

auto-injector ($\kappa = 0.57$, 95% CI 0.38-0.76), and less agreement between self-reported peanut allergy and peanut allergy defined by the 90% specificity decision point only ($\kappa = 0.49$, 95% CI 0.31-0.68).

Each epidemiologic method for assessing peanut allergy prevalence has strengths and limitations. Double-blind, placebo-controlled food challenges are the gold standard for clinical peanut allergy diagnosis, but these are challenging to implement in large, unselected cohorts and have not been done in unselected US cohorts.² As diagnostic adjuncts, component resolved diagnostics may also be increasingly implemented in epidemiologic cohorts going forward. In this letter, we have provided prevalence estimates according to several criteria that can be compared to one another and to previous estimates. Our results come from a US cohort of children not selected for allergy or any disease, and they support that peanut allergy is an increasingly prevalent condition.

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Galactose-alpha-1,3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis

To the Editor:

Delayed type I reactions to red meat are typical for patients sensitized to galactose-alpha-1,3-galactose (α -Gal), and increasing numbers of patients are being recognized worldwide.^{1,2} Interestingly, allergic reactions to pork kidney are mainly observed in Europe and are a good example of how regional differences in meat consumption can influence the clinical presentation of this specific variant of type I allergy.³ The aim of this study was to outline how an understanding of allergy to pork kidney can be helpful for the understanding of red meat allergy in general.

Based on clinical history, 25 German patients (9 female, 16 male; median age 56 years; Table I) with a history of at least 1 allergic reaction to pork kidney were selected and analyzed. The consumption of pork kidney led to anaphylaxis in 72% of the patients (according to the Ring and Messmer severity scale,⁴ 56% of those were grade II, and 44% were grade III) and to urticaria/angioedema without extracutaneous manifestations in the remaining 28%. Using structured interviews, cofactors of anaphylaxis⁵ could be identified in 81% of the patients (21/25 patients, Table I). Additional systemic allergic reactions to other mammalian meat, dairy products, or gelatin were reported in 56% of the patients (Table I). Based on the reported time between consumption of pork kidney and onset of the first symptoms, the reactions were classified as immediate type I reactions (≤ 3 hours) and delayed type I reactions (3 to 6 hours). In this cohort ($n = 21$; mean reaction time 1.25 hours; range 0.25 to 8.0 hours), 67% were immediate type I reactions. Interestingly, patients with a history of hypersensitivity to pork kidney only ($n = 9$; mean reaction time 3.5 hours; range 0.5 to 8.0 hours) were evenly distributed between the immediate type I reaction and the delayed type I reaction groups (ratio 1.25:1). In contrast, patients with hypersensitivity to both pork kidney and red meat ($n = 11$) reacted earlier, with an immediate type I reactions/delayed type I reactions ratio of 3:1 (mean reaction time 1.5 hours; range 0.25 to 5.0 hours). Two or more associated cofactors (ratio 3.5:1) and anaphylaxis (grades II and III) were linked to immediate type I reactions (ratio 2:1).

Commercially available skin prick tests from pork, beef, lamb, or horse meat extracts elicited reactions in only 2 patients, milk extracts in 0 patients. In contrast, prick-to-prick tests using raw and cooked pork kidney showed 100% sensitivity, higher than raw and cooked beef kidney and muscle meat of different species (Fig 1). The process of cooking beef and pork meat decreased sensitivity in prick-to-prick tests. The pattern of prick-to-prick test results was comparable in patients with only pork-kidney

TABLE I. Clinical characteristics of 25 α -Gal-sensitized patients allergic to pork kidney

