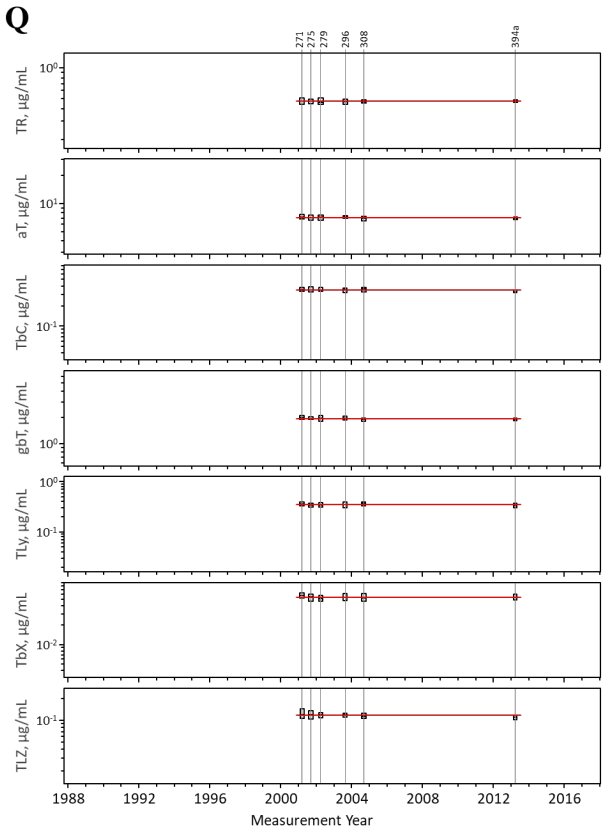


Fig. 12. Summary Distributions for the Most Frequently Reported Measurands.

Measurement results for a given RR are summarized as boxes that bound the interquartile range (IQR), the central 50 % of the quantitative results, with width proportional to the square-root of the number of results. The line within the box represents the median. The horizontal red lines connecting the boxes denote the average median. The thin vertical grey lines connect the boxes to the RR date (at the bottom) and the sample identification code (at the top). The horizontal axis of each segment of each panel denotes the calendar date of the RR, with the years labeled at the bottom (TLZ) segment. The vertical of each segment spans the $\log_{10}$(concentration) range of the measurand over all 27 materials.

6. Community Performance Over Time

The stability of the results for the materials distributed multiple times suggests that the measurement community's measurement capabilities were relatively consistent across changes in sample materials and community composition. However, none of the materials document participant capabilities over the program's entire history.

To enable assessment of the community's measurement performance using results for different samples, the observed measurement scale for each measurand must be transformed to be independent of the measurement consensus value [71]. Assuming a fairly consistent functional relationship between the observed Q_n and the median, quantifying that relationship enables isolation of the location dependence from other potential sources of variability.

To enable assessment of changes in measurement performance over time, the functional relationship must also describe performance during some reference period. The 12 RRs from 1997 through 2001 provide a dense set of results for a diversity of materials for 14 of the 15 most commonly reported measurands; the 8 RRs from 2014 through 2017 provide a dense and diverse set of results for Q_{10}. Only datasets having at least eight quantitative results are used to provide the summary estimates.

6.1. Reproducibility Functions

The observed {median, Q_n} summary statistics for the 15 measurands with sufficient data are displayed in Fig. 13. Empirical interlaboratory reproducibility functions fit to these paired values are also displayed. The empirical function combines constant and location-proportional terms [115,116]:

$$\hat{y} = \sqrt{a^2 + (b \times x)^2} \quad (1)$$

where $\hat{y}$ represents the predicted Q_n, x is the observed median, a is the effective lower limit of quantification, and b is the coefficient of variation expressed as a fraction. These values for these coefficients are estimated using a non-linear optimization tool to minimize the relative differences between the observed and the predicted robust SDs:

$$\text{RMSD} = 100\sqrt{\sum_i^m \left(\frac{y_i - \hat{y}_i}{x_i}\right)^2 / (m-2)} \quad (2)$$

where RMSD is the root-mean-square deviation to be minimized expressed as a percentage, i indexes across the m {median, Q_n} pairs, y_i and $\hat{y}_i$ are the observed and predicted Q_n of the i^{th} sample, and x_i is the median of the i^{th} sample.

Table 7 lists the coefficient values for the 15 measurands.

