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TITLE PAGE

LETTER TO THE EDITOR

Updated threshold dose-distribution data for sesame

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Allergy, anaphylaxis, eliciting dose, food challenge, lowest observed adverse effect level, sesame, thresholds.

Abbreviations

95%CI	95% confidence interval
DBPCFC	Double-blind placebo-controlled food challenge
ED	Eliciting dose
FC	Food challenge
LOAEL	Lowest-observed adverse effect level
NOAEL	No observed adverse effect level

To the Editor:

Sesame is classified as a “major” food allergen for which mandatory disclosure is required. Understanding reaction thresholds and how these vary within the allergic population is crucial in providing appropriate dietary advice to patients, providing guidance to the food industry and informing dosing regimens for oral food challenges (FC). However, the largest data series used to derive a threshold dose-distribution for sesame included blinded challenge data from just 40 individuals.¹ Data from low-dose, open FC can be used to supplement that from blinded FC, reducing uncertainty in estimating threshold dose-distributions for allergenic foods which otherwise lack sufficient data.² We therefore undertook a systematic search of the literature and performed dose-distribution modelling of individual patient FC data (including open FC) to update estimated eliciting doses for sesame.

Eleven studies were included (Table E1), representing data from 246 positive FC. The discrete and cumulative eliciting dose predicted to provoke reactions in 5% of the sesame-allergic population (ED₀₅) were 2.4 (95%CI 1.0-7.7) and 2.5 (95%CI 0.9-9.5) mg sesame protein, respectively. Dose-distributions are shown in Figure 1 and Table E2. These estimates are reassuringly similar to those previously reported,¹ only with much greater precision reflecting the increased number of datapoints (Table 1). Furthermore, these estimates were robust at sensitivity analyses when excluding data from unblinded food challenges or studies with a significant proportion of “first dose reactors” (Table 1).

With this analysis, the dataset for sesame is now similar to that used to inform eliciting doses for other food allergens, and sufficient to inform public policy despite the potential limitations of analyses using FC data.¹⁻³ The CODEX committee of the Food and

Agricultural Organization of the United Nations and the World Health Organization recently commissioned an Expert Consultation which recommended the inclusion of sesame as a global “priority” allergen.⁴ The data presented here will be used to inform a reference dose which might be recommended to guide the use of precautionary allergen (“may contain”) labelling. Given that ED values remain robust at sensitivity analysis when limited to blinded FC in the ED₀₁-ED₁₀ range, we recommend using ED values based on the blinded FC dataset for risk assessment and risk management purposes, to maintain consistency with approaches for other food allergens.⁵

A strength of this dataset is the inclusion of cohorts spanning four of the six global CODEX regions. These data were mostly generated from FC using ground sesame or tahini, and may not be directly extrapolated to the consumption of whole sesame seeds which are commonly used in food preparation. For example, sesame seeds when baked into the surface of bread rolls are frequently not broken during mastication, and thus swallowed whole; this prevents the release of endosperm proteins, resulting in a much lower exposure to sesame allergens. Ovadia et al recently reported a cohort of 51 sesame-allergic children, of whom 41 (80%) were able to tolerate 3 pretzels with sesame seeds (total exposure approximately 36mg sesame protein) baked into the surface.⁶ This would be equivalent to an ED₂₅ level of exposure, implying tolerance in ~25% of sesame-allergic individuals. It is therefore unclear whether baked sesame seeds are tolerated due to the low level of allergen exposure, the lower bioavailability of sesame seed protein with this form of consumption, or both.

Finally, these data confirm that a semi-log dosing regimen for FC (as recommended by PRACTALL) is appropriate for sesame. Tahini is commonly used for the higher doses

used at sesame-FC, however the strong taste can create difficulties, particularly in younger children. Our data indicate that a top dose of 1g protein (around 4g of tahini paste, approximately 1 teaspoon) will cause objective symptoms in ~93% of sesame-allergic individuals (Table E2), and thus inform the risk of a false negative challenge in someone unable to ingest a higher dose at FC.

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FIGURE LEGENDS

Figure 1. Eliciting dose curves from the model averaged population threshold dose distributions for sesame, based on (A) discrete and (B) cumulative dose datasets.