Patient (no.)	Age (y)	Sex	Duration of allergy	Events (no.)	Pork kidney			Mammalian meat		Oral	sIgE
					Symptoms	Delay (min)	Cofactors (code)	Muscular meat	Other	Challenge	α -GAL (kUa/L)
1	56	M	39 y	3	Urt	480	1	No		Yes	3.12
2	69	M	1.5 y	3	Ana III	270	4	No	Lung, heart	Yes	2.87
3	47	M	10 y	>10	Ana II	45	n/a	Pork, beef, deer	Sausages, gelatin	Yes	69.30
4	32	M	6 mo	2	Ana II	90	0	No		Yes	15.50
5	66	M	2.8 y	5	Urt	30	3, 4	Pork	Sausages	Yes	60.10
6	56	F	10 y	2	Urt	n/a	n/a	Pork		Yes	65.90
7	52	F	1.1 y	2	Ana II	30	0	No		No	1.22
8	77	M	3 mo	1	Ana III	30	1, 2, 4	No		No	41.00
9	55	M	12 y	5	Ana III	240	n/a	Pork, beef		Yes	9.13
10	41	F	3 mo	3	Ana III	15	0	No	Sausages, milk	No	84.10
11	73	F	2.4 y	2	Ana II	240	2	Pork, beef		No	11.90
12	53	M	28 y	1	Urt	n/a	n/a	No		No	1.56
13	56	M	19 y	3	Ana II	45	n/a	Pork, deer		No	45.60
14	54	F	24 y	3	Ana III	120	2	Lamb	Sausages	No	9.18
15	62	F	25 y	>10	Ana II	45	n/a	Pork, beef, Lamb		No	2.10
16	72	M	2.2 y	2	Ana II	90	1, 2, 3	Pork		No	11.80
17	76	M	1 mo	1	Ana II	300	1	No		No	48.50
18	68	F	8 mo	7	Ana III	30	2,4	Pork, beef	Sausages, tripe	No	18.90
19	55	F	6 y	1	Urt	120	0	No		Yes	15.40
20	52	M	1 mo	1	Ana II	60	1	No		No	9.30
21	65	F	21 y	>10	Ana II	30	2	Pork, beef		No	63.30
22	70	M	1 mo	1	Ana III	300	3	No		No	18.40
23	55	M	16 y	2	Ana II	180	2	No	Sausages	No	13.20
24	61	M	20 y	3	Urt	n/a	n/a	Beef		No	67.60
25	72	M	52 y	3	Urt	n/a	n/a	No		No	3.50

Cofactors: 0 = none, 1 = exercise, 2 = alcohol, 3 = nonsteroidal anti-inflammatory drug, 4 = ACE inhibitor/ β -agonist.

Ana, Anaphylaxis (according to Ring and Messmer); F, female; M, male; n/a, not available; Urt, urticaria.

allergy and patients with additional red meat allergy in their clinical history. Intradermal testing with gelatin-derived colloid (GelaFundin 4%, B. Braun, Melsungen, Germany) proved to be a test alternative to prick-to-prick tests with fresh meat (sensitivity 85%).⁶ Prick-to-prick tests with fresh meat ($n = 5$) and intradermal testing with gelatin-derived colloid ($n = 10$) performed for other medical reasons in α -Gal-negative individuals were always negative and serve as controls for this study. Cat dander, containing possible cross-reacting allergens, was reactive in 38% of the prick tests. Based on history, co-sensitization and total IgE 60% of the patients were classified as atopics. Serum IgE to α -Gal was detected in all patients using an experimental ImmunoCAP produced by Phadia AB (Uppsala, Sweden) with covalent coupling of natural purified bovine thyroglobulin to ImmunoCAP solid phase (Table I and Table E1, in this article's Online Repository at www.jacionline.org). Additionally, specific IgE was analyzed to the following (% of reactive samples): pork (92%) and beef meat (96%), pork serum albumin (0%) and beef serum albumin (14%), cat dander (44%) and milk (43%; Table E1). *In vitro* assays with serum from 2 selected patients were performed to investigate whether reactivity to pork kidney is mediated by IgE to α -Gal and whether reactivity to pork muscle meat is mainly dependent on IgE to α -Gal. Importantly, IgE reactivity with α -Gal could be completely blocked by pre-incubating the serum with pork-kidney extracts, proving IgE cross-reactivity (Fig 2). Moreover, reactivity to pork meat using the ImmunoCAP assay was also completely blocked by pre-incubation with both pork-kidney extract and bovine thyroglobulin, demonstrating that in these

patients, IgE recognition of the meat extract depends on IgE to α -Gal.

To verify the diagnosis and to assess the individual risk of developing anaphylaxis, including possible cofactors, a total of 35 oral challenge tests (OCT) in 4 patients with exclusive pork-kidney allergy and 4 patients with additional red meat allergy were performed (Table II). OCT with pork kidney was reactive in all patients except for 1 patient, who only had pork-kidney allergy in their clinical history (patient 1). In agreement with our data from the structured interviews, in these patients, the mean time between OCT and elicitation of allergic symptoms was 10 hours; in patients with a history of additional red meat allergy, it was 2.42 hours. Both patients with allergy to only pork kidney (patients 2 and 4), who underwent OCT with mammalian meat, did not react, even after application of cofactors such as acetylsalicylic acid (ASS) or alcohol. In contrast, 2 patients with additional red meat allergy in their history (patients 3 and 5) displayed allergic symptoms upon OCT combined with cofactors. Interestingly, patient 5 also reacted in OCT with beef meat and gelatin, but not with deer meat.⁷ Oral allergic symptoms were never observed during any of the OCT. Consequently, based on diagnostic measures including OCT, an individual risk assessment was made. However, it needs to be emphasized that OCT, even including cofactors, is still an estimate of reactivity. The probability to react might change according to exposure and additional boosts, such as tick bites.^{8,9}

