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Death as a Drug Side Effect in FAERS: Is Glyphosate Contamination a Factor?

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Abstract

An analysis of selected datasets from the FDA's drug Adverse Event Reporting System (FAERS) leads us to hypothesize that glyphosate contamination in both food and drugs is a major contributor to chronic and acute kidney failure respectively. In chronic kidney failure, glyphosate-induced pancreatitis results in the release of trypsin, causing a leaky vasculature. The albumin-bound glyphosate escapes into the tissues, protecting the circulatory system and kidneys but resulting in multiple symptoms related to skin, gut, brain, bones, lungs, etc. The rare and poorly understood acute kidney failure response reported for protamine sulfate and Trasylol® is strikingly similar to that associated with glyphosate poisoning. Both drugs are derived from biological tissues that are plausibly contaminated with glyphosate. These drugs protect from haemorrhage, which leads to retention of glyphosate in the vasculature, are followed by circulatory collapse and a high likelihood of death as an outcome. We support our argument by comparing symptom profiles of selected subsets of FAERS with those related to glyphosate poisoning, anomalous reactions to protamine sulfate, and conditions showing strong statistical time-trend correlations with glyphosate.

Keywords

Drug Side Effects, Drug Contamination, Renal Failure, Glyphosate, Pancreatitis, Osteonecrosis, Protamine Sulfate, Aprotinin, Oedema

1. Introduction

Adverse drug reactions are common among intravenous medications, especially those administered to intensive care unit (ICU) patients [1]. The incidence of serious and even fatal adverse drug reactions in hospitals in the US

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is extremely high. An estimate from data in 1994 suggested that adverse reactions were between the fourth and sixth leading cause of death [2].

The US Food and Drug Administration's (FDA's) Adverse Event Reporting System (FAERS) database is a large collection of drug side effect reports dating back to 2004. While it contains a wealth of information, it is difficult to tease out from the data the cause-and-effect relationships. This is mainly because most of the entries contain multiple drugs and multiple side effects, and some of the drugs are long-term maintenance drugs that may be irrelevant to the event. Furthermore, many of the side effects mentioned are likely preconditions such as diabetes or heart disease, which are probably provided to give additional useful information about the patient, but unfortunately they contribute noise to the task of sorting out cause-and-effect relationships.

Given these caveats, we report here on our attempts to critically analyze a specific subset of FAERS, focusing on an important side effect that is undeniably not a precondition: death. Doctors must be able to rely on pharmaceutical purity of drugs. When dealing with complex, unanticipated and inexplicable patient responses to pharmaceutical drugs, doctors need to be aware that the response may not be due to the drug itself, but rather to an inadvertently included contaminant. When drugs are contaminated with unknown harmful ingredients, it may take time for doctors to realize this and recognize the underlying problem. Analyzing drug side effects statistically is one way to begin to explore the possibility of drug contaminations. In this paper, we offer an explanation for an unusual and acute, life-threatening, adverse reaction to certain biological drugs derived from animal products that we believe may be due to unintended contaminants.

Our broadly specified goals are to establish which drugs are most strongly linked to death as an outcome, as well as which other symptoms co-occur with death, and then to try to explain our results by linking them to previous studies in the research literature. Our quest has yielded a most surprising hypothesis: certain biological drugs may carry a high risk of death due to contamination with glyphosate, the active ingredient in the pervasive herbicide, Roundup®. Furthermore, we believe we have identified a class of patients suffering from chronic kidney disease who statistically and collectively exhibit a profile of symptoms that can be explained as a consequence of chronic exposure to glyphosate in the ingested food and water. Our hypothesis is based, in part, on the increasing amounts of glyphosate found in food, air [3] [4], rain [3] [5], groundwater [5], surface water [4]-[6], soil [5], seawater [7], human serum [8] and urine [9], and even in samples of marijuana [10]. Formal testing of the suspected drugs and ingested foods for glyphosate contamination can and should be done to validate our hypothesis.

We gathered as our first set all the data in FAERS where DEATH was mentioned as a side effect. We then identified the top ten other side effects co-occurring with death. We constructed a second, larger subset of the database by extracting all the entries where at least one of these side effects was mentioned (with or without death). This gives us a contextualized larger population with key symptoms associated with DEATH as a side effect. We then used a formal, mathematical procedure to obtain a short list of drugs most strongly linked to death within this subset population. This allowed us to compare the pooled subsets of our database with and without these particular drugs, and to see which other symptoms occur most frequently in association with the 9 drug classes we identified as potential "High-Death-Association drugs" (HDA DRUGS).

The list of HDA DRUGS was surprising. One noteworthy aspect is that many of them were biologicals derived from animal tissues, such as bovine lung or sturgeon testes, or from blood. This led to the realization that contaminants could be present due to the animals' exposure to certain toxic chemicals. Since we were aware that glyphosate is pervasive in our environment today, we formulated the hypothesis that severe reactions to these biological drugs could be due to contamination with glyphosate. Exploration of the research literature led us to specific papers where lists of side effects were provided for conditions we suspected to be relevant to our hypothesis. We could then systematically compare the side effects associated with our candidate HDA DRUGS and the reactions reported in these papers.

Manufacturers of drugs are aware that unintended contamination through the manufacturing process is a serious issue. Flaum summarized the situation aptly in a review article on this subject: "In fact, the types of contaminants, their relative hazard to human health, the sources of contamination, and the methods for prevention and detection of such contamination are so varied and numerous as almost to defy compilation" ([11], p. 1). For example, in March of 2015, a subsidiary of Johnson & Johnson agreed to pay $25 million in damages due to the discovery of nickel and cadmium contamination in liquid Tylenol® products intended for infants. This is not an isolated occurrence, as a Reuters' press release concerning this story reported: "There were far-reaching multiple recalls from 2008 to 2010 involving hundreds of millions of bottles and packages of consumer brands such as

Tylenol, Motrin, Rolaids, Benadryl and other products due to faulty manufacturing" [12].