Doses are expressed in mg sesame seed protein, and are compared to equivalent data reported by Houben et al used to inform VITAL 3.0 reference doses.⁵

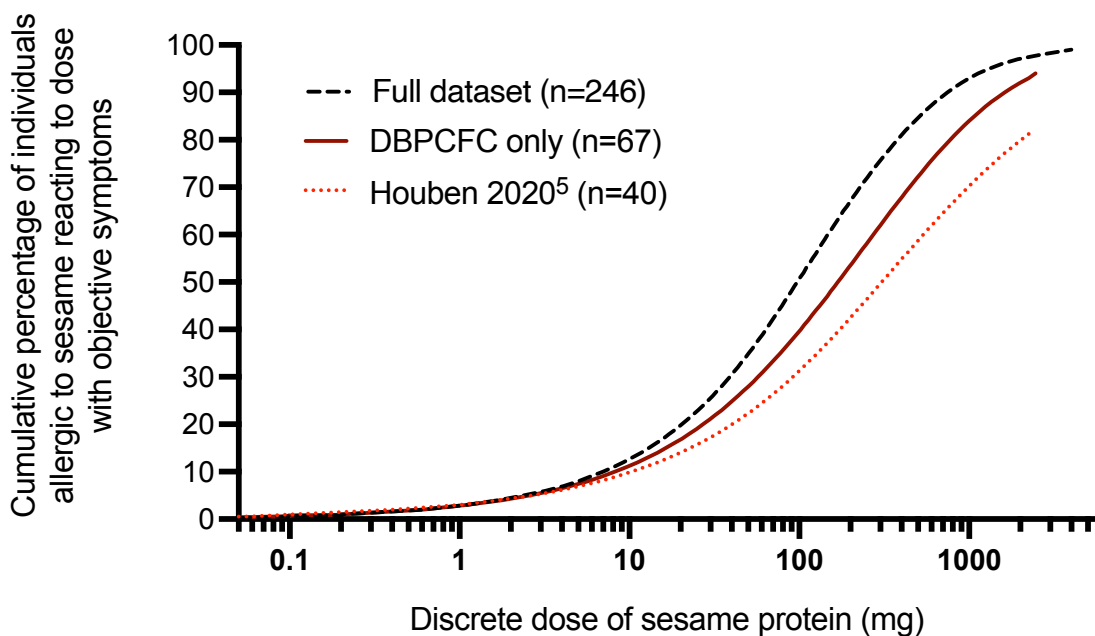
Table 1. Doses of sesame protein predicted to cause a reaction in 1% (ED₀₁), 5% (ED₀₅) and 10% (ED₁₀) of the sesame-allergic population (together with 95% confidence intervals) calculated using both discrete and cumulative dosing schemes.*

	ED ₀₁		ED ₀₅		ED ₁₀	
	Discrete	Cumulative	Discrete	Cumulative	Discrete	Cumulative
Remington et al, 2020 ¹ (n=40)	0.1 (0.03, 2.7)	0.2 (0.04, 4.8)	2.7 (0.4, 33.6)	4.2 (0.6, 57.7)	10.3 (1.9, 106)	16.1 (2.9, 178)
This analysis (n=246)	0.2 (0.09, 1.0)	0.2 (0.08, 1.0)	2.4 (1.0, 7.7)	2.5 (0.9, 9.5)	7.0 (3.1, 19.2)	7.8 (3.1, 25.7)
This analysis (limited to DBPCFC only, n=67)	0.2 (0.05, 1.8)	0.2 (0.05, 2.4)	2.6 (0.6, 17.4)	2.8 (0.6, 28.3)	8.2 (2.2, 48.7)	9.6 (2.3, 85.2)
This analysis (excluding studies with significant left-censoring*, n=172)	0.4 (0.15, 1.5)	0.4 (0.15, 1.6)	3.8 (1.6, 11.6)	4.2 (1.6, 14.0)	10.1 (4.5, 28.1)	12.1 (5.0, 37.0)

Discrete dosing schemes are reported as the mg protein amount of each separate dose within a food challenge when determining the individual NOAEL and LOAEL. Cumulative dosing schemes are reported as the cumulative sum of all prior doses within a food challenge when calculating the individual NOAEL and LOAEL. Population dose distributions were determined using “Stacked Model Averaging” as previously described.^{E2} *Left-censoring of data occurs when participants react to the first dose of the challenge protocol, and is more likely to occur in those studies with a higher initial challenge dose. All doses are presented as mg sesame protein.

