The Use of a Poisson Regression to Evaluate Antihistamines and Fatal Aircraft Mishaps in Instrument Meteorological Conditions

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BACKGROUND: Research indicates that first-generation antihistamine usage may impair pilot performance by increasing the likelihood of vestibular illusions, spatial disorientation, and/or cognitive impairment. Second- and third-generation antihistamines generally have fewer impairing side effects and are approved for pilot use. We hypothesized that toxicological findings positive for second- and third-generation antihistamines are less likely to be associated with pilots involved in fatal mishaps than first-generation antihistamines.

METHODS: The evaluated population consisted of 1475 U.S. civil pilots fatally injured between September 30, 2008, and October 1, 2014. Mishap factors evaluated included year, weather conditions, airman rating, recent airman flight time, quarter of year, and time of day. Due to the low prevalence of positive antihistamine findings, a count-based model was selected, which can account for rare outcomes.

RESULTS: The means and variances were close for both regression models supporting the assumption that the data follow a Poisson distribution; first-generation antihistamine mishap airmen ($N = 582$, $M = 0.17$, $S^2 = 0.17$) with second- and third-generation antihistamine mishap airmen ($N = 116$, $M = 0.20$, $S^2 = 0.18$). The data indicate fewer airmen with second- and third-generation antihistamines than first-generation antihistamines in their system are fatally injured while flying in IMC conditions.

DISCUSSION: Whether the lower incidence is a factor of greater usage of first-generation antihistamines versus second- and third-generation antihistamines by the pilot population or fewer deleterious side effects with second- and third-generation antihistamines is unclear. These results engender cautious optimism, but additional research is necessary to determine why these differences exist.

KEYWORDS: loss of control, controlled flight into terrain, spatial disorientation, visual illusions.

Gildea KM, Hileman CR, Rogers P, Salazar GJ, Paskoff LN. *The use of a Poisson regression to evaluate antihistamines and fatal aircraft mishaps in instrument meteorological conditions.* Aerosp Med Hum Perform. 2018; 89(4):389–395.

Instrument meteorological conditions (IMC) and dark night conditions provide unique and dangerous challenges to pilots. IMC occurs when meteorological phenomena obscure visual sources of reference. Dark night conditions can technically be acceptable for flight by visual flight rules (VFR). However, a second but more important concept is that of maintaining adequate visual references during VFR flight in visual meteorological conditions (VMC). VMC are those weather conditions that allow a pilot to maintain visual reference with a horizon and provide enough visual cues for safe flight, even when VFR visibility and cloud clearance requirements are met. When flying on a clear dark night in remote areas or over open expanses of water where there are few or no lights to serve as visual reference points for a horizon, dark night conditions may effectively be equivalent to flying in instrument conditions. Because of the lack of a visible horizon and other references, in both types of environments, the pilot must rely solely upon flight instruments and/or autopilots for aircraft control and navigation. An increased rate of dark night mishaps than during the daytime for noninstrument rated pilots highlights the

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This manuscript was received for review in January 2017. It was accepted for publication in November 2017.

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DOI: https://doi.org/10.3357/AMHP.4828.2018

greater challenges of night operations.[8,17] Therefore, we evaluated mishaps in both IMC and dark night VMC conditions.

Conditions of reduced visibility substantially increase the likelihood of task saturation, visual or vestibular illusions, loss of control, and controlled flight into terrain.[16,17] First-generation antihistamines have been seen to adversely affect pilot performance though impairment of psychomotor performance, attention, and memory.[6,19,20] Second and third generation antihistamines are substantially less likely to cause such impairment,[10,11,14] and the FAA has authorized several of these for use by pilots during flight.[9] Specifically, the FAA has authorized loratadine, desloratadine, and fexofenadine. Other second- and third-generation antihistamines are approved only if five maximal dosing intervals have passed prior to flight.

Antihistamines are often used for the treatment of allergy symptoms (such as sinus or ear congestion, sleep disturbances, vision changes, and shortness of breath), which can create safety challenges of their own,[2,12] and the sedating antihistamines are often used as sleep aids for individuals with other issues (such as primary insomnia, anxiety, or depression).