The single drug most strongly linked to death in the FAERS database is Trasylol®, a serine protease inhibitor extracted from bovine lung that is used to protect from haemorrhage during open heart surgery. Red blood cells and protamine sulfate, used to neutralize heparin, were also strongly linked to death in our data analysis. A paper published in 1987 [13] brought the exciting news that aprotinin (Trasylol®) administered during cardiac surgery could reduce the need for transfusions by a factor of eight. Aprotinin was approved by the FDA in 1993 to reduce blood loss during coronary-artery bypass grafting [14]. Aprotinin was widely adopted for this purpose over the following years, but by 2008 it was becoming clear that aprotinin could cause an acute reaction terminating in kidney failure and death [15]-[18]. The FDA took action that year to remove aprotinin from the market, but it was later reinstated.

In an observational study published in 2006, involving 4374 patients, use of aprotinin was associated with twice the risk of renal failure requiring dialysis, a 55% increase in the risk of myocardial infarction or heart failure, and a 181% increase in risk of stroke or encephalopathy [15]. Strikingly, this increased risk was not found in association with tranexamic acid or aminocaprioc acid, two other drugs used similarly to prevent haemorrhage.

An analysis of 8548 patients published in 2008 found a lack of a dose-response relationship between aprotinin and renal failure [19], which can be explained by varying levels of glyphosate contamination in the administered drug. In 2008, Fergusson *et al*. [20] compared aprotinin with another antifibrinolytic agent, aminocaproic acid, and found a greater than 50% relative increase for death within the first month linked to aprotinin. The abstract concluded with these harsh words: "Despite the possibility of a modest reduction in the risk of massive bleeding, the strong and consistent negative mortality trend associated with aprotinin, as compared with the lysine analogues, precludes its use in high-risk cardiac surgery".

In contradiction, a meta-analysis of 211 randomized controlled trials published in 2004 showed no risk of renal failure or death [21], but this was representing early data before the large increase in the potential of glyphosate contamination. A much later study from 2011 found nearly a 4-fold increase in odds of death one year later for patients administered aprotinin compared to no aprotinin use [22]. So it appears that the risk of death following aprotinin administration is increasing over time, in step with the increased contamination of glyphosate in animal feed. The Environmental Protection Agency (EPA) currently allows between 100 - 300 ppm of glyphosate residues in livestock feed [23]. In 2014, Kruger *et al*. reported finding 30 ppb of glyphosate residues in bovine lung tissue [9].

Protamine sulfate was the third most strongly associated with death, after "red blood cells" and Trasylol®. In a case study on protamine sulfate, a rare, unexplained, anomalous reaction was identified that matched well with the symptoms linked to death. We again hypothesized that glyphosate contamination might explain the acute reaction. Protamine sulfate is administered as an antidote to heparin therapy following surgery, to inactivate the heparin and protect from haemorrhage. It was originally isolated from the sperm of salmon and sturgeon, but is now produced primarily through recombinant biotechnology. Like aprotinin, protamine sulfate has also been found to produce an inexplicable acute response in rare cases, manifested as a drop in blood pressure, pulmonary hypertension and noncardiac pulmonary oedema with cardiopulmonary collapse [24]. The severity of the reaction is not dose-related.

Holland *et al*. reported in 1984 on four unusual cases of an anomalous reaction to protamine sulfate [25]. These four represented only 0.2% of the patient pool exposed to the drug in their population, but their reaction was uniquely different from the usual anaphylaxis due to an antibody-mediated response, well recognized as a risk factor in association with this drug. While protamine sulfate was known to sometimes evoke an allergic reaction, an autoimmune reaction was ruled out for these four cases. Symptoms involved a drop in blood pressure within the first hour following administration associated with profound vascular damage with pulmonary oedema or total vascular collapse. Mortality is high at 30%, with survivors suffering significant morbidity. What is striking to us is that intravenous administration of glyphosate salts to piglets induced a very similar reaction, with a precipitous drop in blood pressure within the first hour and high mortality rate [26]. These symptoms are also remarkably similar to those of acute glyphosate poisoning. We therefore identified a set of symptoms linked to glyphosate exposure following suicide attempts [27], and showed that these symptoms were over-represented in our death-related dataset.

A very fruitful avenue of exploration was to look specifically at the side effects related to kidney failure, which was the number two (after PAIN) side effect coincident with DEATH. Kidney failure is reaching epi-

demic proportions worldwide, and kidney failure has been strongly linked to glyphosate exposure among agricultural workers in Sri Lanka [28], where glyphosate is currently banned from usage on crops for this reason. We hypothesized that the American population with chronic kidney failure had a high likelihood of having experienced chronic exposure to glyphosate during their lifetime. By subselecting for oedema along with conditions relating to the skin and gut, we were able to obtain a subpopulation with kidney failure that also exhibited characteristic symptoms of adrenal insufficiency. Adrenal insufficiency has recently been linked to low-dose glyphosate exposure [29].

