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Anaphylaxis to PEGylated Liposomal Echocardiogram Contrast in a Patient with IgE-Mediated Macrogol Allergy

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To The Editor:

Polyethylene glycols (PEG), or macrogols, are employed in high molecular weight (HMW) (> 1000 g/mol) forms as active ingredients or drug excipients, such as bowel preparations and parenteral steroids.[1] We and others have previously reported immediate and life-threatening hypersensitivity reactions to PEG of increasing importance.[1] Here, we report on a case of anaphylaxis to PEG 5000-conjugated liposomal perflutren, a perfluorocarbon gas used as echocardiography contrast.

The two existing formulations of perflutren, human albumin conjugated (Optison™) and PEGylated liposomal (Definity®), were approved by the Food and Drug Administration (FDA) in 1997 and 2001, respectively.[2, 3] In 2007, the FDA issued a black box warning for perflutren due to 4 deaths within 30 minutes of administration during post-marketing surveillance, without reference to a mechanism; therefore, contraindicating their use in patients with serious cardiopulmonary conditions.[2]

Based on subsequent safety data, the FDA warning has been revised twice, first in 2008 when the cardiopulmonary contraindication was changed to a warning.[4] This revision was based in part upon a multicenter, retrospective analysis of 78,383 doses of perflutren (66,164

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PEGylated liposomal and 12,219 human albumin conjugated), that reported only 8 probably-related serious adverse events within 30 minutes of administration, of which all were associated with PEGylated liposomal perflutren.[5] Anaphylaxis accounted for 4 of these reactions.[5] In 2011, the warning was changed to a statement that cardiopulmonary events were uncommon.[6] A prior proposed mechanism for the observed hypersensitivity reactions has been complement activation-related pseudoallergy.[7] However, we previously outlined 2 cases of PEG 3350 anaphylaxis that were confirmed by skin prick testing (SPT) and the detection of specific IgE to PEG, suggesting the importance of IgE-mediated as opposed to non-IgE mediated mechanisms for some HMW PEG reactions[1] (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Our patient was a 58-year-old white male with an occupational history as a car audio mechanic and paint department manager, who presented to our drug allergy clinic at Vanderbilt University Medical Center for evaluation of suspected prior immediate reactions associated with PEG-containing medications. One month prior to his clinic visit, he was given PEGylated liposomal perflutren as part of a stress myocardial perfusion scan. Within minutes, he developed shortness of breath, urticaria and hypotension. He was given intramuscular epinephrine, steroids, and antihistamines, but ultimately required intravenous epinephrine drip and intensive care unit admission for continued hypotension. Stabilization over the 4 hours after admission led to wean of his vasopressors, and he was discharged the following day.

Eight months prior, he had anaphylaxis to oral PEG 3350 while undergoing colonoscopy preparation. Within 15 minutes of drinking the first cup of PEG 3350, he developed urticaria, shortness of breath, angioedema, and hypotensive syncope. He was treated with intramuscular epinephrine, steroids and antihistamines, observed in the emergency department, and discharged several hours later. Days before this colonoscopy preparation, while using paints containing HMW PEG, he developed pruritic, swollen hands. Three years prior to consultation, he reported an immediate reaction to a steroid knee injection, characterized by lightheadedness and throat tightness that abated with antihistamine administration.

In our clinic, he underwent a previously described skin test protocol and was positive to PEG 3350 at all concentrations, as well as methylprednisolone acetate and triamcinolone acetonide that contain PEG 3350 and polysorbate 80, respectively[1] (Figure 1, Table E1, available in this article's Online Repository at www.jaci-inpractice.org). He was SPT and oral challenge negative to PEG 300, a lower MW macrogol and methylprednisolone sodium succinate which does not contain PEG 3350. Based on his clinical history and SPT results, we concluded his prior immediate reactions to PEG were likely IgE-mediated.