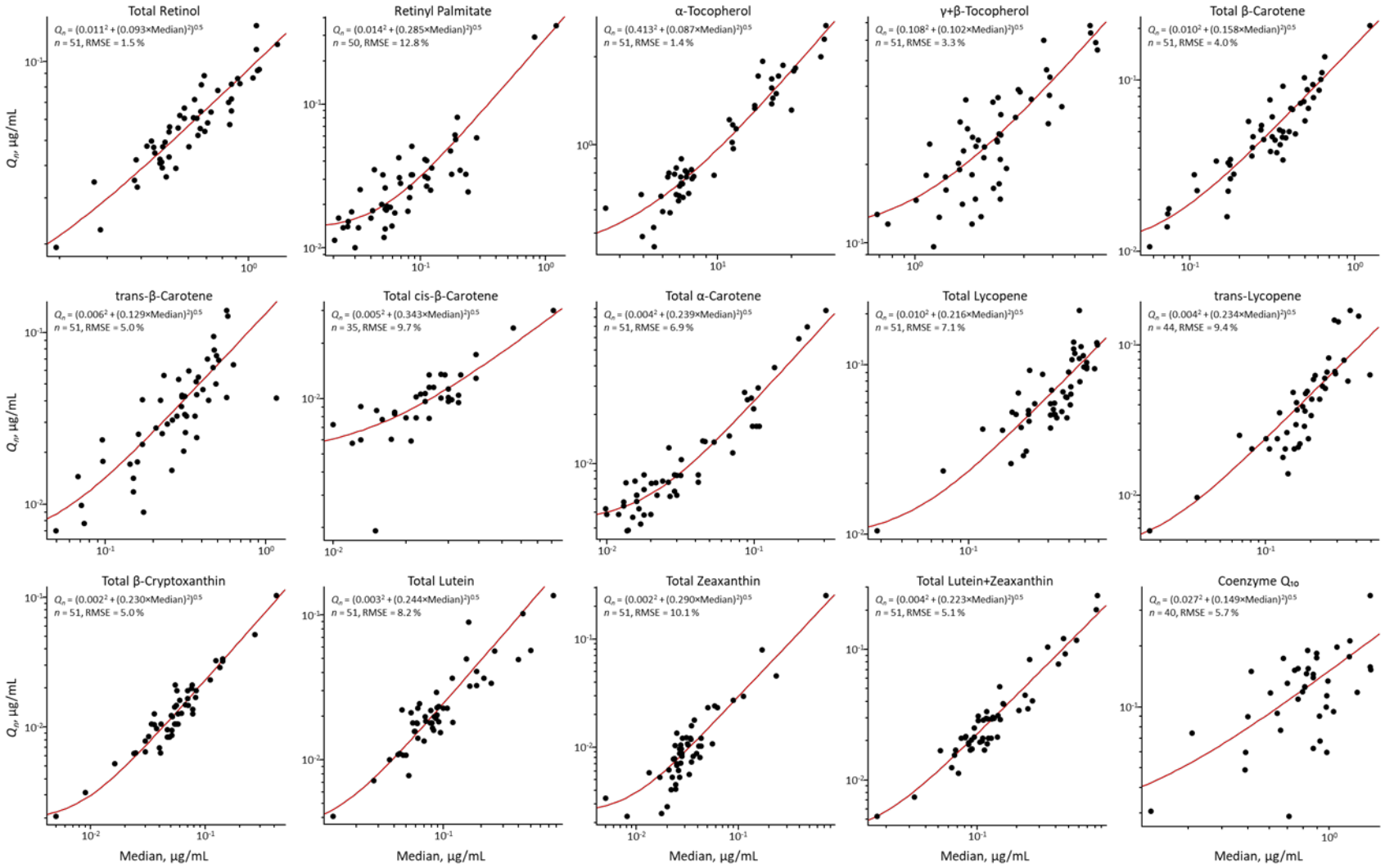


Fig. 13. Reproducibility Functions for the 15 Most Frequently Reported Measurands.

Functions for the first 14 measurands use data from studies from 1997 through mid-2001; the function for coenzyme Q_{10} uses data from 2014 through 2017.

Table 7. Reproducibility Function Parameters.

Measurand	Code	*n*	*a*	*b*	RMSD
Total Retinol	TR	51	0.0110	0.093	1.5
Retinyl Palmitate	RP	50	0.0135	0.285	12.8
α-Tocopherol	aT	51	0.4128	0.087	1.4
γ+β-Tocopherol	gbT	51	0.1081	0.102	3.3
Total β-Carotene	TbC	51	0.0103	0.158	4.0
Trans-β-Carotene	t-bC	51	0.0060	0.129	5.0
Cis-β-Carotene	c-bC	35	0.0050	0.343	9.7
Total α-Carotene	TaC	51	0.0044	0.239	6.9
Total Lycopene	TLy	51	0.0096	0.216	7.1
Trans-Lycopene	t-Ly	44	0.0042	0.234	9.4
Total β-Cryptoxanthin	TbX	51	0.0019	0.230	5.0
Total Lutein	TLu	51	0.0032	0.244	8.2
Total Zeaxanthin	TZ	51	0.0025	0.290	10.1
Total Lutein+Zeaxanthin	TLZ	51	0.0037	0.223	5.1
Coenzyme Q_{10}	Q10	40	0.0272	0.149	5.7

n number of {median, Q_n} pairs used in the parameter optimization
a constant, effectively the measurement community's lower limit of quantitation
b proportional, the coefficient of variation for large median values
RMSD root-mean-square deviation of the non-linear regression, expressed as a percentage

6.2. Within- and Between-Participant Community Performance Metrics

One approach to evaluating the performance of a measurement community over time estimates among-participant concordance, *C*, and the expected within-participant "apparent precision" (*AP*, a composite of measurement reproducibility and sample-specific biases) using reproducibility function standardized *z*-scores [71]. For a given measurand, the *z*-scores are defined as

$$z_{ijk} = \frac{(x_{ijk} - \bar{x}_k)}{\sqrt{a^2 + (b \times \bar{x}_k)^2}} \quad (3)$$

where z_{ijk} is the *z*-score for the measurement result reported for the k^{th} sample, by the j^{th} participant, in the i^{th} RR, x_{ijk} is that result, $\bar{x}_k$ is the median of all quantitative results for the k^{th} sample, and *a* and *b* are the coefficients of the interlaboratory reproducibility function for the measurand as described in Section 6.1.

The mean *z*-score for participant *j* in RR *i* is an estimate of the participant's average bias from the consensus median in units of interlaboratory reproducibility,

$$\bar{z}_{ij} = \sum_{k=1}^{n_{ij}} z_{ijk} / n_{ij} \quad (4)$$

where $\bar{z}_{ij}$ is the mean *z*-score for the measurement results reported by the j^{th} participant in the i^{th} RR, and n_{ij} is the number of those *z*-scores. The expected magnitude of the among-participant agreement with the community's consensus for the i^{th} RR can be estimated as the median of the absolute value of the means,

$$C_i = \text{MEDIAN}\left(\left|\bar{z}_{ij}\right|\right), \quad (5)$$

where MEDIAN is the function "calculate the median of the set of values." Note: the expected median of the signed average *z*-scores is zero.