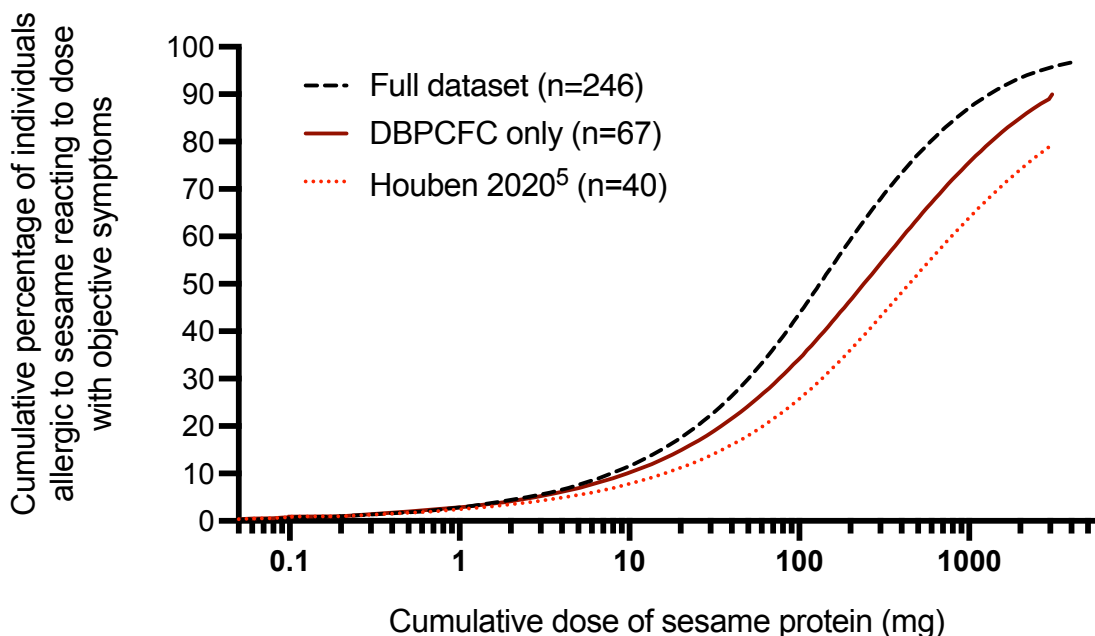
A

Discrete dose



B

Cumulative dose



Updated threshold dose-distribution data for sesame

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SUPPLEMENTARY INFORMATION

Supplementary Methods

We searched Medline for articles published between January 1988 and June 2021 which described double-blind, placebo-controlled FC (DBPCFC) or open FC to sesame, using a search strategy and inclusion criteria previously described.^{E1} We also reviewed reference lists of included studies and review articles to identify other relevant studies. Authors were contacted where needed to confirm data extracted. Analyses were planned prospectively. Data relating to the No Observed Adverse Effect Level (NOAEL, highest dose with no objective symptoms) and Lowest Observed Adverse Effect Level (LOAEL, first dose with objective symptoms) were extracted in duplicate; any discrepancies identified between extracted data and published data were resolved by discussion and/or by contacting authors for clarifications. Population dose-distributions were determined using “Stacked Model Averaging” as previously described,^{E2} utilizing Bayesian stacked parametric survival methods with frailty components and interval censored failure times.

Thirteen published studies were identified for sesame FC (Table E1), representing data from 246 positive FC.^{5,E3-E14} Two studies were excluded: Li et al reported FC data from 10 adults but the starting dose, subsequent increments and interval times varied from patient to patient and are not reported;^{E13} Sokol et al reported 15 children with sesame allergy,^{E14} but only 3 underwent FC and due to unresolved data queries, were not included in this analysis.

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Table E1: Studies reporting food challenges to sesame

Study	Study cohort (positive FC only)	Food challenge protocol	Initial dose (mg protein)	Dose interval	Number with objective symptoms	Right censored	Left censored
Brough 2020 ^{E3} UK, Switzerland	8 children Median age 5.5y	Open FC	30mg	15-20min	8	0	4
Salari 2020 ^{E4} Iran	16 adults (median 38y) Median ED 133mg	Open FC Tahini	3mg	15-30min	16	0	0
Saf 2020 ^{E5} USA	106 children (sufficient data available for 45) Median ED 500mg	Open FC Tahini or seed	Variable, ≤100mg	15min	45	0	17
Houben 2020 ⁵ The Netherlands	5 children	DBPCFC	1.25 mg	30min	1	4	0
Yanagida 2019 ^{E6} Japan	46 children (median 6y) Median ED 609mg	Open FC Ground sesame in steamed cake	38mg	15min	46	0	12
Appel 2018 ^{E7} Israel	40 children (median 7y) 12 adults (median 19y) Median ED 180mg	Open FC	0.3mg	15min for ≤15mg, then 30min	43	0	0
Purington 2018 ^{E8} USA	30 children & adults Median ED 25mg	DBPCFC	5mg	15min	27	0	5
Chan 2017 ^{E9} Australia	21 children, age 4y Median ED 11mg	Open FC Tahini	69mg	20min	21	0	16
Dano 2015 ^{E10} France	9 children, 5 adults Median ED 85mg	DBPCFC Crushed seed	0.85mg	15min	14	5	1
Leduc 2006 ^{E11} France	5 children, 9 adults (data available for 12) Median ED 164mg	DBPCFC Crushed seed	0.85mg	20min	12	0	1
Kanny 1996 ^{E12} France	1 child, 8 adults Median ED 1539mg	Blinded FC Crushed seed	1.54mg	20min	7	1	1