As demonstrated, the reactivity in skin tests with fresh meat or gelatin in this study seems to reflect the content of accessible α -Gal epitopes in these preparations (Fig 1). Unfortunately, skin

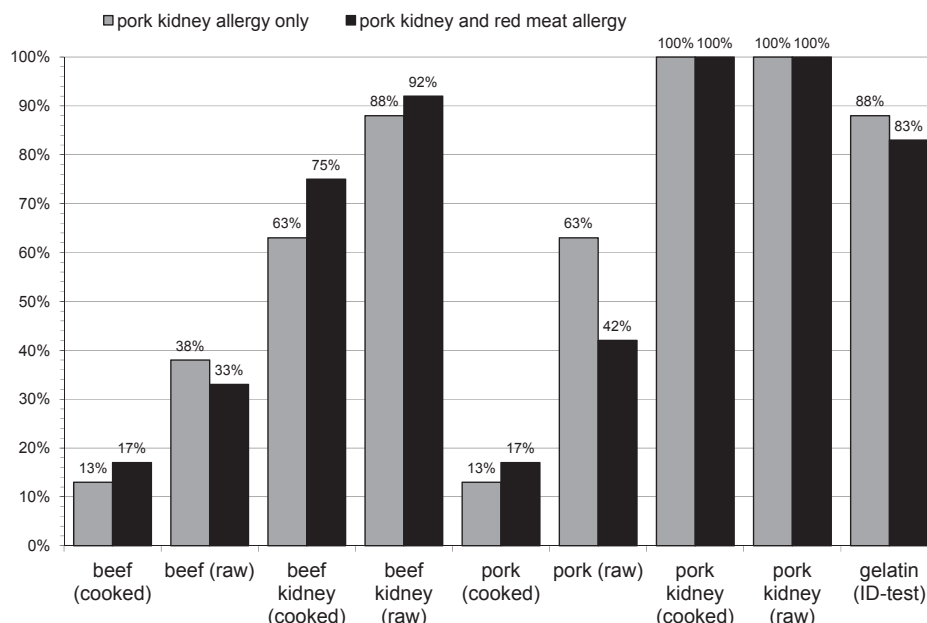


FIG 1. Percentage of reactive prick-to-prick tests using kidney and muscle meat from pork and beef with raw and cooked samples. Intradermal test with gelatin in 20 α -Gal-sensitized patients, divided into 2 subgroups: patients with only pork-kidney allergy and patients with pork-kidney and additional red meat allergy in their clinical history. *ID-test*, Intradermal test.