The SD of the *z*-scores for participant *j* in RR *i* estimates the participant's apparent precision, also in units of interlaboratory reproducibility

$$s_{ij} = \sqrt{\sum_{k=1}^{n_{ij}} \left(z_{ijk} - \bar{z}_{ij}\right)^2 / \left(n_{ij} - 1\right)}, \tag{6}$$

where s_{ij} is the SD of the *z*-scores. The expected apparent precision for the i^{th} RR can be estimated as the median of the SDs

$$AP_i = \text{MEDIAN}\left(s_{ij}\right). \tag{7}$$

6.3. Evolution of Community Performance Metrics Over Time

The evolution of the MMQAP community's concordance and apparent precision performance can be visualized by charting C_i and AP_i as functions of RR date. The metrics for coenzyme Q_{10}, where the reproducibility function is defined by the results reported in the final eight RRs (RR 75 to RR 82), are displayed in Fig. 14.

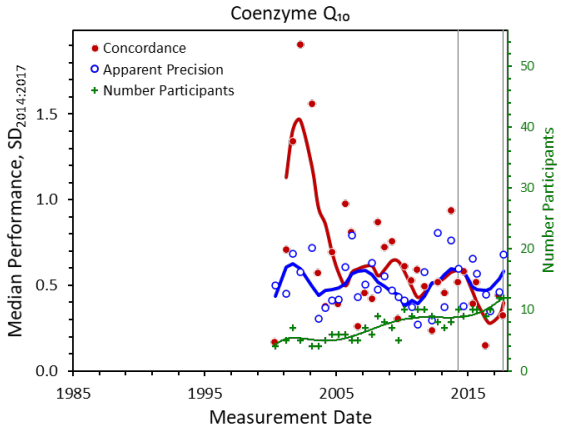
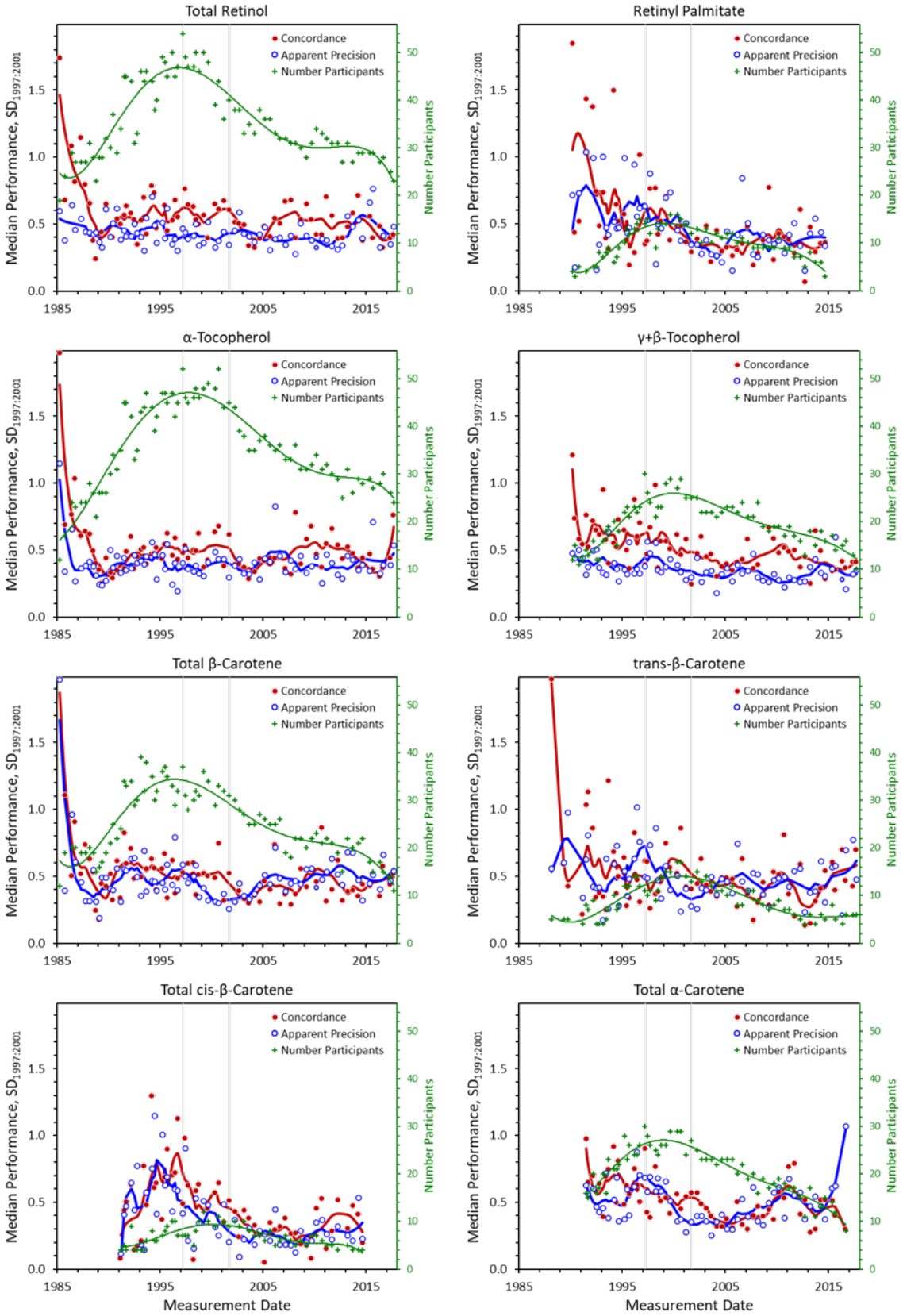


Fig. 14. Evolution of Community Performance for Coenzyme Q_{10}.

The red filled-circles denote the between-participant variability over time; the open blue circles denote the within-participant variability. The solid red and blue curves are running cubic fits to the estimated values of the two performance metrics. The green "+" symbols represent the number of participants reporting the measurand in each RR; the green curve is a best-fit quartic polynomial through these values. The performance metrics have been standardized to the reproducibility function derived from the {median, Q_n} pairs for samples distributed in RRs conducted within the time period indicated by the light grey vertical lines: here, from 2014 through 2017.

The metrics for the other 14 most commonly reported measurands, where the reproducibility function is defined by the results reported in the 12 studies from RR 39 to RR 50, are displayed in Fig. 15. In addition to the performance metrics, these figures also display the number of participants who reported results for the measurand in each RR.