Remarkably, the remaining group with kidney failure but without evidence of adrenal insufficiency has a much higher chance of dying. The two drugs that are most strongly linked to death, Trasylol® and protamine sulfate, are also strongly biased towards the group without the symptoms of adrenal insufficiency. We hypothesize that these drugs interact with glyphosate by interfering with the body's ability to export the toxic chemical into the tissues via oedema, so as to ultimately eliminate it through the skin or the gut. Instead, glyphosate accumulates in the terminal watershed of the kidneys and brain stem, leading to a characteristic set of mood-disorder symptoms along with acute kidney toxicity, and vascular failure.

Glyphosate is by far the most-used herbicide in the United States today. The use of glyphosate on corn and soy crops has risen steadily in the US following the rise in the adoption of Roundup®-Ready (RR) seeds, first introduced in the mid 1990s [30], as well as the increasingly popular practice of desiccation with Roundup® right before the harvest, for crops such as sugar cane, grains (especially wheat) and legumes. The increased usage was compounded by the emergence of multiple glyphosate-resistant weeds following the adoption of RR crops [31]. Recently, Swanson *et al.* [32] published a list of disorders that were rising in step with glyphosate usage on corn and soy crops. We compared those disorders with the two classes of kidney failure events and found that most of these were significantly over-represented in the kidney failure group that included the adrenal insufficiency symptoms.

Today, we face a crisis which is precipitating rapid regulatory approval of mixed herbicides containing two active ingredients, such as glyphosate and 2,4-D or glyphosate and dicamba. This parallels the development of stacked GM crops that harbor resistance to both herbicides. While Monsanto, the inventor of glyphosate, maintains that it is nontoxic to humans, recent evidence has caused the WHO to relabel glyphosate as a "probable carcinogen" in March of 2015 [33]. Multiple biological explanations for how glyphosate could cause cancer are presented in [34].

2. Materials and Methods

FAERS, containing information on both adverse events and medication errors, is a central part of the FDA's post-marketing safety surveillance program for drugs and biological products. The system is voluntary for healthcare professionals and consumers, but mandatory for regulated industry and user facilities. The data are made available on the Web for free download. Each report is a structured entry containing the date of the incident, the age, gender and race of the person, a list of drugs that were taken and a list of side effects that were experienced. It is widely acknowledged that spontaneous reporting systems substantially under-represent the actual number of cases of adverse reactions that occur, estimated at only 6% of actual events [35].

In this work, we have utilized data sets ranging from 2004 to 2012. Our methods are based on a multi-step procedure as outlined in **Figure 1**. Our goal is to first identify which drugs are most likely linked to death based on death being reported as a side effect. We then attempt to explain the biological link between those particular drugs and death, in part through identifying the other symptoms that co-occur with the drugs which are linked to death.

We began by extracting from the FAERS database all of the records where "DEATH" is a symptom. We then tabulated the number of times symptoms other than death were reported in this dataset, and selected the top-10 most frequent side effects as our focus. We then returned to the database and extracted all cases where at least one of these top-10 symptoms occurred, with or without death. In this way, we obtained a dataset with enrichment in death as a side effect along with death-related symptoms.

Our next step was to determine which drugs co-occur with death. This task is made more difficult because there are many drug classes with multiple drugs available within the class, such that the frequency of any one of those drugs might be small, but collectively they could become a major factor. We began by finding the top 15 single drugs co-occurring with each of our ten side effects. We pooled these drug lists as a guide to formulate

drug classes, and manually produced a set of 34 distinct drug classes, as illustrated in **Table 1**. We used a web search to identify the major drug names associated with each of the classes. The full list of drugs (a total of 267 distinct drug names) is available online for download from http://people.csail.mit.edu/seneff/DRUG_CLASSES.txt.

Based on this list, we now needed a mechanism to score these drug classes for their potential to induce death. We took our subset of pooled data from our top symptoms linked to death and then divided it into two subsets: those with death as a co-occurring side effect ("DEATH" subset), and the remainder ("NOT DEATH" subset). We computed a score for the bias in the distribution of each drug class between the "DEATH" and "NOT DEATH" subsets. The score we chose will be used throughout this paper to assess biases between different subsets of the data, for both drugs and symptoms.

Let F1 = Count1/N1 = Frequency of drug-class or symptom in subset 1 (target).

Let F2 = Count2/N2 = Frequency of drug-class or symptom in subset 2 (comparison).

$$\text{Score} = 1000 * \left(F1 / \left(F1 + F2 \right) \right) \quad (1)$$

The score ranges from 0 to 1000, with 500 denoting that a drug or symptom occurs with equal frequency in the two datasets. Any score over 800 is highly skewed towards the target set: 800 means that the drug or symptom is four times more frequent in the target score set than in the comparison set (e.g., F1 = 4*F2). Armed with this method, it was then possible to define a lower cutoff for the score and focus on all the drugs that exceeded this cutoff, which we now label as "High-Death-Association (HDA) DRUGS". Having identified the drugs of interest, we could then re-sort our entire data set into two new subsets: one containing all the events where at least one of our drugs of interest was mentioned, and the other containing the events where none were mentioned.

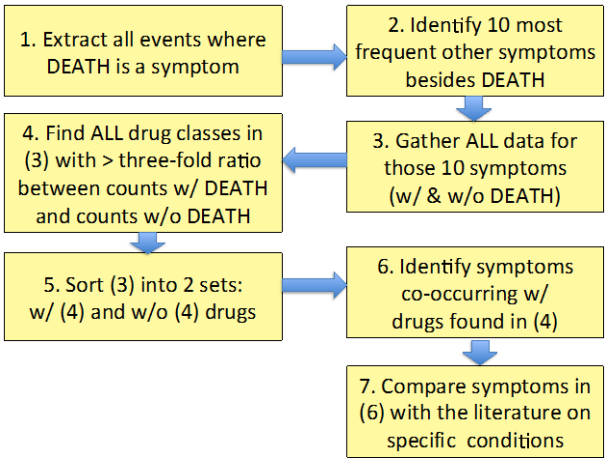

Figure 1. Block diagram of our analysis procedures. See text for details.