All doses are mg sesame seed protein. ED, eliciting dose; FC, food challenge. ^aRight Censored: Individuals who did not objectively react to the highest dose of the progressive dosing scheme but are believed to be allergic to sesame on the basis of a strong clinical history. This individual would have an established NOAEL but not a defined LOAEL. ^bLeft Censored: Individuals reacting to the first dose of the FC, and therefore do not have an established dose where no symptoms occur, but do have a defined LOAEL.

Table E2: Discrete and cumulative dose dataset ED values (mg sesame protein) with 95% lower (LCI) and upper confidence interval (UCI)

ED	DISCRETE Complete dataset (n=246)			DISCRETE DBPCFC only (n=67)			CUMULATIVE Complete dataset (n=246)			CUMULATIVE DBPCFC only (n=67)		
	Mean	LCI	UCI	Mean	LCI	UCI	Mean	LCI	UCI	Mean	LCI	UCI
ED00.1	0.02	0.008	0.06	0.01	0.004	0.08	0.02	0.008	0.06	0.01	0.004	0.09
ED00.2	0.03	0.02	0.1	0.02	0.009	0.2	0.03	0.02	0.1	0.02	0.008	0.2
ED00.3	0.05	0.02	0.2	0.04	0.01	0.3	0.05	0.02	0.2	0.03	0.01	0.4
ED00.4	0.07	0.03	0.3	0.05	0.02	0.5	0.07	0.03	0.3	0.05	0.02	0.6
ED00.5	0.09	0.04	0.4	0.07	0.02	0.7	0.09	0.04	0.4	0.06	0.02	0.9
ED00.6	0.1	0.05	0.5	0.09	0.03	0.9	0.1	0.05	0.5	0.08	0.03	1.1
ED00.7	0.1	0.06	0.6	0.1	0.03	1.1	0.1	0.06	0.6	0.09	0.03	1.4
ED00.8	0.2	0.07	0.7	0.1	0.04	1.3	0.1	0.07	0.7	0.1	0.04	1.7
ED00.9	0.2	0.08	0.8	0.2	0.04	1.5	0.2	0.08	0.9	0.1	0.04	2.1
ED01.0	0.2	0.09	1	0.2	0.05	1.8	0.2	0.08	1	0.2	0.05	2.4
ED02.0	0.6	0.2	2.3	0.6	0.1	4.7	0.6	0.2	2.6	0.5	0.1	6.8
ED03.0	1.1	0.4	3.9	1.1	0.3	8.3	1.1	0.3	4.6	1.1	0.2	12.8
ED04.0	1.7	0.7	5.7	1.8	0.4	12.6	1.7	0.6	7	1.9	0.4	19.9
ED05.0	2.4	1	7.7	2.6	0.6	17.4	2.5	0.9	9.5	2.8	0.6	28.3
ED06.0	3.2	1.3	9.7	3.5	0.9	22.7	3.4	1.2	12.3	3.8	0.8	37.7
ED07.0	4.1	1.7	11.9	4.5	1.2	28.5	4.4	1.6	15.4	5.1	1.1	48.1
ED08.0	5	2.1	14.3	5.7	1.5	34.8	5.4	2	18.6	6.4	1.5	59.5
ED09.0	5.9	2.6	16.7	6.9	1.8	41.5	6.6	2.5	22	8	1.9	72
ED10.0	7	3.1	19.2	8.2	2.2	48.7	7.8	3.1	25.7	9.7	2.3	85.2
ED11.0	8.1	3.6	21.9	9.7	2.6	56.3	9.2	3.6	29.5	11.5	2.8	99.3