Previous research has evaluated the correlation between antihistamine usage by pilots and fatal mishaps across all types of flights.[4,5,15] Caution should be taken in interpreting results as the base rate usage of antihistamines among the pilot population can only be inferred. The lack of denominator data also means that many analyses and drawing certain conclusions are not possible. For this study, we hypothesized that toxicological findings positive for second- and third-generation antihistamines are less likely to be associated with pilots involved in fatal mishaps under IMC and dark night conditions than findings of first generation antihistamines.

METHODS

The evaluated population consisted of 1475 pilots fatally injured between September 30, 2008, and October 1, 2014, where toxicology specimens were available. There were 1484 fatally injured pilots but after a review of the NTSB probable cause reports, 9 cases were removed because of either insufficient information as to the weather or the circumstances surrounding the mishap (**Appendix A**). In some cases, it was undetermined by the NTSB who was piloting the aircraft. In those occasions, toxicology reports were analyzed for both the pilot and copilot.

All data used in this study were extracted from the Civil Aerospace Medical Institute (CAMI) Medical Analysis Tracking registry (MANTRA). MANTRA is an application used to store autopsy, toxicology, and airmen aeromedical records data from fatal aircraft mishaps and is hosted at CAMI in Oklahoma City. MANTRA is a subset of the ToxFlo®, which is the application used by the toxicology lab for sample analyses.

Toxicological findings from Toxflo® are imported into MANTRA and are used in conjunction with autopsy findings and airmen aeromedical records in an effort to identify aeromedical hazards.

The NTSB, charged by Congress to determine probable cause of the mishap, has an agreement for toxicological analysis on pilots and/or aircrew involved in fatal aircraft mishaps to be performed at CAMI. It is the responsibility of the NTSB investigator-in-charge to assure specimens are submitted for testing.[7] Autopsy services for airmen involved in fatal aviation mishaps are performed by local medical examiners and coroners. At the time of the autopsy, biological samples such as blood, brain, heart, kidney, liver, lung, spinal fluid, urine, and/or vitreous fluid are submitted for toxicological analysis to CAMI.[1,5] On occasion, it was undetermined who was piloting the aircraft. In those instances, specimens are analyzed for someone that may have been in control of the aircraft. The specimens are analyzed for the presence of combustion gas such as carbon monoxide and hydrogen cyanide. Additionally, the lab screens for illicit, prescription, and nonprescription drugs as well as alcohol/volatiles.[3] This research was exempt from review by the Institutional Review Board as it involved "the collection or study of existing data, documents, records, and the information was recorded by the investigators in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects".[13]

Mishap factors evaluated included year, weather conditions, airman rating (e.g., instrument), general location, recent airman flight time, quarter of year, and time of day. The perishable nature of flying skills in general and instrument flying skills in particular, led to the analyses focusing on flight time within the last 6 mo. Because dark night conditions also do not provide external visual cues for position and navigation information, they are considered to fall into the IMC category and were included as such in our analyses. A statistical model was constructed to examine the potential association of these factors with antihistamine effects during flight. The research question was multi-part because of the three generations of antihistamine medications and their variable effects.

The first generation of antihistamine medications consisted of chlorpheniramine, clemastine, diphenhydramine, hydroxyzine, tripolidine, and brompheniramine. Because of the similar nonsedating nature of second- and third-generation antihistamines and the limited observations of these medications in the autopsy data, they were combined into a single category. These medications consisted of cetirizine, loratadine, azelastine, olapatidine, levocetirizine, fexofenadine, and desloratadine. Not all of these medications were present in the MANTRA system. Out of the first-generation of medications, only diphenhydramine, chlorpheniramine, and brompheniramine were present. The toxicology lab has the ability to detect clemastine, hydroxyzine, tripolidine, azelastine, levocetirizine, and desloratadine, but these substances were not detected in any of the screenings for this study. Olapatidine is not currently in the screen libraries and would not be identified. If a medication was found on the screening but below the cut-off standard, it might have been noted internally but would not have appeared on a final report and was considered a negative finding for the purpose of this study. Cetirizine, loratadine, and fexofenadine were the medications present in the combined category of second- and third-generation antihistamines. If specimens were not received for

testing or are found to be inadequate, the results would be reported as not performed or not collected. CAMI receives samples from approximately 90% of fatally injured pilots and around 98% of specimens the lab receives are adequate for testing.