Table 1. List of representative drug names for the drug classes we investigated in this paper.

ACE INHIBITORS	ALBUMIN	ASPIRIN	ATENOLOL
AVASTIN	BONIVA	NORVASC	CELEXA
CIPRO	COUMADIN	ERYTHROPOIETIN	GLEEVEC
HEPARIN	HIRUDIN	HUMIRA	LASIX
LIPITOR	MORPHINE	METOCLOPRAMIDE	METHOTREXATE
NEXIUM	NITROGLYCERIN	NSAID	PREDNISONE
PROTAMINE SULFATE	RED BLOOD CELLS	TRASYLOL	TYLENOL
PLATELETS	VANCOMYCIN	VERSED	VIOXX
YAZ	VITAMIN A		

The formula we used to select drugs can just as well be used to select symptoms. We can characterize each symptom by a score reflecting its degree of bias towards the HDA DRUGS. This provides a set of symptoms characterizing these drugs. We quantify as a significant result for our discovered symptoms anything which surpasses a 95% confidence interval (CI). Given that our two datasets are of fixed size, it is easy to determine the 95% CI for each frequency count, and from this we can define the minimum count required in the target dataset to assure 95% CI at a given score (from 500 to 1000).

Our targeted dataset of events linked to death-related drugs contained 43,434 entries, with 775,377 entries in the contrastive dataset without those drugs. A chart, presented in **Table 2**, shows the minimum count required in the target set for each score, over the range from 530 to 675. To compute scores that correspond to non-overlapping frequency distributions in the two datasets, at the 95% confidence interval level, we started with a fixed count for Count1, e.g., 20, and calculated the 95% interval based on the size of dataset 1. We then varied Count2 until its 95% interval was close to, but did not overlap with the interval of Count1. We then calculated the score from these two counts, and defined this as the minimum score for 95% CI for Count1 = 20. The process was repeated for higher numbers of Count 1. Results are shown in **Table 2** over the range from 530 to 675. Since we have discarded any symptoms with a count less than 20 in our target set, due to expected sparse data issues, any score over 675 is automatically significant at the 95% CI level.

An investigation of the research literature can help us define a unique "death syndrome" based on our symptom profile. Our final processing step is to compare symptoms found in association with various health conditions in the research literature with the symptoms we have identified as "death-drug related." We have hypothesized that glyphosate contamination in the drug is a major factor in a substantial percentage of the acute reactions leading to DEATH as a side effect. We further hypothesize that synergistic toxicity between certain drugs and glyphosate plays an important role. We explain our reasoning for this hypothesis, along with support from the research literature, in the Discussion section.

3. Results

Our results will be illustrated in a series of tables, beginning with the table that lists the set of drug classes we chose to investigate (see **Table 1**). These include the popular maintenance drug classes such as statin drugs, blood pressure control drugs, and blood thinning drugs, as well as ERYTHROPOIETIN to stimulate red blood cell production, and drugs to treat acid reflux (NEXIUM), or cancer (GLEEVEC), depression (CELEXA), bone density loss (BONIVA), pain (MORPHINE), hormone therapy (YAZ), or inflammation (NSAID). It also includes some unusual and surprising "drugs" such as "RED BLOOD CELLS" and "PLATELETS." We would not have thought to include these if not for the evidence revealed by our investigations of the most frequent drugs mentioned in our top-10 diseases.

Table 3 lists the top-10 side effects that co-occurred with death in the FAERS database. There are anticipated conditions linked to brain, heart and kidney problems. The list includes three mood-related disorders: "FEAR", "ANXIETY", and "ANHEDONIA". "PAIN" is generally associated with disease, and therefore perhaps not unexpected. "UNEVALUABLE EVENT" is an interesting but vague symptom tag, and we explore this symptom class more fully at the end of this section.

3.1. High-Death-Rate (HDR) DRUGS

Table 4 lists the 9 drug classes that had scores over 750, the cut-off point that we used to select the candidate

Table 2. Table specifying counts required to gain 95% confidence intervals for the scores presented in the tables providing data on frequency distributions for counts in the "death-related drugs" events compared to the "not death-related drugs" events. The scores capture skewed distributions of each side effect over our contrastive datasets, computed as: 1000 * [frequency (Target)/(frequency (Target) + frequency (Control))]. A score of 1000 is the highest achievable score, indicating that all of the cases were in the Target set. With total counts of 43,434 entries in the Target set and 775,377 entries in the Comparison set, any score above 675 is automatically significant at the 95% confidence level (since we have a lower cutoff of 20 for the counts).

Count 1	>450	>270	>170	>75	>50	>35	>25	>20
95% CI on score	>530	>540	>550	>575	>600	>625	>650	>675

Table 3. Ten most frequent side effects co-occurring with death, along with their frequency counts for all cases, and for the subset of cases linked to death. The order is in decreasing frequency of association with death.

Side Effect	Total Count	Death Count
PAIN	105,243,992	6696
RENAL FAILURE	34,345,332	6118
INJURY	27,011,433	5975
ANXIETY	30,621,209	5748
MYOCARDIAL INFARCTION	23,866,542	5610
UNEVALUABLE EVENT	5,200,213	4340
FEAR	3,654,890	4083
CEREBROVASCULAR ACCIDENT	16,338,461	4019
ANHEDONIA	5,133,355	3793
RENAL IMPAIRMENT	5,559,612	3778

Table 4. Nine "death-related" drug classes ("HDA DRUGS"), with average scores for over-representation in the "DEATH" subset above 750 (more than three times more frequent in the DEATH subset).