Electrochemiluminescent immunoassay was used to detect anti-PEG sIgE.[1] The samples were processed with Protein G Plus Agarose then incubated at 1:10 dilution in PEGylated bovine catalase coated Meso-Scale Multi Array plate. A biotin-conjugated goat anti-human IgE (BioRad) antibody was added at 1:10,000 dilution. SULFO-TAG labeled Streptavidin was used as the detection reagent. Plates were read with a Sector Imager 6000 Analyzer (Meso Scale Discovery, Rockville, MD). Anti-PEG sIgE from the patient's serum capable of

binding to PEGylated catalase was detected with a measured luminescence intensity of 347.5. This was comparable in magnitude to previous PEG allergic patients, and significantly higher than PEG exposed controls assayed previously (99% confidence interval [CI] = 54.3 ± 9.3).[1]

To evaluate the scope at which the differing formulations of perflutren might be associated with anaphylaxis in the United States, we reviewed the FDA Adverse Event Reporting System (FAERS) database from 1989 through 2019. Using the search terms “perflutren” and “anaphylactic shock” or “anaphylactic reaction,” we encountered 90 unique cases of anaphylactic shock or reaction in which perflutren was reported as the primary agent suspected as causal (Table E2, available in this article’s Online Repository at www.jaci-inpractice.org). The formulations of perflutren reported were PEGylated liposomal 84/90 (94%), human albumin 4/90 (4%) and unspecified 2/90 (2%).

For PEGylated liposomal perflutren, the average age at reaction was 61.2 years (11% missing data), and 64% of those who reacted were male (8% missing data). At the time of reaction, 35% reported that PEGlyated liposomal perflutren was the sole agent administered before anaphylaxis. The other 65% were taking concomitant medications at the time of their reaction. Reactions for PEGylated liposomal perflutren were distributed from 2005 to 2019, with an average of 6 cases per year (Figure 2). There were no reports of PEGylated liposomal perflutren anaphylactic reactions before 2005.

In this report we demonstrate the presence of anti-PEG specific IgE and positive SPT to HMW PEG in a patient with anaphylaxis to PEGylated liposomal perflutren and two prior immediate hypersensitivity reactions to HMW PEG-containing medications. This patient’s occupational history, of repeated exposures to mechanical fluids and paints, is similar to other patients with repeated cutaneous exposure to PEG-containing products who subsequently develop anaphylaxis to PEG, adding support for a possible cutaneous mode of sensitization.[1]

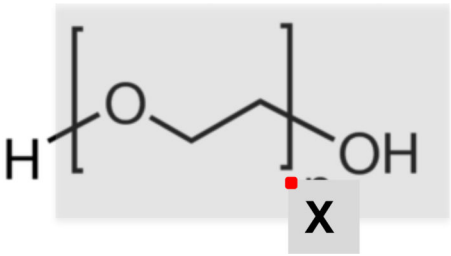
In our literature review, only 2 cases focusing on immediate hypersensitivity reactions to perflutren have been reported, and no mechanism has been elucidated thus far.[8, 9] Our findings are therefore novel, as they suggest that an IgE-mediated type I hypersensitivity to PEG underlies at least some cases of immediate hypersensitivity to PEGylated liposomal perflutren. We were limited by being unable to devise an assay to prove that our patient’s PEG specific antibodies bind directly to PEGylated liposomal perflutren, due to its gaseous formulation. Further, while we did not use PEG 5000 for SPT because we could not find it in a medical grade source, we believe based upon previous studies that PEG 3350 is representative of PEG 5000 and that IgE-mediated reaction potential to HMW PEG may increase with increasing side chain polyether repeats. This is supported by our previous observation that increasing molecular weight correlates with increasing PEG-specific antibody avidity, since the primary determinant of molecular weight with PEGs is the number of side chain polyether repeats.[1] In the future, studies are needed to demonstrate whether preexisting PEG-specific antibodies are behind the disproportionate number of cases of anaphylaxis reported to PEGylated liposomal perflutren compared to human albumin conjugated perflutren.

Anaphylactic reactions to PEGylated liposomal perflutren appear to be rare overall, reported by Wei et al. as occurring in 0.006% of patients.[5] We encountered only 84 cases of anaphylaxis to PEGylated liposomal perflutren reported in FAERS. However, self-reported databases are potentially limited due to under-recognition and reporting.

In conclusion, given the severity of these reactions, allergists, cardiologists, and radiologists should become aware of the possibility of hypersensitivity reactions to macrogols to facilitate prompt diagnosis, treatment, and future avoidance. We suggest that use of PEGylated liposomal perflutren and other drugs and devices containing HMW PEG should be avoided in favor of alternatives when patients report prior immediate hypersensitivity reactions consistent with severe macrogol allergy. Further studies are needed to assess how often this emerging drug allergy mechanism is responsible for reactions when they do occur.