We constructed two count-based regression models to represent the two categories of antihistamines as independent variables. In our models, the independent variables representing first- and second-/third-generation antihistamines were AntiHistGen1 and AntiHistGen2_3, respectively. We linked these count-based outcomes to factors known at the time of the fatal mishap. That is, these two models were initially identical to one another in terms of model covariates but differed in their dependent variables representing the two different categories of antihistamines. These factors included instrument meteorological conditions (IMC) and dark night conditions, whether the pilot was instrument rated (Instrument), the number of flight hours the pilot reported on his or her medical application over the previous 6 mo (Recent Experience), the time of the mishap (Accident Time), the year (Year), the quarter of the year of the mishap (Quarter), and whether the mishap took place in a "North" or "South" region (Region) of the country. It was also reasonable to check for interactions between instrument meteorological conditions (IMC), Dark Night conditions, and number of flight hours reported by the airman over the preceding six months (Recent Experience) as well as IMC and Region.

Due to the low prevalence of the outcome (a positive antihistamine finding) a count-based model was selected for both regression models. A count-based model, such as one based on the Poisson distribution, can account for rare outcomes such as those found with aircraft mishaps. The Poisson distribution is known as the "Law of Small Numbers" for this reason.

IMC was a binary variable coded as a 1 if the NTSB report mentioned instrument meteorological conditions and a 0 otherwise. This was determined using a text search for variants of the string "IMC" or "instrument meteorological conditions" from the NTSB Factual Report. The NTSB reports were manually reviewed in cases in which weather conditions were ambiguous. The time and date of the mishap along with the location, historical weather reports, astronomical tables of moonrise/moonset adjusted for latitude and longitude, phase of the moon, and statements in the NTSB reports were used to determine if dark night conditions prevailed at the mishap site and were coded as IMC. Instrument was a binary variable coded as a 1 if the mishap airman was instrument rated and a 0 otherwise.

Airmen reported the number of hours they had flown in the last 6 mo at the time of their application for an airman medical certificate on FAA Form 8500-8. This was considered as a measure of recent flight experience by individual airmen. This is strictly a self-reported number of flight hours and is not checked against the airman's logbook. The median number of flight hours reported by fatally injured airmen in the study time frame for the last 6 mo was 35 h. Recent Experience was given the value of 1 if the airman reported 35 or more hours; otherwise, it was noted as a 0 to represent less than 35 h.

The variable Year represented the government fiscal year of the mishap and ranged from 2009 through 2014. This variable ranged from October 1st of the previous year to September 30th of the current year. For example, the year 2009 would contain mishaps, which occurred between October 1, 2008, and September 30, 2009.

The variable Quarter represented the quarters of the calendar year and is coded with a 1, 2, 3, or 4 to represent the first (Jan. - Mar.), second (Apr. – Jun.), third (Jul. – Sep.) and fourth (Oct.- Dec.) quarters of the year, respectively. This variable was designed to represent the seasonal effect on numbers of mishaps with antihistamines.

We wanted to classify the numbers of fatal mishaps along the lines of Federal Aviation Administration (FAA) regions. The regions were consolidated into a single binary variable by their latitudes to determine whether there was a geographic effect. Region was a dichotomous variable coded as 0 for Northern regions (FAA Regions Alaska, Northwest Mountain, Great Lakes, Eastern, and New England) and a 1 to represent southern latitude regions (FAA Regions Western Pacific, Southwest, Central, Southern, and Other, i.e., Puerto Rico).

The time of the mishap was classified into one of four categories (0001-0600 = 1; 0601-1200 = 2; 1201-1800 = 3; 1801-0000 = 4) and chronicled in the variable Accident Time. Another predictor in the Poisson model was the offset, or exposure, which does not have a regression coefficient to be estimated. The offset represents the denominator, or total number of airmen in a particular category or covariate pattern. The need to include this offset was to calculate incident rate ratios (IRR) within the Poisson regression model. The unit of our rates was in person-years. Our initial two Poisson regression model equations, including interaction terms, appeared as follows:

$$\begin{aligned} Log\left[Count\left(1^{\text{rst}}\,\text{Gen.Antihistamine}\right)\right] &= \beta_0 + \beta_1(\text{IMC}) \\ &+ \beta_2(\text{Instrument}) + \beta_3\left(\text{Recent Experience}\right) \\ &+ \beta_4(\text{Quarter}) + \beta_5\left(\text{Accident Time}\right) \\ &+ \beta_6\left(\text{Region}\right) + \beta_7(\text{Year}) \\ &+ \beta_8\left(\text{IMC*Recent Experience}\right) \\ &+ \beta_9\left(\text{IMC*Region}\right) + Log\left(\text{Offset}\right) \end{aligned} \qquad \text{Eq. 1}$$