Total Retinol
Retinyl Palmitate
α-Tocopherol
γ+β-Tocopherol
Total β-Carotene
trans-β-Carotene
Total cis-β-Carotene
Total α-Carotene
Concordance
Apparent Precision
Number Participants
Median Performance, SD1997:2001
Number Participants
Measurement Date
0.0
0.5
1.0
1.5
0
10
20
30
40
50
1985
1995
2005
2015

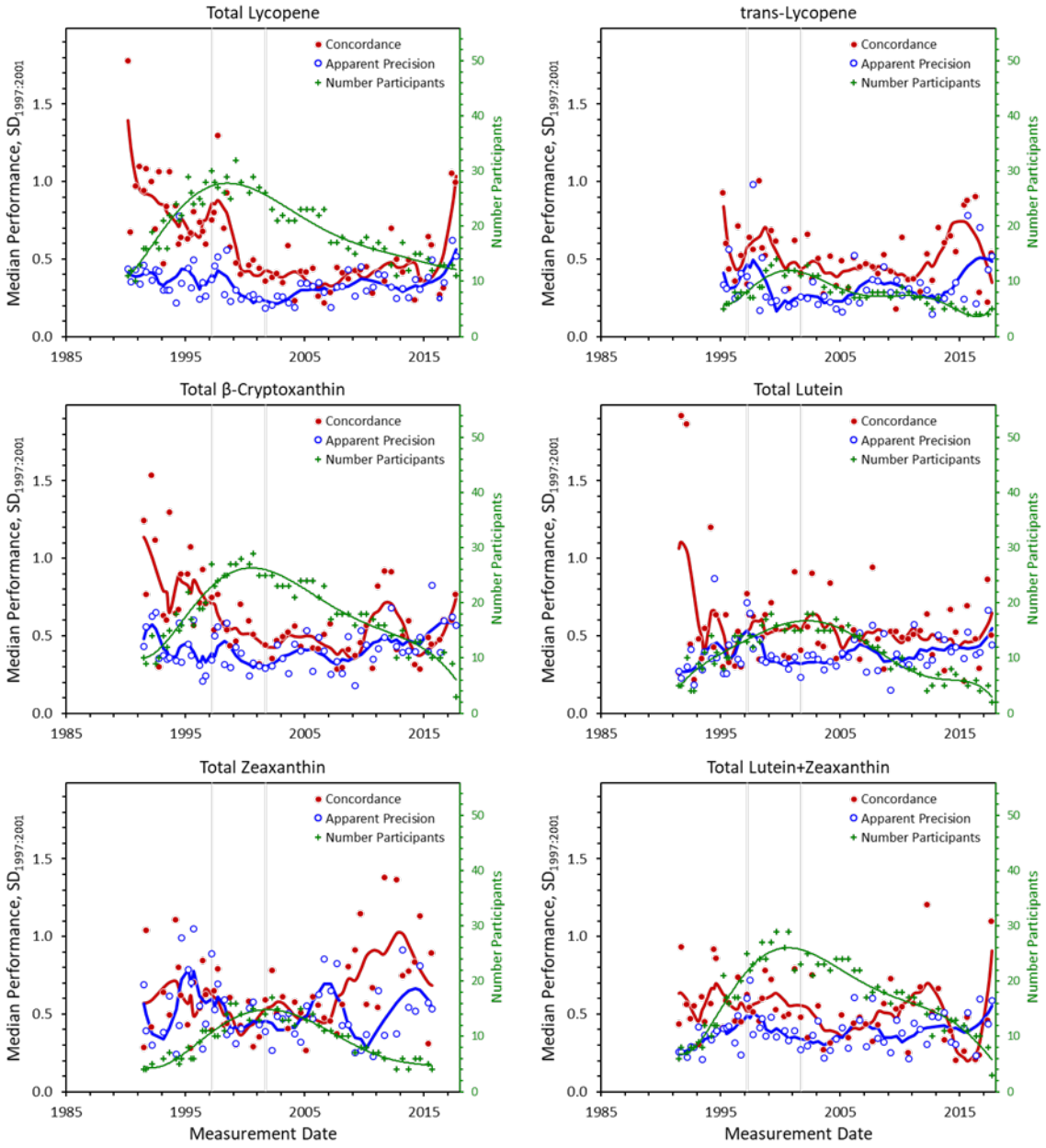


Fig. 15. Evolution of Community Performance for Fourteen Measurands.

The red filled-circles denote the between-participant variability over time; the open blue circles denote the within-participant variability. The solid red and blue curves are running cubic fits to the estimated values of the two performance metrics. The green "+" symbols represent the number of participants reporting the measurand in each RR; the green curve is a best-fit quartic polynomial through these values. The performance metrics have been standardized to the reproducibility function derived from the {median, Q_n} pairs for samples distributed in RRs conducted within the time period 1997 through mid-2001; this period is indicated by the light grey vertical lines.

6.4. Within- and Between-Participant Community Performance Metrics

The *C* and *AP* metrics are in units of measurand-specific ILS reproducibility, which are not directly comparable. However, the reproducibility functions are dominated at higher concentrations by their proportional constant, *b*. Scaling the metrics by 100 *b* yields "high concentration" coefficient of variation (CV)-like metrics having units of percentage that can be compared across different measurands

$$C_{\mathrm{CV},i} = 100 \times b \times C_i \tag{8}$$

$$AP_{\mathrm{CV},i} = 100 \times b \times AP_i \ . \tag{9}$$

The transformed metrics for six selected measurands are displayed in Fig. 16.