Extended Data

Polyethylene Glycol 3350



Polyethylene Glycol 5000

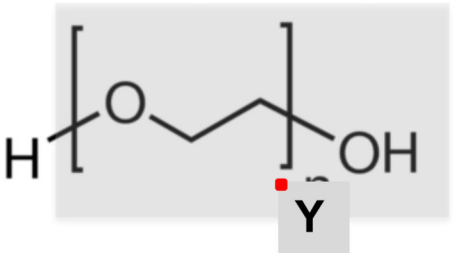


Figure E1.

X and Y indicate the repeating oxyethylene group. The number of repeats determines the length of the molecule's chain, and thereby determines the molecular weight. A polyethylene glycol of molecular weight 3350 would be a mixture of molecules with enough oxyethylene repeats to have an average molecular weight of 3350 g/mol.

Table E1.

Skin prick and intradermal testing with corticosteroids and polyethylene glycols

Agent (concentration)	Wheal (mm)	Flare (mm)	Interpretation
Skin Prick Test Results			
Histamine control (0.1 mg/mL)	6	30	Positive
Saline	3	3	Negative
PEG 3350	11	45	Positive
PEG 3350 (1:10 dilution)	7	40	Positive
PEG 3350 (1:100 dilution)	7	40	Positive
PEG 300	0	0	Negative
Betamethasone (0.6 mg/mL)	4	5	Negative
Dexamethasone (0.4 mg/mL)	3	3	Negative
Hydrocortisone (5 mg/mL)	4	4	Negative
Methylprednisolone acetate (4 mg/mL)	9	15	Positive
Methylprednisolone sodium succinate (5 mg/mL)	4	4	Negative
Triamcinolone acteonide (1 mg/mL)	4	4	Negative
Intradermal Skin Test Results			
Triamcinolone acetonide (0.1 mg/mL)	17	36	Positive

Table E2.

Cases of anaphylaxis reported to the FDA from 2004 to 2019 where perflutren contrast was the primary drug suspected, including PEGylated liposomal, human albumin, and unspecified formulations

FAERS Report ID Number	Age	Sex	Year of report	Formulation of perflutren	Patient taking any other medications concomitantly
4305851-X	57	Female	2004	Human albumin	No
4799863-X	83	Female	2005	Unspecified	Yes
4854899–5	65	Male	2005	PEGylated liposomal	No
4856232–1	75	Male	2005	PEGylated liposomal	No
4897423–3	64	Male	2006	PEGylated liposomal	No
5098650–5	48	Female	2006	PEGylated liposomal	Yes
5143226–4	47	Female	2006	PEGylated liposomal	Yes
5169390–9	N/A	N/A	2006	PEGylated liposomal	No
5226997–8	35	Female	2007	PEGylated liposomal	Yes
5235427–1	51	Female	2007	PEGylated liposomal	Yes
5237726–6	N/A	N/A	2007	PEGylated liposomal	No
5386792–6	N/A	N/A	2007	PEGylated liposomal	No
5444176–6	65	Male	2007	PEGylated liposomal	Yes
5456457–0	N/A	Female	2007	PEGylated liposomal	No
5870366–4	N/A	N/A	2007	PEGylated liposomal	No
5870449–9	N/A	N/A	2007	PEGylated liposomal	No
6385659–4	47	Male	2009	PEGylated liposomal	Yes
8986382	57	Male	2012	PEGylated liposomal	Yes
8991087	57	Male	2012	PEGylated liposomal	No
12114192	59	Male	2013	PEGylated liposomal	No
9174101	87	Female	2013	PEGylated liposomal	Yes
9478127	65	Female	2013	PEGylated liposomal	Yes
9496468	84	Female	2013	PEGylated liposomal	Yes
9535950	31	Male	2013	PEGylated liposomal	Yes
9547479	76	Male	2013	PEGylated liposomal	Yes
9758411	84	Male	2013	PEGylated liposomal	No
10979100	52	Male	2014	PEGylated liposomal	No
10979122	57	Male	2014	PEGylated liposomal	Yes
10981361	61	Male	2014	PEGylated liposomal	Yes
10981661	55	Male	2014	PEGylated liposomal	No
10981674	75	Male	2014	PEGylated liposomal	Yes
10983516	57	Male	2014	PEGylated liposomal	Yes
12114174	60	Male	2014	PEGylated liposomal	No
12173673	29	Female	2014	PEGylated liposomal	Yes
9973637	N/A	N/A	2014	Human albumin	No
11115484	43	Female	2015	Unspecified	Yes