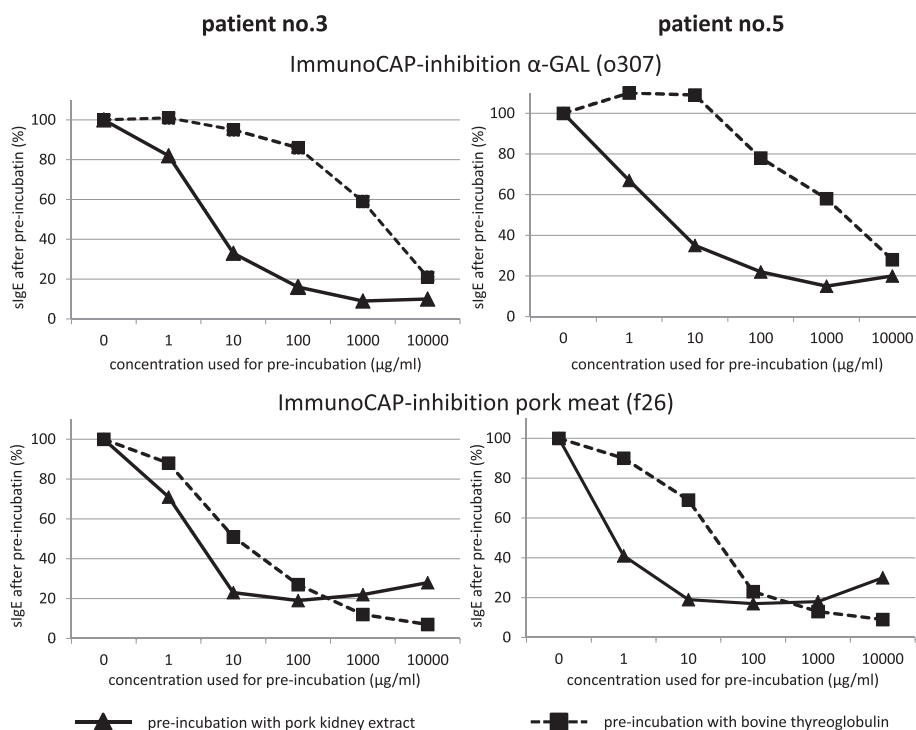


FIG 2. ImmunoCAP inhibition was performed for patients 3 and 5 by pre-incubating sera with increasing dilution of bovine thyroglobulin (*square*) and pork-kidney extract (*triangle*) for 12 hours at 4°C and then testing for allergen-specific IgE antibodies to α -GAL (*upper row*) and pork meat (*lower row*). The allergen-specific IgEs are displayed as the percentage of the non-incubated titer. Inhibition of >75% was interpreted as complete inhibition of the ImmunoCAP by the substrate used. *slgE*, Allergen-specific IgE.

test results seem to be not predictive for clinical tolerance or reactivity to a certain type of mammalian meat. OCT is the only option, but a risky one, to assess the individual risk of patients

sensitized to α -Gal for developing anaphylaxis in response to different mammalian meats. Pork kidney most constantly elicits a result in skin tests, and *in vivo* our results confirm that pork

TABLE II. Results of OCT with pork kidney and meat (with and without cofactors of anaphylaxis) in 8 α -Gal-sensitized patients

Patient (no.)	OCT pork kidney without cofactors						OCT mammalian meat without cofactors†			OCT mammalian meat with cofactors§			
	OCT	Reaction	Total dose (g)	Time OCT* (min)	Last dose (g)	Delay† (min)	OCT	Species	Reaction	OCT	Species	Cofactors	Reaction
Only kidney allergy in history													
1	Done	None	190	na	95	na	Done	Pork	None	nd			
								Beef	None				
2	Done									Done			
		U	80	750	40	495	nd				Pork	+ exe	None
4	Done									Done			
		U	82	600	50	240	Done	Pork	None		Pork	+ exe	None
												+ exe/ass	None
								Beef	None		Beef	+ exe	None
												+ exe/ass	None
19	Done												
		U	200	120	120	60	nd			nd			
Kidney and red meat allergy in history													
3	Done	U, AE	48	120	36	45	Done	Pork	None	Done	Pork	+ exe	U
								Beef	U				
								Deer	None		Deer	+ exe	None
												+ exe/alc	None
5	Done	U, AE	94	160	50	45	Done	Pork	None	Done	Pork	+ ass	None
												+ exe/ass	None
												+ exe/ass/alc	U
6	Done	U	70	130	50	30	Done	Pork	None	Done	Pork	+ exe	None
												+ exe/ass	None
												+ exe/ass/alc	None
								Beef	None		Beef	+ exe	None
												+ exe/ass	None
												+ exe/ass/alc	None
9	Done	U	200	300	100	180	nd			nd			

AE, Angioedema; alc, alcohol; ass, acetylsalicylic acid; exe, exercise; na, not available; nd, not done; U, Urticaria.

*Time between start of OCT with first consumed portion of pork kidney and elicitation of allergic symptoms.

†Time between last consumed dose of pork kidney and elicitation of allergic symptoms.

‡Beef or pork (raw weight 350 g, portioned in 10%, 30%, 60%); 2-hour delay between each step.

§Alcohol (0.25 L wine or 0.5 L beer; 1000 mg ASS); beef, pork or deer (raw weight 350 g, single portion); bicycle ergometry (20 min/70-90 watts); 30-min delay between each step.

kidney is the mammalian meat with the highest concentration of α -Gal, or at least with the highest levels of accessible α -Gal epitopes.³ Indeed, the results we show in Fig 2 demonstrate that reactivity to α -Gal can be completely blocked using pork-kidney extracts. Moreover, even the reactivity to pork meat in this assay could be blocked using both pork-kidney extracts and bovine thyroglobulin (the substrate in the α -Gal assay). This suggests that IgE recognizing α -Gal is responsible for both *in vitro* and *in vivo* reactivity in our patients.