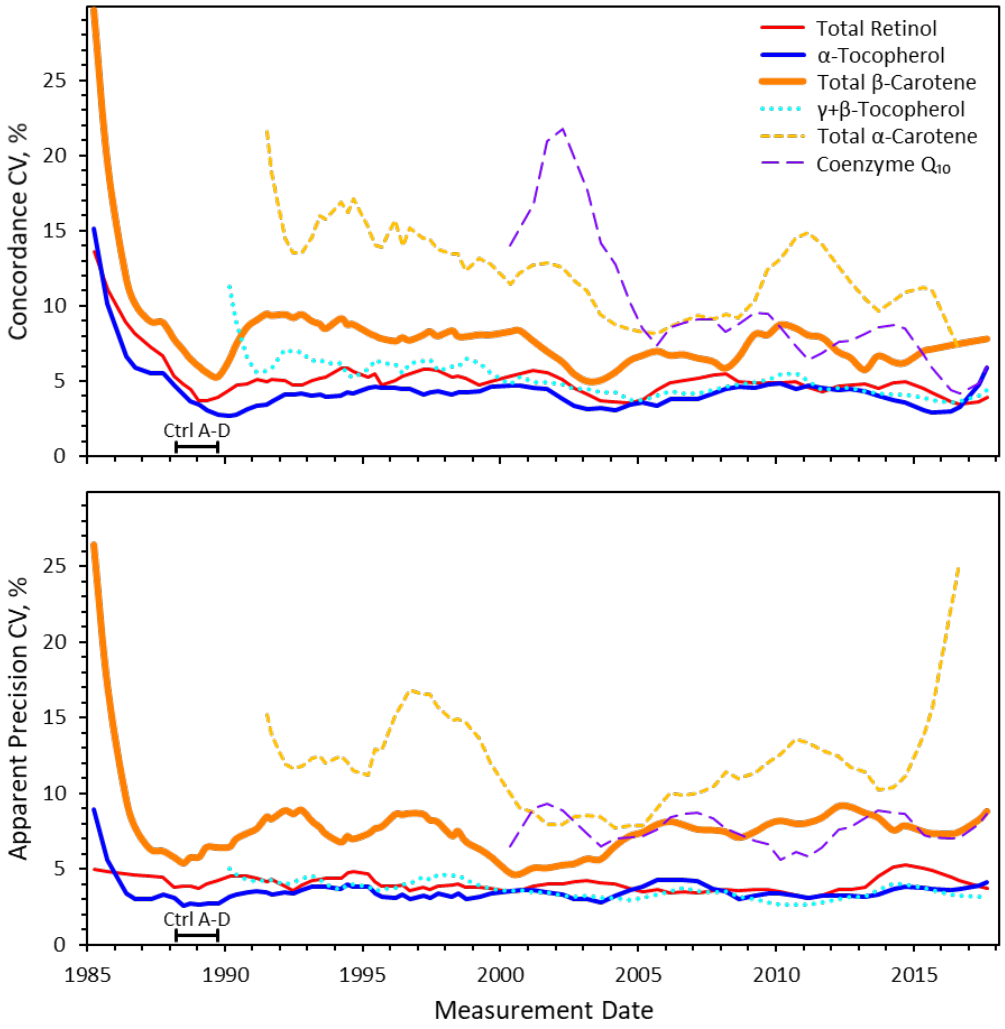


Fig. 16. Comparison of Performance Metrics Across Measurands.

Each of the various curves represents the concordance or apparent precision metric transformed into a coefficient of variation (CV) expressed as percentage. The interval marked "Ctrl A-D" represents the period during which control samples A through D were provided to participants to enable validation of their measurement processes before they analyzed RR unknowns.

For most measurands, concordance (agreement among-participants) improves over the course of the first three to six years after its first reporting and then remains approximately constant. The apparent precision (within-participant consistency) trends are similar, but improvement takes less time.

The total β-carotene CVs are consistently larger than for total retinol and the tocopherols. This may reflect the wider analytical range spanned by this measurand [68,117].

The slow improvement and large CVs for total α-carotene probably reflects the generally low concentrations of this measurand in the MMQAP materials and the relatively few participants who regularly reported it.

The improved concordance for coenzyme Q_{10} accompanied by essentially no change in apparent precision reflects participant recognition that only the sum of the oxidized and reduced forms was characteristic of the material. The fairly stable but large apparent-precision CV probably reflects both the consistency of the various methods used by the participants and the heterogeneity of the redox states of the measurand.

7. Comparison of Liquid-Frozen and Lyophilized Material

To explore potential significant measurement differences in measurand concentrations between the liquid-frozen and lyophilized delivery of the same materials, eight {liquid-frozen, lyophilized} pairs were prepared and distributed in various MMQAP RRs. All were prepared from native serum pools. Two pairs, {34,35} and {44,33}, were prepared and distributed just once each in 1986 when only the three measurands TR, aT, and TbC were regularly reported. The five pairs {259,261}, {260,262}, {267,270}, {268,265}, and {271,266} prepared in 1998 and distributed in 1999. Three of the pairs were only distributed once, but pairs {267,270} and {271,266} were prepared in quantity and distributed multiple times. The {290,292} pair was likewise prepared in quantity in 2002 and distributed multiple times.

7.1. Regression Estimates of the Lyophilized/Liquid-Frozen Ratio

Participants were instructed to reconstitute the lyophilized sample 33 and 35 using 1.2 mL water; all of the later paired materials were to be reconstituted with 1.0 mL water. Because participants were instructed to reconstitute lyophilized materials *with* these volumes rather than attempting to bring the reconstituted volumes back *to* the originally dispensed 1.0 mL, measurand concentrations in the liquid-frozen materials are expected to be uniformly higher than in the more-dilute reconstituted lyophilized materials. As shown in Fig. 17 and Fig. 18, plotting measurand values for the lyophilized materials as a function of the values in the liquid-frozen pair suggests a lyophilized/liquid-frozen ratio of about 0.95, compatible with the expected 1.04 g/mL density of normal human serum.