FAERS Report ID Number	Age	Sex	Year of report	Formulation of perflutren	Patient taking any other medications concomitantly
12111173	53	Male	2015	PEGylated liposomal	No
12111176	72	Male	2015	PEGylated liposomal	Yes
12111182	69	Male	2015	PEGylated liposomal	Yes
12111186	48	Male	2015	PEGylated liposomal	No
12111187	58	Female	2015	PEGylated liposomal	Yes
12115134	40	Male	2015	PEGylated liposomal	Yes
12115143	36	Male	2015	PEGylated liposomal	Yes
12115145	58	Male	2015	PEGylated liposomal	No
13266056	62	Male	2015	PEGylated liposomal	Yes
13265913	77	Male	2016	PEGylated liposomal	No
13265929	46	Female	2016	PEGylated liposomal	Yes
13265933	75	Female	2016	PEGylated liposomal	Yes
13265937	68	Female	2016	PEGylated liposomal	Yes
13265956	59	Male	2016	PEGylated liposomal	Yes
13266052	68	Male	2016	PEGylated liposomal	Yes
13266058	67	Male	2016	PEGylated liposomal	Yes
13266071	82	Male	2016	PEGylated liposomal	No
13266075	87	Female	2016	PEGylated liposomal	Yes
14542996	43	Male	2016	PEGylated liposomal	Yes
13265967	89	Female	2017	PEGylated liposomal	No
13376730	N/A	N/A	2017	Human albumin	No
1423988	37	Male	2017	PEGylated liposomal	Yes
14373279	55	Female	2017	Human albumin	Yes
14542977	58	Male	2017	PEGylated liposomal	Yes
14542978	63	Female	2017	PEGylated liposomal	Yes
14542979	50	Male	2017	PEGylated liposomal	No
14542982	57	Male	2017	PEGylated liposomal	Yes
14542987	58	Female	2017	PEGylated liposomal	Yes
14542992	62	Female	2017	PEGylated liposomal	No
14542999	92	Male	2017	PEGylated liposomal	Yes
14543018	57	Female	2017	PEGylated liposomal	Yes
14543024	34	Male	2017	PEGylated liposomal	Yes
15244981	57	Female	2018	PEGylated liposomal	Yes
15985388	47	Female	2018	PEGylated liposomal	Yes
15985389	55	Female	2018	PEGylated liposomal	Yes
15985398	91	Male	2018	PEGylated liposomal	Yes
15985401	50	Male	2018	PEGylated liposomal	Yes
15985402	63	Male	2018	PEGylated liposomal	Yes
15985408	76	Male	2018	PEGylated liposomal	Yes
15985412	48	Male	2018	PEGylated liposomal	Yes
15985419	N/A	N/A	2018	PEGylated liposomal	No

FAERS Report ID Number	Age	Sex	Year of report	Formulation of perflutren	Patient taking any other medications concomitantly
15985424	56	Female	2018	PEGylated liposomal	Yes
15985445	69	Male	2018	PEGylated liposomal	No
15985448	84	Female	2018	PEGylated liposomal	Yes
15985453	55	Male	2018	PEGylated liposomal	Yes
15985454	61	Male	2018	PEGylated liposomal	Yes
15985458	70	Female	2018	PEGylated liposomal	Yes
15985471	65	Male	2018	PEGylated liposomal	No
15985480	75	Female	2018	PEGylated liposomal	Yes
15985483	N/A	Male	2018	PEGylated liposomal	Yes
15914392	57	Male	2019	PEGylated liposomal	No
15942179	67	Female	2019	PEGylated liposomal	No
15985392	N/A	N/A	2019	PEGylated liposomal	No
16043833	75	Female	2019	PEGylated liposomal	Yes

Data marked as N/A indicate that the information was not contained in the primary report to the FDA.

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Clinical Implications: IgE-mediated macrogol allergy is a potential mechanism for anaphylaxis to PEGylated liposomal perflutren. In patients with a history of severe macrogol allergy, high molecular weight PEG-containing drugs should be avoided in favor of alternatives.