$$\begin{aligned} Log\left[Count\left(2^{\text{nd}}\,\text{or}\,3^{\text{rd}}\,\text{Gen.Antihistamine}\right)\right] \\ = \beta_0 + \beta_1(\text{IMC}) + \beta_2(\text{Instrument}) \\ + \beta_3\left(\text{Recent Experience}\right) \\ + \beta_4(\text{Quarter}) + \beta_5\left(\text{Accident Time}\right) \\ + \beta_6\left(\text{Region}\right) + \beta_7(\text{Year}) \\ + \beta_8\left(\text{IMC * Recent Experience}\right) \\ + \beta_9\left(\text{IMC * Region}\right) + Log\left(\text{Offset}\right) \end{aligned} \qquad \text{Eq. 2}$$

Descriptive statistics including the minimum, maximum, median, and the standard deviation were included for the

dependent variables. The Poisson distribution can be defined in terms of a single parameter (λ), representing the event rate, as:

$$f(\mathrm{k};\lambda)=\frac{e^{-\lambda}\lambda^{k}}{k!},\quad k=0,1,2,\ldots\ldots$$

In addition to data independence, one of the fundamental assumptions in Poisson regression is that the mean and variance were equal; that is $\lambda = \mu$ is a necessary condition for producing valid standard errors for the regression coefficients. Although the data did not appear to be overly dispersed, we scaled the standard errors with Pearson's Chi-Square statistic divided by the degrees of freedom.

Each of the two regression models was assessed with all terms in the model removing the least significant covariates and then running the model again. That is, we began with all terms in the model and removed the least significant covariate after each iteration, starting with interaction terms before moving on to the main effects. All analyses were performed in Statistical Analysis Software (SAS) version 9.4. The level of significance for all tests was set at an alpha of 0.10 (α).

The statistical power of the Poisson regression models described in Eq. 1 and 2 were dependent on a number of factors including the significance level and effect size. Initially, we desired to have statistical power at 80% for an effect size involving at least a 10% difference in the ratio of incidence rates. Our power calculations were based on the work by Signorini.[18] At a significance level (α) of 0.05 and using an incidence rate ratio of 1.08 (8% difference) as an effect size, then with a sample size of 1475 cases, we have an estimated statistical power of 84%. In terms of statistical power and effect size, we considered the model viable.

RESULTS

The assumption of equal mean and variances was examined for both regression models. The means and variances were found to be very close for both regression models, supporting the assumption that the data follow a Poisson distribution (**Table I**); first-generation antihistamine mishap airmen ($N = 582$, $M = 0.17$, $S^2 = 0.17$) and for second- and third-generation antihistamine mishap airmen ($N = 116$, $M = 0.20$, $S^2 = 0.18$).

Table I. Poisson Regression Results for First-Generation Antihistamines.

PARAMETER	ESTIMATE	STANDARD ERROR	90% CONFIDENCE LIMITS		WALD CHI- SQUARE	*P*-VALUE	INCIDENT RATE RATIO (IRR)	90% IRR CONFIDENCE LIMITS	
Instrument Meteorological Condition									
IMC (Reference*) vs. No IMC	0.1075	0.1270	-0.1014	0.3164	0.72	0.3973			
Recent Experience									
< 35 h (Reference) vs. ≥ 35 h	0.1352	0.0969	-0.0242	0.2945	1.95	0.1629			
Instrument									
Instrument Rating (Reference) vs. No Instrument Rating	0.4351	0.1440	0.1983	0.6719	9.14	0.0025	**1.5451**	1.2192	1.9581
Quarter									
First (Reference) vs. Second	1.0307	0.3184	0.5069	1.5544	10.48	0.0012	**2.8030**	1.6601	4.7326
First (Reference) vs. Third	1.2220	0.3050	0.7202	1.7238	16.05	<0.0001	**3.3940**	2.0550	5.6054
First (Reference) vs. Fourth	1.2845	0.3169	0.7632	1.8057	16.43	<0.0001	**3.6129**	2.1451	6.0848
Region									
Northern (Reference) vs. Southern	0.3630	0.1727	0.0790	0.6470	4.42	0.0355	**1.4376**	1.0821	1.9100
Year									
2009 (Reference) vs. 2010	0.0099	0.4296	-0.6968	0.7166	0.00	0.9815			
2009 (Reference) vs. 2011	0.0147	0.4231	-0.6812	0.7106	0.00	0.9723			
2009 (Reference) vs. 2012	-0.0641	0.4427	-0.7924	0.6641	0.02	0.8848			
2009 (Reference) vs. 2013	0.1407	0.4420	-0.5863	0.8677	0.10	0.7502			
2009 (Reference) vs. 2014	0.1765	0.4166	-0.5088	0.8618	0.18	0.6718			