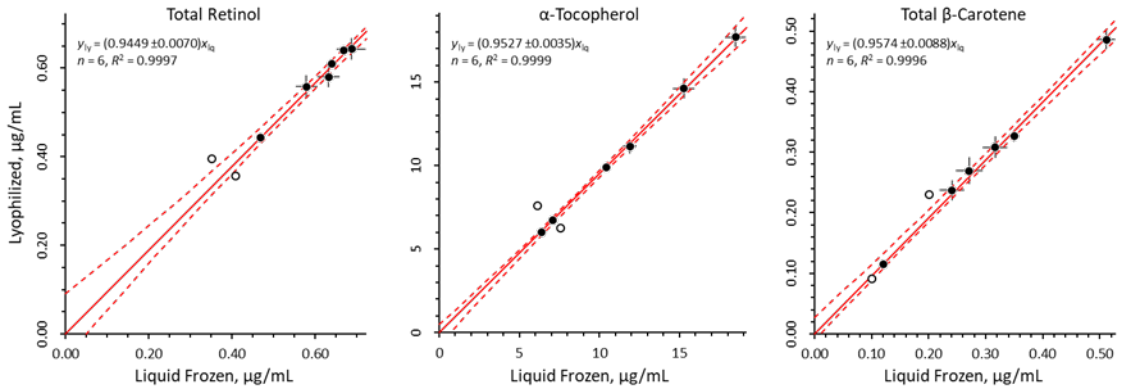


Fig. 17. Comparison of Lyophilized and Liquid-Frozen Pairs for the Original Measurands

Solid circles represent the MMQAP for the six {liquid-frozen, lyophilized} serum pairs prepared in and after 1998. The open circles represent results for the two pairs prepared in 1986, following adjustment for the different reconstitution value used at that time. Error-crosses represent 1 standard uncertainty. Solid red lines represent regression fits to the function $y = qx$, where y represents results for the lyophilized material and x the results for its liquid-frozen partner. Dashed red lines bound approximate 95 % confidence regions around the proportional relationships.

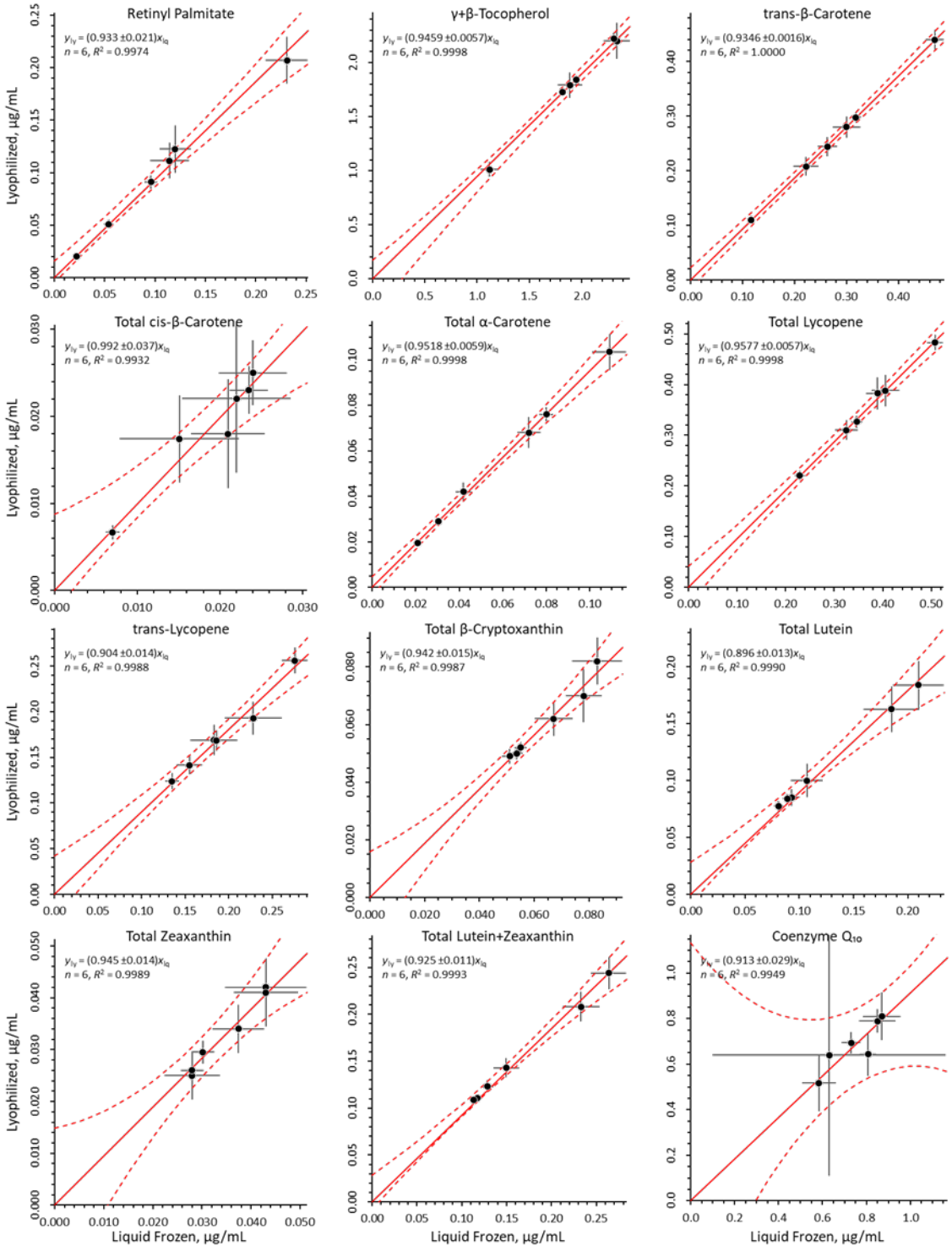


Fig. 18. Comparison of Lyophilized and Liquid-Frozen Pairs for Twelve Measurands

Solid circles represent the MMQAP for the six {liquid-frozen, lyophilized} serum pairs prepared in and after 1998. Error-crosses represent 1 standard uncertainty. Solid red lines represent regression fits to the function $y = qx$, where y represents results for the lyophilized material and x the results for its liquid-frozen partner. Dashed red lines bound approximate 95 % confidence regions around the proportional relationships.