ED12.0	9.2	4.1	24.7	11.2	3.1	64.4	10.6	4.3	33.4	13.5	3.3	114
ED13.0	10.4	4.7	27.5	12.8	3.6	72.9	12.1	4.9	37.6	15.6	3.9	130
ED14.0	11.7	5.3	30.5	14.6	4.1	81.7	13.7	5.6	41.9	17.9	4.5	147
ED15.0	13	6	33.5	16.4	4.6	91.1	15.4	6.4	46.4	20.3	5.1	165
ED16.0	14.4	6.7	36.7	18.3	5.2	101	17.2	7.2	51	22.9	5.8	183
ED17.0	15.8	7.4	40	20.4	5.8	111	19	8.1	55.8	25.6	6.6	203
ED18.0	17.2	8.1	43.3	22.5	6.5	122	20.9	8.9	60.8	28.5	7.4	223
ED19.0	18.8	8.9	46.8	24.8	7.2	133	22.9	9.9	65.9	31.5	8.2	244
ED20.0	20.3	9.7	50.4	27.1	7.9	144	25	10.9	71.1	34.7	9.1	266
ED21.0	22	10.5	54	29.6	8.6	156	27.1	11.9	76.6	38	10.1	289
ED22.0	23.7	11.4	57.8	32.2	9.4	169	29.4	12.9	82.2	41.6	11.1	313
ED23.0	25.4	12.2	61.7	34.9	10.2	182	31.7	14	88	45.2	12.1	337
ED24.0	27.2	13.2	65.7	37.7	11.1	195	34.1	15.2	93.9	49.1	13.2	363
ED25.0	29	14.1	69.8	40.6	12	209	36.5	16.4	100	53.1	14.3	389
ED26.0	30.9	15.1	74.1	43.6	12.9	223	39.1	17.6	106	57.3	15.5	416
ED27.0	32.8	16.1	78.4	46.8	13.9	238	41.7	18.8	113	61.7	16.7	445
ED28.0	34.8	17.1	82.9	50.1	14.9	253	44.4	20.2	119	66.3	18	473
ED29.0	36.9	18.1	87.4	53.6	15.9	269	47.2	21.5	126	71.1	19.3	503
ED30.0	39	19.2	92.1	57.1	17	285	50.1	22.9	133	76.1	20.7	534
ED31.0	41.1	20.3	97	60.9	18.1	302	53.1	24.3	141	81.3	22.1	566
ED32.0	43.4	21.4	102	64.7	19.3	320	56.1	25.8	148	86.8	23.6	598
ED33.0	45.6	22.6	107	68.7	20.4	338	59.3	27.3	156	92.4	25.2	632
ED34.0	48	23.8	112	72.9	21.7	357	62.5	28.8	164	98.4	26.7	667
ED35.0	50.4	25	118	77.3	22.9	376	65.8	30.3	172	105	28.4	703
ED36.0	52.9	26.2	123	81.8	24.2	396	69.3	31.9	180	111	30.1	739
ED37.0	55.4	27.5	129	86.5	25.6	417	72.9	33.6	189	118	31.8	777
ED38.0	58.1	28.7	135	91.4	27	438	76.5	35.2	197	125	33.6	816
ED39.0	60.8	30	141	96.5	28.4	460	80.3	36.9	206	132	35.5	856
ED40.0	63.6	31.4	147	102	29.9	483	84.2	38.7	216	140	37.4	897
ED41.0	66.5	32.7	154	107	31.5	506	88.3	40.4	225	148	39.4	940
ED42.0	69.4	34.1	160	113	33	530	92.5	42.2	235	156	41.4	983
ED43.0	72.5	35.4	167	119	34.7	555	96.8	44	246	165	43.5	1027
ED44.0	75.7	36.8	174	125	36.4	580	101	45.9	256	174	45.6	1073
ED45.0	79	38.3	182	132	38.1	607	106	47.7	267	184	47.8	1120