* The reference group is the group to which all other categories were compared.

Table II. Poisson Regression Results for Second- and Third-Generation Antihistamines.

PARAMETER	ESTIMATE	STANDARD ERROR	90% CONFIDENCE LIMITS		WALD CHI- SQUARE	*P*-VALUE
Recent Experience						
< 35 h (Reference*) vs. ≥ 35 h	-0.2050	0.2001	-0.5341	0.1242	1.05	0.3057
Accident Time						
0001-0600 (Reference) vs. 0601-1200	-0.5556	1.0804	-2.3327	1.2215	0.26	0.6071
0001-0600 (Reference) vs. 1201-1800	-0.5893	1.0519	-2.3196	1.1410	0.31	0.5753
0001-0600 (Reference) vs. 1801-0000	-0.2432	1.0853	-2.024	1.5421	0.05	0.8227
Instrument						
Instrument Rating (Reference) vs. No Instrument Rating	-0.1280	0.1969	-0.4519	0.1958	0.42	0.5155
Quarter						
First (Reference) vs. Second	0.2065	0.4962	-0.6096	1.0226	0.17	0.6773
First (Reference) vs. Third	-0.6089	0.5393	-1.4961	0.2782	1.27	0.2589
First (Reference) vs. Fourth	-0.6671	0.6493	-1.7351	0.4009	1.06	0.3042
Region						
Northern (Reference) vs. Southern	0.0839	0.2173	-0.2734	0.4413	0.15	0.6993

* The reference group is the group to which all other categories were compared.

In the model of second- and third-generation antihistamines there was a lack of observations for the covariates of Year and IMC. That is, the years 2009 and 2010 had no observations of second- and third-generation antihistamines. IMC had one observation out of the 23 total of second- and third-generation positive findings. It is for these reasons that Year and IMC were removed from the second- and third-generation of antihistamine model. Results are presented in **Table II**.

It simply was not clear whether any statistically significant association concerning these covariates was in fact real or due to low numbers of positive findings for second- and third-generation antihistamines. There were 23 cases that tested positive for a second- or third-generation antihistamine while 97 cases tested positive for a first-generation antihistamine. Descriptive frequencies for both models are given in **Table III**.

The numbers reported for 2009 are lower than for the other years in the study. The discrepancy in 2009 is due to the time lag in recording the mishap data in MANTRA for Fiscal Year 2009. MANTRA did not go online as on operational system until well into the 2009 fiscal year. As a result, records were entered into the system as they were received for fiscal years 2010, 2011, 2012, 2013, and 2014, but not for 2009. The autopsy team entered the back-log of records from 2009 as time permitted. At the time these data were extracted, the data restoration for FY 2009 was not yet complete. We decided to use the available records as they were deemed to be an unbiased sample from fiscal year 2009.

Examining counts of fatally injured aviators with positive findings of a first-generation antihistamine, we found that only the covariates Instrument, Quarter, and Region were statistically significant. Fatally injured pilots without an instrument rating were 55% more likely to be found positive for a first-generation antihistamine than pilots with an instrument rating.

Table III. Distribution of Frequencies of Antihistamines.