Translating this for the daily life of our patients, pork kidney elicits red meat allergy more consistently than muscle meat, possibly because a threshold of accessible α -Gal that is enough to elicit an allergic reaction is reached much more easily with pork kidney. Patients who also react to muscle meat may therefore be at higher risk, as much lower levels of accessible α -Gal may be triggering red meat allergy in these patients. In agreement with this assumption, subgroup analyses showed a shorter delay in the appearance of allergic reactions in these patients. Alternatively, cofactors in anaphylaxis that can increase intestinal absorption (for example, alcohol, ASS, physical exercise) can substitute for higher sensitivity, marking red meat allergy as another example of food-dependent, exercise-induced anaphylaxis. However, further clinical and experimental research is warranted to better understand this peculiar disease.

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Control lymphocyte subsets: Can one country's values serve for another's?

To the Editor:

Reliable interpretation of abnormal immunity depends on an understanding of what constitutes “normal.” We and others have reported that lymphocyte patterns are affected by ethnicity, sex, and environmental factors.¹⁻³ Differing exposure to infectious agents, such as malaria, tuberculosis, and cytomegalovirus, could underlie differences in lymphocyte subset patterns in contrasting settings.⁴⁻⁶ In this study we analyzed combined data from 3 studies of healthy children from Thailand,¹ Malawi,² and the United States³ who had used similar standard flow cytometric methods and markers, thus allowing assessment of immune heterogeneity across settings with differences in ethnicity and infectious disease exposure.

We used lymphocyte subset data from healthy children aged 0 to 15 years enrolled in our previously published studies¹⁻³; additional Thai subjects less than 2 years of age were recruited to allow comparisons with the youngest children. Exclusion criteria were febrile illness, clinical infection at screening, concomitant medical illnesses potentially resulting in abnormal immunity, or abnormal growth (defined as <3rd or >97th percentiles of the country's growth chart for Thai and US children or a weight-for-height *z* score <70% for Malawian children). Rapid HIV diagnostic kits were used with PCR to confirm discordant results. Statistical analyses were performed in a manner similar to previous publications (details are shown in the [Methods](#) section in this article's Online Repository at www.jacionline.org).¹⁻³

Of 1399 children enrolled (Thailand, *n* = 281; Malawi, *n* = 397; and the United States, *n* = 721), approximately 50% were male (see [Table E1](#) in this article's Online Repository at www.jacionline.org), and approximately 50% were between 0 and 2 years of age. The Thai and Malawian cohorts were ethnically homogenous; the US cohort had a mix of African American (53%), Hispanic (29%), and Euro-Caucasian (17%) subjects.

The following lymphocyte subpopulations were identified as percentages of the lymphocyte gate in all 3 cohorts: T cells (CD3⁺), CD4⁺ T cells (CD3+CD4⁺), CD8⁺ T cells (CD3⁺CD8⁺), B cells (CD19⁺), and B memory cells (CD19⁺CD27⁺). [Fig 1](#) compares cell counts of total T cells, CD4⁺ T cells, and CD8⁺ T and B cells by age and country. Graphs representing other cells and percentages are provided online (see [Figs E1 and E2](#) in this article's Online Repository at www.jacionline.org).

Thai children had higher total T-cell counts compared with the US and Malawian cohorts aged 6 months to 4 years and 0 to 24 months, respectively. Malawian children aged 0 to 5 months had lower total T-cell counts compared with US children. Compared with the US and Thai cohorts, Malawian children aged 0 to 11 and 0 to 17 months, respectively, had lower T-cell percentages.

Thai children aged 6 to 11 months had higher CD4⁺ T-cell counts but a lower percentage of CD4⁺ T cells compared with US children of the same age group. Compared with US children, Malawian children had lower CD4⁺ T-cell counts from 0 to 5 months of age and greater CD4⁺ T-cell counts from 8 to 15 years of age, whereas CD4⁺ T-cell percentages were lower from 0 to 17 months of age but greater from 8 to 11 years of age. Compared with Thai children, CD4⁺ T-cell counts were lower in Malawian children aged 0 to 11 and 18 to 24 months of age but greater in those aged 5 to 7 and 12 to 15 years of age. Percentages of CD4⁺ T cells were similarly lower in Malawian children aged 0 to 12 months of age but consistently higher than those seen in Thai children aged 2 to 15 years of age.