ED46.0	82.3	39.7	189	139	39.9	634	111	49.6	278	194	50.1	1169
ED47.0	85.9	41.2	197	146	41.7	663	116	51.5	289	205	52.4	1220
ED48.0	89.5	42.6	205	153	43.6	692	121	53.4	301	216	54.7	1271
ED49.0	93.3	44.1	213	161	45.5	722	127	55.4	314	228	57.1	1325
ED50.0	97.2	45.6	221	169	47.5	753	132	57.3	327	240	59.6	1379
ED51.0	101	47.1	230	177	49.6	786	138	59.3	340	253	62.1	1435
ED52.0	106	48.7	239	186	51.7	819	144	61.4	354	267	64.8	1495
ED53.0	110	50.4	249	195	53.9	854	151	63.6	369	281	67.5	1557
ED54.0	115	52.1	258	205	56.2	891	158	65.9	384	296	70.4	1623
ED55.0	120	53.8	269	215	58.6	930	165	68.2	400	312	73.5	1693
ED56.0	125	55.7	280	225	61.1	969	172	70.7	417	329	76.7	1767
ED57.0	130	57.6	291	236	63.7	1011	180	73.3	435	347	80	1844
ED58.0	135	59.6	302	248	66.5	1055	188	76	454	366	83.6	1926
ED59.0	141	61.7	314	260	69.3	1100	197	78.9	474	386	87.3	2012
ED60.0	147	63.9	327	273	72.3	1147	206	81.9	495	407	91.2	2103
ED61.0	154	66.2	340	286	75.4	1197	216	85.1	516	429	95.4	2199
ED62.0	160	68.7	354	300	78.7	1250	226	88.5	539	453	99.8	2304
ED63.0	167	71.3	369	315	82.1	1304	237	92.1	563	478	104	2413
ED64.0	175	74	384	331	85.7	1361	248	95.9	589	505	109	2528
ED65.0	182	76.9	399	347	89.5	1422	260	100	615	533	115	2651
ED66.0	191	80	416	365	93.5	1485	273	104	644	564	120	2782
ED67.0	199	83.2	433	383	97.7	1553	287	109	674	596	126	2922
ED68.0	208	86.7	452	403	102	1624	302	114	705	631	132	3057
ED69.0	218	90.4	471	423	107	1700	317	119	739	669	139	>3078
ED70.0	228	94.4	491	445	112	1779	334	125	775	708	147	>3078
ED71.0	239	98.7	513	469	117	1864	352	132	813	751	155	>3078
ED72.0	251	103	536	494	123	1954	371	138	854	798	163	>3078
ED73.0	263	108	560	520	129	2049	391	146	898	848	172	>3078
ED74.0	276	114	585	549	135	2150	414	154	945	902	182	>3078
ED75.0	290	119	613	579	142	2259	438	163	995	960	193	>3078
ED76.0	305	126	642	612	149	2375	463	172	1049	1024	205	>3078
ED77.0	322	133	673	647	156	2460	491	183	1108	1093	217	>3078
ED78.0	339	140	706	685	165	>2462	522	195	1172	1170	231	>3078
ED79.0	358	148	742	727	174	>2462	555	208	1242	1253	247	>3078
ED80.0	378	157	781	772	183	>2462	592	222	1321	1345	264	>3078
ED81.0	400	167	824	821	193	>2462	632	238	1406	1447	282	>3078
ED82.0	424	179	871	875	205	>2462	676	256	1502	1561	303	>3078
ED83.0	451	191	923	934	217	>2462	725	277	1609	1689	325	>3078
ED84.0	480	204	981	1000	230	>2462	780	300	1731	1832	350	>3078
ED85.0	512	219	1046	1073	244	>2462	841	326	1871	1995	378	>3078
ED86.0	547	236	1120	1155	260	>2462	910	356	2035	2182	410	>3078
ED87.0	587	256	1206	1248	278	>2462	990	390	2227	2398	446	>3078
ED88.0	633	277	1308	1354	297	>2462	1081	429	2456	2651	486	>3078
ED89.0	684	301	1429	1476	318	>2462	1187	474	2739	2949	532	>3078
ED90.0	744	328	1575	1619	342	>2462	1312	527	3092	>3078	584	>3078
ED91.0	814	359	1761	1788	369	>2462	1463	589	3548	>3078	645	>3078
ED92.0	898	395	2004	1993	400	>2462	1648	661	4156	>3078	715	>3078
ED93.0	1001	435	2336	2247	436	>2462	1881	745	5002	>3078	798	>3078
ED94.0	1132	482	2814	>2462	478	>2462	2188	844	>6000	>3078	895	>3078
ED95.0	1304	538	3544	>2462	529	>2462	2613	964	>6000	>3078	1015	>3078
ED96.0	1548	606	>4000	>2462	593	>2462	3250	1109	>6000	>3078	1165	>3078
ED97.0	1932	693	>4000	>2462	677	>2462	4342	1297	>6000	>3078	1364	>3078
ED98.0	2681	818	>4000	>2462	800	>2462	>6000	1566	>6000	>3078	1655	>3078
ED99.0	>4000	1043	>4000	>2462	1023	>2462	>6000	2057	>6000	>3078	2187	>3078