	ANTIHISTAMINE FINDING			
	FIRST-GENERATION		SECOND-/THIRD-GENERATION	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Instrument Meteorological Condition				
IMC	15	190	1	204
No IMC	82	1188	22	1248
Instrument				
Rated	40	737	10	767
Not Rated	57	641	13	685
Recent Experience				
< 35 h	46	685	14	717
≥ 35 h	51	693	9	735
Accident Time				
0001-0600	2	45	1	46
0601-1200	30	403	6	427
1201-1800	47	656	10	693
1801-2400	18	274	6	286
Quarter of Accident				
First	6	252	5	253
Second	24	350	9	365
Third	42	501	6	537
Fourth	25	275	3	297
Region				
North	21	385	7	399
South	76	993	16	1053
Year				
2009	9	115	0	124
2010	17	260	0	277
2011	19	278	5	292
2012	15	251	5	261
2013	16	220	6	230
2014	21	254	7	268

There were five cases that tested positive for both first- and second-/third-generation antihistamines. The NTSB numbers for these cases were ERA13FA133, WPR14FA182, CEN12FA638, ERA12FA008, and CEN14FA004 (www.ntsb.gov).

These cases were identified in the event there was an interest in examining the specifics of these accidents. These cases were included in each of the models as part of the dependent variable.

There was no association between the covariates and dependent variable. Analysis and interpretation of the risk results were accomplished by examination of the incident rate ratios.

In our model examining counts of fatally injured aviators with positive findings of a second- or third-generation antihistamine, we removed the covariates Year and IMC from the model due to low numbers of observations found with positive antihistamine outcomes (Table II). If left in the model, Year and IMC would be found to be statistically significant but it is unknown if this effect is true or related to a lack of observations. Of the remaining model terms, there were no statistically significant covariates.

When we examined Region, we found that fatally injured pilots in the Southern Region were 44% more likely to be found positive for a first-generation antihistamine than those in the Northern Region.

DISCUSSION

In this study, we used Poisson Regression to examine the relationships between the uses of different generations of antihistamines with factors associated with mishaps among fatally injured pilots. These factors were selected as being descriptive of dark night or obscured weather conditions. We used two regression models, which were identical in the covariates examined, but differed in the generation of antihistamines used as the dependent variable. In the first model, counts of mishap airmen who tested positive for first-generation antihistamines were used as the dependent variable. In the second model, counts of mishap airmen who tested positive for a second- or third-generation antihistamine were used as the dependent variable.

The finding that fatally injured pilots without an instrument rating were more likely to be found positive for a first-generation antihistamine than pilots with an instrument rating raises a number of questions. Although the cause of this disparity is unknown, it may be due to the protective effect of additional training. Instrument rated pilots are arguably more able to ignore feelings of disequilibrium and rely on the instruments for aircraft control. Experienced instrument rated pilots may also be aware of the sedating and disorienting effects of certain antihistamines and elect to abstain from usage prior to flight. There also could be effects from the additional training and experience of the typical instrument rated pilot. Future research is warranted to evaluate these factors.

When considering the finding that there were more mishaps in the Southern than in the Northern Region, it is possible that this is an artifact of population density and the small number of mishaps that occurred in the north central United States.

In summary, the data indicate fewer airmen with second- and third-generation antihistamines than first-generation antihistamines in their system are fatally injured while flying in IMC conditions. While these results are encouraging, these results are not definitive. Whether the lower incidence is a factor of greater usage of first-generation antihistamines vs. second- and third-generation antihistamines by the pilot population in general or a direct result of fewer deleterious side effects with second- and third-generation antihistamines is a difficult question to answer. The higher incidence of fatal mishaps with first-generation antihistamines present may also be an artifact of pilots using them as sleep aids because of their low cost and availability. The failure of the combined second- and third-generation antihistamines results to reach significance may be due to the low number of positive findings of these drugs (23 total observations) and leads to a conservative conclusion from this analysis. Without verifiable statistics on the usage of the various generations of antihistamines, interpretations of the findings are subject to potential base rate biases and must be interpreted carefully. These results engender cautious optimism, but additional evidence is necessary to determine why these differences exist.

Appendix A. The NTSB and CAMI Accident Identification Numbers.

NTSB NUMBER	CAMI ACCIDENT ID
CEN12FA088	112911LA01×
WPR14FA132	030914NV01×
CEN12NA222	040212WI01×
ERA10FAMS1	121509FL01×
ERA09LA325	060609TN01×
ERA09LA398	071109FL01×
ERA09LA527	091909SC01×
CEN10FA316	061310AR01×
CEN10LA491	082210MN01×

Nine cases were removed because of either insufficient information as to the weather or the circumstances surrounding the mishap.

ACKNOWLEDGMENTS

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