Higher CD8⁺ T-cell counts (birth to 4 years and 8-11 years) and percentages (birth to 18 months and 2-7 years) were observed in Thai compared with US children and also compared with Malawian children for absolute counts from 0 to 17 months and 8 to 11 years and percentages from 0 to 5 months and 8 to 11 years. These values were also higher among Malawian compared with US children for certain age groups (6-17 months for absolute CD8⁺ T-cell counts and percentages and 2-4 years for percentages only). B-cell and natural killer (NK) cell results are presented in the [Results](#) section in this article's Online Repository at www.jacionline.org.

In secondary analyses geometric mean ratios were predominantly consistent with the significance results from nonparametric tests, with few apparent sex differences, although the power to detect these differences was limited male (see [Table E2](#) in this article's Online Repository at www.jacionline.org).

This analysis of lymphocyte subsets of children from countries within 3 different continents demonstrates a marked heterogeneity in subset patterns of HIV-uninfected children, the extent of which is most marked in children younger than 2 years. The differences in subset patterns might be driven by several factors, including ethnicity, with participants from the 3 countries being of different ethnicities. Previous healthy control studies in Asian and African subjects have reported smaller proportions of CD4⁺ T-cell subsets and larger proportions of CD8⁺ T-cell subsets in these populations compared with those observed in populations in the developed world.^{2,7-10} However, ethnic differences alone might not account for all subset differences because variations within specific ethnic groups have also been reported.^{2,8,11,12} Environmental factors, particularly prevalent infectious diseases, might affect cellular phenotypic patterns.¹³

TABLE E1. Serum analysis of 25 α -Gal-sensitized patients allergic to pork kidney

Patient (no.)	Total IgE kUa/L	Specific IgE (kUa/L)								Cat dander
		α -GAL	Ratio α -GAL/IgE	Pork meat	Pork serum albumin	Beef meat	Beef serum albumin	Milk	Lactalbumin	
1	144	3.12	0.022	0.33	n.d.	0.59	n.d.	0.10	<0.1	0.54
2	42	2.87	0.068	0.47	<0.1	0.78	<0.1	0.15	<0.1	0.68
3	594	69.30	0.117	4.00	<0.1	4.30	0.14	1.60	<0.1	1.20
4	167	15.50	0.093	2.70	<0.1	3.50	0.04	n.d.	<0.1	2.00
5	761	60.10	0.079	21.90	<0.1	46.60	0.93	10.60	<0.1	2.63
6	148	65.90	0.445	6.30	<0.1	7.80	<0.1	1.24	<0.1	0.95
7	38	1.22	0.032	1.20	n.d.	1.60	n.d.	0.86	n.d.	0.67
8	384	41.00	0.107	0.88	<0.1	1.91	<0.1	0.36	<0.1	0.19
9	116	9.13	0.078	0.41	<0.1	0.72	<0.1	0.14	<0.1	<0.1
10	955	84.10	0.088	16.10	<0.1	21.00	<0.1	8.80	<0.1	2.00
11	163	11.90	0.073	2.90	n.d.	6.90	n.d.	0.79	n.d.	0.12
12	75	1.56	0.021	0.13	<0.1	0.28	<0.1	n.d.	n.d.	<0.1
13	401	45.60	0.114	24.00	0.10	30.80	3.09	11.00	<0.1	6.70
14	75	9.18	0.122	1.00	<0.1	1.80	<0.1	0.23	<0.1	0.14
15	1099	2.10	0.002	0.72	<0.1	1.00	<0.1	0.16	<0.1	<0.1
16	47	11.80	0.251	0.40	<0.1	0.65	<0.1	0.05	<0.1	<0.1
17	2115	48.50	0.023	8.18	0.10	18.60	0.20	0.76	0.22	19.10
18	157	18.90	0.120	2.10	n.d.	4.10	n.d.	n.d.	n.d.	0.73
19	257	15.40	0.060	1.90	n.d.	3.80	n.d.	n.d.	n.d.	0.43
20	106	9.30	0.087	1.70	n.d.	2.90	n.d.	0.53	n.d.	0.32
21	2834	63.30	0.022	24.80	n.d.	32.10	n.d.	9.90	n.d.	3.50
22	137	18.40	0.134	0.84	n.d.	2.00	n.d.	0.19	n.d.	0.08
23	29.9	13.20	0.441	2.60	n.d.	3.50	n.d.	0.21	n.d.	0.22
24	419	67.60	0.161	18.50	n.d.	31.10	n.d.	7.10	n.d.	4.30
25	72.9	3.5	0.048	0.90	n.d.	1.20	n.d.	0.34	n.d.	0.15

n.d., Not done.