Drug Aliases	Score
TRASYLOL; APROTININ	925
RED BLOOD CELLS	908
PROTAMINE SULFATE	903
PLATELETS; PLATELET TRANSFUSION	902
ALBUMIN	881
VERSED; MIDAZOLAM; DORMICUM; HYPNOVEL	872
HEPARIN; ENOXAPARIN; DALTEPARIN; TINZAPARIN	831
VANCOMYCIN; VANCOCIN	826
NITROGLYCERIN; NITROSTAT	777

death-related drugs. A score of 750 means that the drug is three times as common in the DEATH subset compared to the NOT-DEATH subset. The set of drug classes that made the cut was unexpected. The worst-scoring drug was TRASYLOL, a bovine pancreatic trypsin inhibitor, commonly used to reduce bleeding during surgery. As described in the Introduction, it has had a checkered history, and was suspended beginning in May of 2008 [36], but the suspension was lifted in 2012. PLATELETS, RED BLOOD CELLS, and PROTAMINE SULFATE all scored over 900, which was very surprising, considering that these are all biologicals. ALBUMIN, which scored 881, like PLATELETS and RBCs, is a product of blood. It is normally produced by the liver and is one of the more abundant plasma proteins. VERSED is used to induce sedation before surgery, but also as a sleep aid and to treat epilepsy. VANCOMYCIN is an antibiotic used to treat bacterial infections. HEPARIN is a biological injectible anticoagulant, produced by mast cells. It is derived from mucosal tissues of slaughtered animals such as pig intestines or bovine lungs [37].

3.2. Symptom Profile

Once we had assigned a set of drugs to investigate, the next step was to determine which symptoms are significantly over-represented in the subset of our events where at least one of these drugs was administered. We identified a total of 1305 symptoms with a biased distribution predicting increased risk associated with the HDA

DRUGS, at the 95% CI level. This entire list is available for download from http://people.csail.mit.edu/seneff/symptoms_linked_to_HDA_drugs.csv. **Table 5** provides the most highly significant symptoms, namely, all those with more than 1000 counts and with a score greater than 720. As can be seen from the table, these symptoms can be grouped into five primary categories, aside from a miscellaneous set of six side effects, one of which is "DEATH". The blood-related category is likely linked to all the rest, reflecting multiple organ failures consequential to impaired blood flow following a catastrophic effect on the circulation. We hypothesize that hypotension, thrombocytopenia, sepsis, and haemorrhage are the initial response which quickly cascades into a multiple-organ crisis. "OSTEONECROSIS OF JAW", in the "OTHER" category, is completely unexpected, but it probably has high significance that needs to be explained.

3.3. Comparison between Trasylol® and the Remaining HDA DRUGS

Since Trasylol® was, with a wide margin, the drug that was most strongly associated with death (see **Table 4**), we thought it would be interesting to compare symptoms associated with Trasylol® with those associated with the remaining HDA DRUGS. There were 11,344 events where TRASYLOL was among the listed drugs, but none of the other HDA DRUGS were present. The number of events where ANY of the HDA DRUGS except TRASYLOL was present was 25,753. These two datasets were highly differentiated by their manifested symptoms. In fact, many of the symptoms associated with death identified in **Table 3** were highly skewed between the two datasets, in such a way that symptoms linked to the kidneys, mood disorders, and "other" (including

Table 5. Top scoring side effects linked to HDA DRUGS. This is an exhaustive list of all side effects with counts > 1000 and score > 720.

Side Effect	Count	Score	Side Effect	Count	Score
			Blood Related		
HYPOTENSION	3739	770	THROMBOCYTOPENIA	1698	785
SEPSIS	2073	773	GASTROINTESTINAL HAEMORRHAGE	1091	759
			Lung Disorders		
PLEURAL EFFUSION	1981	783	RESPIRATORY FAILURE	1991	793
ATELECTASIS	1085	795	PULMONARY OEDEMA	1086	763
			Heart Disease		
CARDIAC ARREST	1550	749	ATRIAL FIBRILLATION	2191	756
CARDIOMEGALY	1108	760			
			Kidney Disease		
RENAL INJURY	12900	992	RENAL IMPAIRMENT	12069	933
RENAL FAILURE	20359	879	RENAL FAILURE CHRONIC	1593	752
ORGAN FAILURE	1329	903	MULTI-ORGAN FAILURE	9425	968
			Mood Issues		
FEAR	14836	969	ANHEDONIA	12028	966
STRESS	10766	963	EMOTIONAL DISTRESS	13010	932
ANXIETY	18851	806	NERVOUSNESS	1336	756
			Other		
INJURY	17955	918	UNEVALUABLE EVENT	16579	950
PAIN	21497	786	OSTEONECROSIS OF JAW	1455	769
DEATH	9455	933	DISABILITY	1401	935

DEATH) aligned with TRASYLOL, and symptoms related to the vasculature, the lungs, and the heart aligned with the remaining HDA DRUGS (see **Table 6**).

3.4. Comparison to Anomalous Reaction to Protamine Sulfate

We previously described the rare, unusual reaction to protamine sulfate involving a precipitous drop in blood pressure over the first hour, and a high risk of death, which occurred in only 0.2% of the patient population [25]. These authors identified a specific set of symptoms that could be compared. **Table 7** shows the degree of alignment with our symptoms associated with HDA DRUGS (target dataset) and the ones they identified. Our data show significant over-representation of death, as well as symptoms related to pulmonary oedema, vascular damage, vascular collapse, ascites, hypotension, and wheezing, with less support for rashes and a poor match with angioedema.