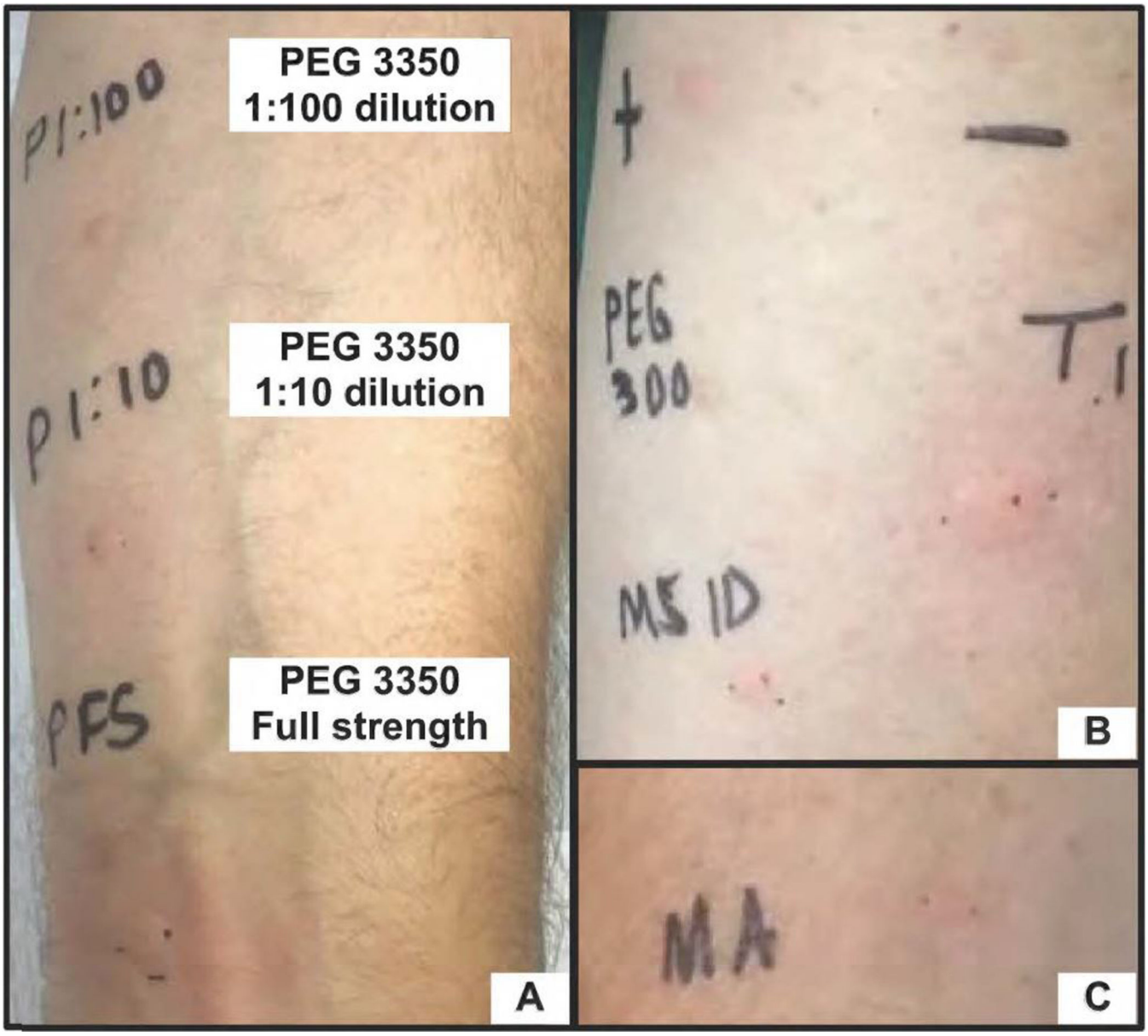

Figure 1.

Selected skin testing images for the patient. In panel A, skin prick testing (SPT) read at 15 minutes had positive responses to polyethylene glycol (PEG) 3350 at all 3 concentrations tested. In panel B, intradermal testing (IDT) is positive for triamcinolone acetonide (contains polysorbate 80), SPT is negative for PEG 300, and IDT is negative for methylprednisolone sodium succinate, all read at 15 minutes. In panel C, SPT is positive for methylprednisolone acetate (contains PEG 3350). (Measurements are recorded in Table E1). Key: + = histamine control (0.1 mg/mL), − = saline, PEG 300 = PEG 300 full strength, MS ID = methylprednisolone sodium succinate intradermal test, T_I = triamcinolone acetonide intradermal test, MA = methylprednisolone acetate