7.1.1. Reconstitution Volume Adjustment

Because samples 33 and 35 were reconstituted with 1.2 mL water rather than the later standard of 1.0 mL, the results for these two sera have been multiplied by a factor of 1.2/1.0 = 1.2. Since this factor may not bring the ratios for these early comparisons into alignment with the later, the adjusted ratios are not used in the regressions but are displayed in Fig. 17 for visual evaluation.

7.1.2. Choice of Regression Model

Preliminary analysis confirmed that the results for the lyophilized materials were well modeled as linear functions of the results for the liquid-frozen materials:

$$y = p + qx \tag{10}$$

where y is the consensus result for a given measurand in the lyophilized material, x the consensus result in the paired liquid-frozen material, p is the intercept, and q the slope. For 12 of the 15 most commonly reported measurands, the estimated p was within the interval $\pm 1.4u(p)$, where $u(p)$ is the standard uncertainty of the intercept. The estimated p was outside the interval $\pm 2.4u(p)$ only for total lutein.

Since the intercept term for most of the measurands was not statistically significant and because of the small number of pairs, the proportional model was used for all measurands:

$$y = qx. \tag{11}$$

7.1.3. Standard Uncertainties

The standard uncertainties shown in the figures as error crosses are estimated as the maximum of the observed Q_n and the value predicted by the interlaboratory reproducibility function for the measurand. The standard uncertainty of the median of a normal distribution is about $1.25/\sqrt{v}$ the standard deviation (however estimated) of those values where v is the effective number of available degrees of freedom (i.e., the number of *independently* determined values). Since many participants participated in multiple RRs using the same methods of analysis, the number of *independent* values for MMQAP data can be far fewer than the total number of values. The standard uncertainties of the median values are thus estimated

$$u(x) = 1.25 \times \mathrm{MAX}\left(Q_n, \sqrt{a^2 + (bx)^2}\right)/\sqrt{v} \tag{12}$$

where x is the median of the available results, a and b are the coefficients reported in Table 7, and v is number of values per RR reported in Table 4.

7.1.4. 95 % Confidence Intervals

The approximate 95 % confidence regions shown in Fig. 17 and Fig. 18 are estimated using Monte Carlo perturbation of normal kernels centered on the consensus medians with variance equal to their squared standard uncertainty. One thousand sets of "pseudo data" were generated by randomly sampling from the relevant $N\left(x, u^2(x)\right)$ and $N\left(y, u^2(y)\right)$ distributions of each of

the six {liquid-frozen, lyophilized} pairs, estimating *p* for these data, generating and storing predicted *y* (lyophilized) values for fixed *x* (liquid-frozen) values from zero to a maximum. The confidence intervals were then estimated as the upper and lower boundaries of the central 95 % of the predicted *y* values.

7.2. Regression Estimates of the Lyophilized/Liquid-Frozen Ratio

Table 8 lists the regression estimates of the lyophilized/liquid-frozen ratio for the 15 most commonly reported measurands. While uniformly less than unity, the ratios are not all the same. The distribution of the estimated slopes of the proportional relationships, sorted in order of increasing ratio, is displayed in Fig. 19.

Table 8. Summary of the Lyophilized/Liquid-Frozen Ratios.

Measurand	Code	*n*	*q*	*u*(*q*)	R^2
Total Retinol	TR	6	0.945	0.007	0.9997
Retinyl Palmitate	RP	6	0.933	0.021	0.9974
α-Tocopherol	aT	6	0.953	0.003	0.9999
γ+β-Tocopherol	gbT	6	0.946	0.006	0.9998
Total β-Carotene	TbC	6	0.957	0.009	0.9996
Trans-β-Carotene	t-bC	6	0.935	0.002	1.0000
Total *cis*-β-Carotene	c-bC	6	0.992	0.037	0.9932
Total α-Carotene	TaC	6	0.952	0.006	0.9998
Total Lycopene	TLy	6	0.958	0.006	0.9998
Trans-Lycopene	t-Ly	6	0.904	0.014	0.9988
Total β-Cryptoxanthin	TbX	6	0.942	0.015	0.9987
Total Lutein	TLu	6	0.896	0.013	0.9990
Total Zeaxanthin	TZ	6	0.945	0.014	0.9989
Total Lutein+Zeaxanthin	TLZ	6	0.925	0.011	0.9993
Coenzyme Q_{10}	Q10	6	0.913	0.029	0.9949

n number of {liquid-frozen, lyophilized} pairs used in the regression
q slope
u(*q*) regression-estimated standard uncertainty on the slope
R^2 coefficient of determination

While uniformly less than unity, the ratios range from (0.896 ± 0.013) for total lutein to (0.992 ± 0.037) for *cis*-β-carotene. An analysis provided by the NIST Consensus Builder (NICOB) [118] is reported in Fig. 19. The relatively large error-bars for *cis*-β-carotene in Fig. 18 suggest that this measurand's near-unity ratio is an artifact of the low concentrations of this measurand and the relatively few participants that reported values. The NICOB analysis therefore displays the slope for *cis*-β-carotene but does not include the value in the consensus evaluation.