3.5. Comparison to Attempted Suicide through Glyphosate Ingestion

Table 8 lists a set of symptoms that were identified in a review of 131 cases of attempted suicide by ingesting

Table 6. Comparisons between TRASYLOL (target dataset) and all the other HDA DRUGS (control dataset) with respect to the distributions of selected symptoms most likely to co-occur with death. C1: total number of TRASYLOL events; C2: total number of events with any combination of the other HDA DRUGS; SCORE: score reflecting bias towards TRASYLOL (1000: max), as defined in Equation (1).

Symptom	C1 (target)	C2 (control)	Score
Blood Related			
HYPOTENSION	72	3645	74
THROMBOCYTOPENIA	22	1673	50
SEPSIS	68	1986	122
Lung Disorders			
PLEURAL EFFUSION	37	1936	72
PULMONARY OEDEMA	37	1041	126
Heart Disease			
CARDIAC ARREST	80	1409	187
ATRIAL FIBRILLATION	52	2122	90
Kidney Disease			
RENAL INJURY	4580	49	997
RENAL IMPAIRMENT	3831	1252	925
MULTI-ORGAN FAILURE	2887	1096	914
Mood Issues			
FEAR	5170	183	991
ANHEDONIA	3676	928	941
EMOTIONAL DISTRESS	4491	1000	948
Other			
INJURY	5672	1987	920
UNEVALUABLE EVENT	5717	524	977
DEATH	2746	797	933

Table 7. Evidence from our study of FAERS that the target dataset of HDA DRUGS is associated with increased risk to several side effects that aligned with those observed in four unusual cases where protamine sulfate brought on an unexpected response [25]. The control dataset is all events in FAERS that do NOT include the HDA DRUGS. The values are an indicator of the skewed distribution of each side effect over our contrastive datasets, where the first number is the raw count in the target set and the second number is the score as defined in Equation (1). Key: * = Not significant to 95% confidence level; ** = Symptom is under-represented in target set.

Death					
death	9455	933	brain death	66	727
Pulmonary Oedema					
pulmonaryoedema	1086	763	acute pulmonary oedema	127	696
Vascular Damage					
vascular pseudoaneurysm	81	820	pulmonary vascular disorder	49	872
peripheral vascular disorder	465	743	cerebrovascular disorder	136	601
Vascular Collapse					
circulatory collapse	290	712	poor peripheral circulation	60	624
Ascites					
ascites	500	702			
Angioedema/Urticaria					
urticaria**	253	453	angioedema*	71	565
Hypotension					
hypotension	3739	770	orthostatic hypotension	181	625
Wheezing					
wheezing	524	745			
Rash					
exfoliative rash	41	762	rashmaculo-papular	140	691
drug rash with eosinophilia and systemic symptoms				140	757
rash pruritic	192	593	rash erythematous*	135	523
rash generalised**	92	450	rash*	1011	523
rash macular*	94	554	rashpapular**	58	484

glyphosate [27]. The table shows that these symptoms, for the most part, strongly fit the profile of our target dataset of HDA DRUG symptoms. Symptom classes include respiratory distress, renal failure, shock, altered consciousness, hyperkalaemia, hyperphosphataemia, lowered bicarbonate, pulmonary oedema, hypoxemia, leukocytosis, acidosis, and dysrrhythmia. The only opposing symptom was lactic acidosis which was underrepresented in the HDA DRUGS cases, but many other forms of acidosis were highly significantly positive, including "ACIDOSIS," "RESPIRATORY ACIDOSIS," and "METABOLIC ACIDOSIS." It should be noted that the minerals are highly unstable in association with HDA DRUGS, for example with significant over-representation of both "HYPEKALAEMIA" and "HYPOPHOSPHATAEMIA."

3.6. Renal Failure and Adrenal Insufficiency

Renal failure was the second most likely symptom associated with DEATH in the FAERS database (second to PAIN). According to Swanson *et al*. [32], death due to end stage renal disease ($R = 0.958$, $p \leq 4.2E\text{-}6$) and death due to acute renal failure ($R = 0.978$, $p \leq 5.95E\text{-}9$) are very strongly correlated in their temporal frequency

Table 8. Evidence from our study of FAERS that the target dataset of HDA DRUGS are strongly associated with side effects of attempted suicide by glyphosate ingestion (see **Table 3** of a review of 131 cases of attempted suicide by ingesting glyphosate [27]). These symptoms were indicators of poor patient outcomes. The score for the distribution of each side effect over our contrastive datasets is computed as defined in Equation (1). The first number in each pair represents the raw count in the target set, and the second number is the score.