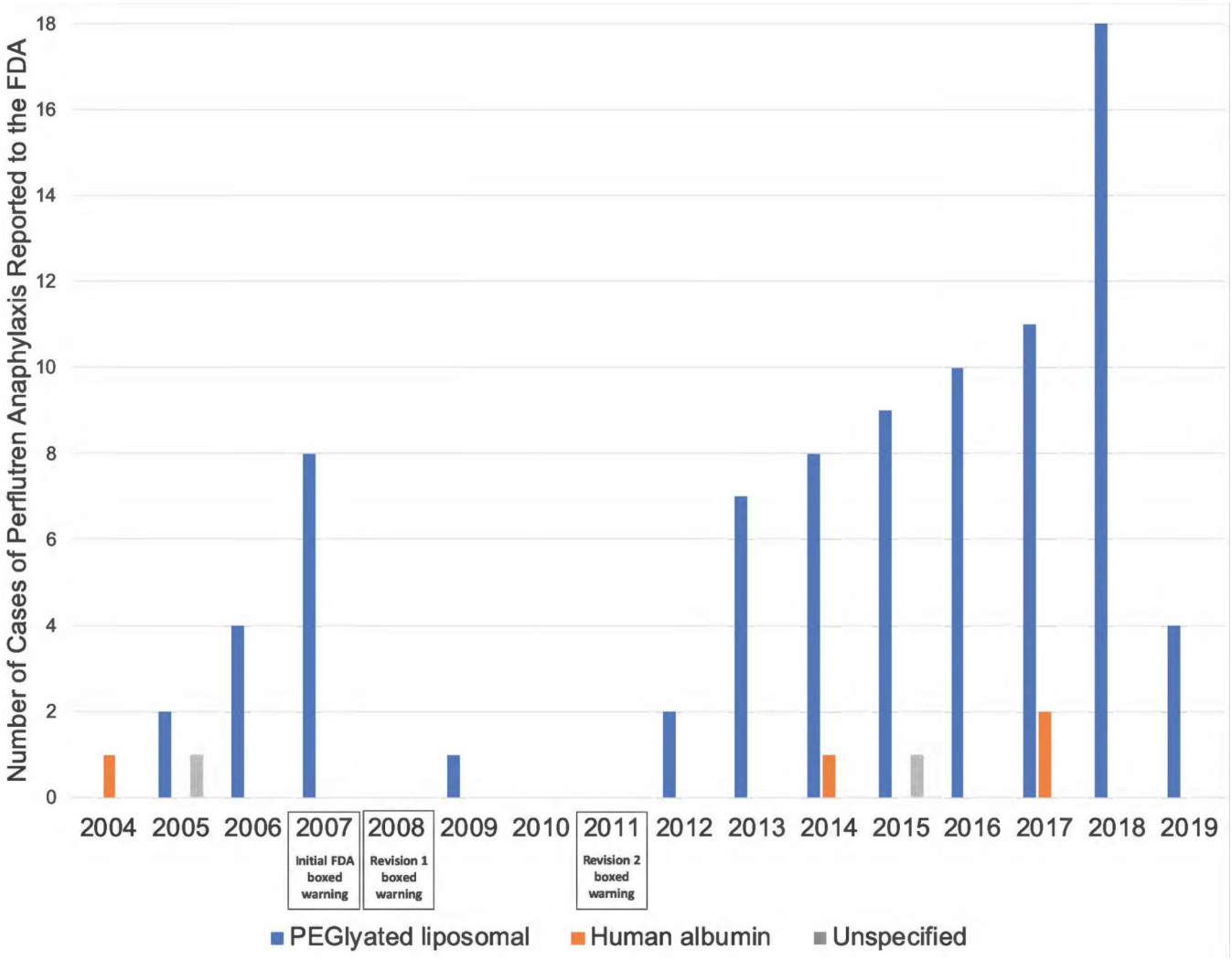

Figure 2.

Cases of anaphylaxis reported to the FDA (FAERS) implicating PEGylated liposomal, human albumin, and unspecified formulations of perflutren echocardiography contrast, by year, along with annotations of key FDA boxed warning revisions. *FAERS,* FDA Adverse Event Reporting System; *FDA,* US Food and Drug Administration; *PEG,* polyethylene glycol.