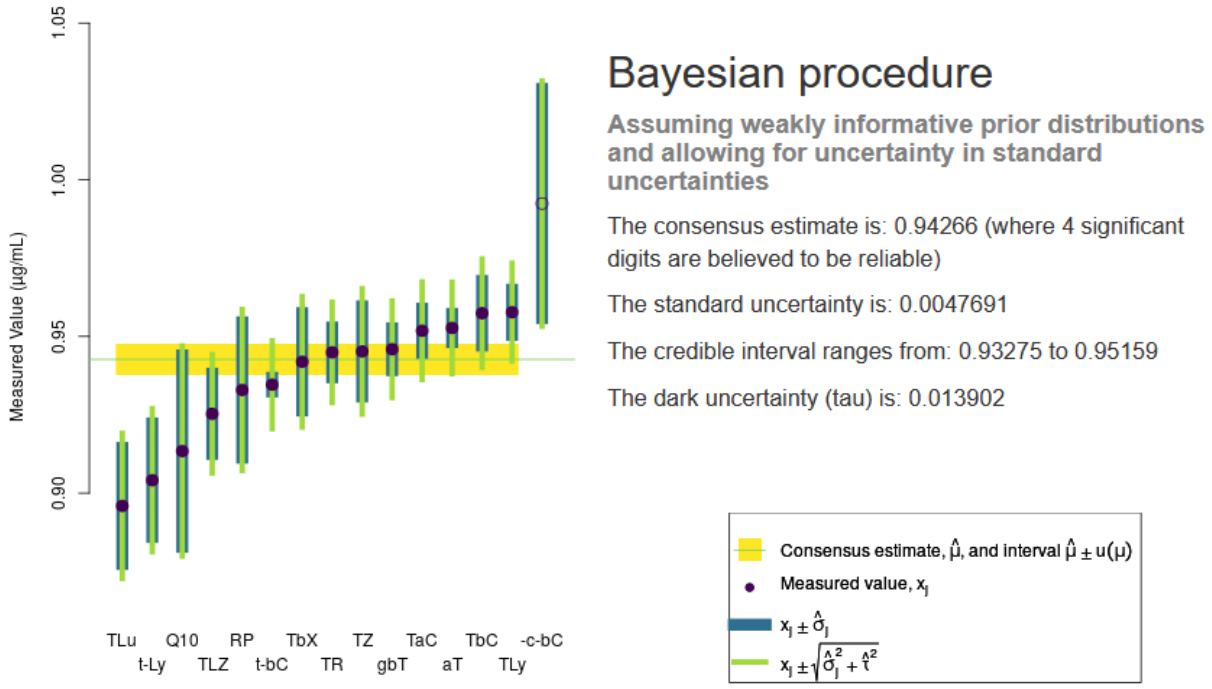


Fig. 19. Analysis of the Lyophilized/Liquid-Frozen Ratios

The credible range, 0.933 to 0.952, is an approximate 95 % confidence interval on the estimated consensus value of 0.943. The "dark uncertainty" [119] is the between-measurand uncertainty that is not explained by the standard uncertainties of the slopes. The Bayesian procedure used half-Cauchy minimally informative priors for both the within-and between-measurand variances.

Only the slopes for total lutein and *trans*-lycopene are inconsistent with the consensus estimate of (0.943 ± 0.005). Given the ambiguity in the separation and quantification of these minor measurands from their much more commonly reported relatives (total lutein plus zeaxanthin and total lycopene), these inconsistencies are probably measurement artifacts rather than indicating differences in extraction efficiency or measurand integrity due to lyophilization.

The likely equivalence of the lyophilized/liquid-frozen ratios for the different measurands is compatible with the results of an isochronous study conducted in 2014 [120].

Conclusions

The MMQAP exercises served as a model for other quality assurance programs that NIST has subsequently provided. It also served as a foundation for our careers. We met, helped, and were helped by hundreds of interesting people, and we remember them fondly to this day.

As a result of efforts to support and improve the analytical measurements of selected health-related measurands, several MMQAP-related awards were received. Listed below are some of these awards.

1992 Willie E. May. Department of Commerce Gold Medal Award for Distinguished Achievement in Federal Service

1995 Jeanice Brown Thomas, Katherine Sharpless. NIST Standard Reference Materials Measurement Service Award for research, SRM development, and quality activities related to the determination of fat-soluble vitamins and carotenoids in SRM 968b

2000 David Duewer, Margaret Kline, Katherine Sharpless, Jeanice Brown Thomas. American Statistical Association W. J. Youden Award in Interlaboratory Testing for "*Micronutrients Measurement Quality Assurance Program: Helping participants use interlaboratory comparison exercise results to improve their long-term measurement performance*"

2002 David Duewer. US DOC Bronze Medal Award "For innovative use of visualization techniques to summarize and communicate complex statistical information"

2003 David Duewer. NIST Edward Bennett Rosa Award "For innovative use of visualization techniques to summarize and communicate complex statistical information"

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Appendix A. List of Symbols, Abbreviations, and Acronyms

AP	apparent precision, a composite of within-participant measurement reproducibility and sample-specific biases
aT	α-tocopherol
C	concordance, a measure of among-participant agreement
c-bC	*cis*-β-carotene
CDC	US Centers for Disease Control and Prevention
CLIA	Clinical Improvement Amendments
ClinQAP	Clinical Quality Assurance Program
COA	certificate of analysis
CRM	certified reference material
CV	coefficient of variation (relative standard deviation as a percentage)
EQA	external quality assessment
FAQAP	Fatty Acids Quality Assurance Program
gbT	γ-tocopherol plus β-tocopherol
ILS	interlaboratory study
IQR	interquartile range
NGO	non-governmental organization
HAMQAP	Health Assessment Measurement Quality Assurance Program
ID	sample identification code
MAD_E	median absolute deviation, a robust SD estimator scaled for normal distributions
MMQAP	Micronutrients Measurement Quality Assurance Program
NCI	National Cancer Institute
NICOB	NIST Consensus Builder
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
ODS	Office of Dietary Supplements
SD	standard deviation
SRM®	Standard Reference Material®
Q_{10}	coenzyme Q_{10}
Q_n	a robust SD estimator scaled for normal distributions
RP	retinyl palmitate
RMSD	root-mean-square deviation
RR	Round Robin (name given to MMQAP interlaboratory studies)
t-bC	*trans*-β-carotene
t-Ly	*trans*-lycopene
TaC	total α-carotene
TbC	total β-carotene
TbX	total β-cryptoxanthin
TLu	total lutein
TLy	total lycopene
TLZ	total lutein plus zeaxanthin
TR	total retinol
TZ	total zeaxanthin
VITAL-EQA	Vitamin A Laboratory – External Quality Assurance
VitDQAP	Vitamin D Metabolites Quality Assurance Program