Side Effect	Count	Score	Side Effect	Count	Score
Respiratory Distress Necessitating Intubation					
chronic respiratory failure	34	859	respiratory failure	1991	793
cardio-respiratory arrest	729	729	respiratory distress	646	793
acute respiratory failure	357	773			
Renal Failure Necessitating Hemodialysis					
postoperative renal failure	55	944	renal failure	20,359	879
renal failure chronic	1593	752	haemodialysis	555	672
Shock < (SBP < 90 mmHg)					
cardiogenic shock	721	855	shockhaemorrhagic	65	702
shock	485	742	septic shock	818	776
hypovolaemic shock*	45	579	anaphylactic shock*	55	514
Altered Consciousness					
depressed level of consciousness	411	624	coma	404	589
altered state of consciousness	117	599	loss of consciousness	891	526
Hyperkalemia/Hyperphosphatemia					
hyperkalaemia	730	658	hyperphosphataemia	63	775
Lowered bicarbonate					
blood bicarbonate decreased*	35	554			
Pulmonary Oedema/Hypoxemia					
pulmonaryoedema	1086	763	hypoxia	828	769
hypoxic-ischaemic encephalopathy	92	839			
Leukocytosis					
leukocytosis	613	766			
Acidosis					
respiratory acidosis	84	796	acidosis	198	713
diabetic ketoacidosis*	69	570	metabolic acidosis	635	709
lactic acidosis**	202	477			
Dysrhythmia					
sinus arrhythmia	75	748	tachyarrhythmia	56	671
ventricular arrhythmia	73	747	arrhythmia	722	587
arrhythmia supraventricular	46	693	bradyarrhythmia	28	664

Key: * = Not significant to 95% confidence level; ** = Symptom is under-represented in target set. Any unmarked symptoms were significantly over-represented in the Target set, some by a wide margin (no overlap at 99% CI).

curves with the trend upward in glyphosate usage on corn and soy crops. Therefore, we hypothesized that a subset of our database restricted to renal failure would provide a more specific signal of potential chronic or acute glyphosate exposure. There were 127,652 records in the database where renal failure was one of the side effects. We constructed a working hypothesis that chronic renal failure would be linked to chronic exposure to glyphosate prior to the side-effect event, and that acute renal failure might correspond with glyphosate contamination in the administered drug or a direct toxicity of the drug to the kidneys. We further hypothesized that oedema and blood pressure drop immediately following exposure to the drug represented a physiological response aimed to try to flush a toxic exposure out of the blood, likely as a mechanism to protect the terminal watershed (kidneys and brainstem) from further damage. We reasoned that the skin rashes and other skin issues could be a consequence of penetration of the toxic chemical into the skin subsequent to oedema, and sweating could indicate a pathway towards excretion and therefore removal of the noxious chemical. Likewise, nausea, vomiting, diarrhea and gastrointestinal issues could indicate mechanisms to flush the chemical out through the digestive tract.

Thus, we constructed two datasets linked to kidney failure, where one set (KIDNEY-FAILURE1, 38,347 records) included any symptoms which contained a unique substring that was a member of the set: "SKIN", "RASH", "GASTRO", "OESOPH", "OEDEMA", "NAUSEA", and "VOMITING", and the other set (KIDNEYFAILURE2, 89,306 records) contained none of these substrings among the listed symptoms. This was intended to capture most of the symptoms related to issues of the skin or gut along with oedema.

Guided by a recent paper studying the effects of small doses of Roundup® on rats [29], we decided to investigate how our two renal failure subsets distributed with respect to symptoms related to adrenal insufficiency. Pandey *et al*. [29] showed that 10 mg/kg doses of Roundup® administered over a two-week period to male rats resulted in a marked drop in steroidogenesis in the adrenal glands. They showed that this was related to a reduced supply of adrenocorticotrophic hormone (ACTH) from the pituitary gland, which caused reduced expression of steroidogenic acute regulatory protein (StAR) in the adrenal glands. Further evidence comes from a study on sublethal exposures of fish to glyphosate, which showed a significant reduction in the amount of cortisol produced in response to a stress stimulus ($P < 0.01$) [38]. The StAR protein controls the rate-limiting step in steroidogenesis. It was indicated in an earlier paper that testosterone synthesis was sharply reduced in testicular Leydig cells exposed to Roundup®, an effect that was linked to marked reduction in the expression of StAR [39]. The fact that "BLOOD TESTOSTERONE DECREASED" was strongly over-represented in KIDNEYFAILURE1 (score = 942) was encouraging in this respect. Pandey *et al*. wrote: "The findings that Roundup® treatment down-regulates endogenous ACTH, is similar to the condition known as adrenal insufficiency in humans. This condition manifests as fatigue, anorexia, sweating, anxiety, shaking, nausea, heart palpitations and weight loss." ([29], p. 1084). Based on this list, we created a table showing how these symptoms distributed among KIDNEYFAILURE1 and KIDNEYFAILURE2. We constructed a significance chart similar to **Table 2** for the new kidney failure datasets. It is remarkable, as shown in **Table 9**, that all of these symptoms, as well as ADRENAL INSUFFICIENCY itself, ADDISON'S DISEASE (chronic adrenal insufficiency) and SJOGREN'S SYNDROME were strongly over-represented in the KIDNEYFAILURE1 subset. Sjögren's syndrome is a pathology of the salivary glands but it is linked to low pituitary function and reduced expression of ACTH (adrenocorticotrophic hormone) [40]. We will henceforth refer to the KIDNEYFAILURE1 subset as the "adrenal insufficiency dataset."

3.7. Comparison to Conditions Correlated with Glyphosate Usage

A list of conditions whose incidence has been increasing alarmingly in the past two decades, in step with the increasing use of glyphosate on corn and soy crops was obtained from Swanson *et al*. [32]. The conditions and the associated p-values for their correlations with the temporal trends in glyphosate usage are shown in the headings of **Table 10**. We analyzed a set of symptoms which are more likely in the adrenal insufficiency group and which are representative of the conditions identified in Swanson *et al*. The acute renal failure and acute myeloid leukaemia do not pass our significance test, which is in agreement with our hypothesis that KIDNEYFAILURE1 and adrenal insufficiency are associated with chronic exposure to glyphosate.

"UNEVALUABLE EVENT" is an unusual category which, statistically, closely characterizes the reaction that we are detecting in our studies. We hypothesize this is linked to glyphosate exposure from the administered biologicals (blood products), along with the administration of other drugs that protect from haemorrhage, which includes protamine and Trasylol®, but also AMICAR (aminocaproic acid). TRASYLOL is remarkably over-

Table 9. Counts and scores for the KIDNEYFAILURE1 set (kidney failure with associated oedema, skin, or gut issues), compared to KIDNEYFAILURE2 (the remainder of the KIDNEY FAILURE cases), for various symptoms linked to adrenal insufficiency, as defined in [29]. The scores are computed as previously defined. Key: * = Not significant at 95% confidence level.

Side Effect	C1 (target)	C2 (control)	Score
Adrenal Insufficiency			
SJOGREN'S SYNDROME	80	10	949
ADDISON'S DISEASE	28	4	942
ADRENAL INSUFFICIENCY	200	103	818
Fatigue			
FATIGUE	5411	0	1000
Anorexia			
ANOREXIA NERVOSA	33	1	987
Sweating			
NIGHT SWEATS	299	52	930
COLD SWEAT	112	52	833
Anxiety			
ANXIETY DISORDER	96	18	925
GENERALISED ANXIETY DISORDER	48	9	925
ANXIETY*	4741	15344	418
Shaking			
TREMOR	972	422	842
DELIRIUM TREMENS	27	7	899
Heart Palpitations			
ARRHYTHMIA	1589	0	1000
TACHYARRHYTHMIA	207	0	1000
VENTRICULAR ARRHYTHMIA	150	0	1000
ARRHYTHMIA SUPRAVENTRICULAR	133	0	1000
SINUS ARRHYTHMIA	133	0	1000
PALPITATIONS	1036	206	921
Weight Loss			
WEIGHT FLUCTUATION	48	12	903
ABNORMAL LOSS OF WEIGHT	61	20	876
WEIGHT DECREASED	3060	1041	872
WEIGHT INCREASED	1332	675	821

Table 10. Evidence that the adrenal insufficiency kidney failure dataset is associated with increased risk to several diseases and conditions that correlate in temporal patterns with glyphosate usage on corn and soy crops. The values are an indicator of the skewed distribution of each side effect over the contrastive dataset (KIDNEYFAILURE2). The first number is the raw counts in the adrenal insufficiency dataset and the second number is the SCORE as defined in Equation (1). The p-values associated with the diseases are taken from **Table 3** in Swanson *et al*. [32], and reflect the strength of the correlation with glyphosate usage.

Symptom	C1	Score	Symptom	C1	Score
Thyroid Cancer (p < 7.6E−9)					
thyroid cyst	28	942	thyroid neoplasm	192	965
thyroid mass	29	957			
Liver Cancer (p < 4.6E−8)					
metastases to liver	278	854	hepatic cyst	209	875
hepatic lesion	198	942	hepatic neoplasm	42	874
metastases to liver	278	854	haemangioma of liver	48	982
hepatic mass	97	937	hepatic neoplasm malignant	71	786
Bladder Cancer (p < 4.7E−9)					
bladder cancer	128	812	bladder mass	39	968
Pancreatic Cancer (p < 4.6E−7)					
pancreatic carcinoma	75	843	pancreatitis acute	373	668
pancreatic cyst	38	808	Pancreatitis chronic	49	820
Kidney Cancer (p < 2.0E−8)					
renal cyst	998	895	renal tubular necrosis	1116	692
renal cancer	36	671	metastatic renal cell carcinoma*	28	692
Myeloid Leukemia (p < 1.5E−6)					
Bence Jones proteinuria	42	960	acute myeloid leukaemia*	61	509
multiple myeloma	744	705	myeloma recurrence	144	946
chronic myeloid leukaemia	26	761			
Lipoprotein Metabolism (p < 7.9E−9)					
dyslipidaemia	508	920	hyperlipidaemia	1842	911
Hypertension (p < 1.6E−7)					
accelerated hypertension	51	881	essential hypertension	185	888
hypertension	5025	814			
Stroke (p < 1.5E−7)					
haemorrhagic stroke	48	766			
Obesity (p < 1.7E−8)					
obesity	477	878	central obesity	22	878
Diabetes (p < 8.3E−8)					
type 1 diabetes	58	675	type 2 diabetes	171	734
diabetes mellitus	1450	743	diabetes mellitus inadequate control	522	822
ESRD (p < 7.2E−9), Renal Failure (p < 6.0E−9)					
chronic renal failure	4812	657	acute renal failure*	17028	536
acuteprerenal failure	709	738			
Neurological Disease (p < 1.7E−8)					
dementia Alzheimer's type	135	853	dementia	423	858
Parkinsonism	63	859	Parkinson's disease	159	876
Immune Disease (p < 1.7E−8)					
Multiple sclerosis	111	759	Inflammatory bowel	164	964
Viral infection	397	870	Crohn's disease	194	887

Key: * = Not significant at 95% confidence level.

represented within the UNEVALUABLE EVENT dataset, with over 16,000 cases and a score of 996. AMICAR is also one of the drugs that is highly over-represented (403 count, with a score of 986). Both HEPARIN and PROTAMINE SULFATE score over 950, as do RED BLOOD CELLS, PLATELETS, and PLASMA. Other drugs that are highly associated with UNEVALUABLE EVENT are drugs used in anaesthesia and drugs used to treat heart failure.

Table 11 lists side effects that are linked to UNEVALUABLE EVENT, contrasted with side effects linked to adrenal insufficiency. Among other side effects, UNEVALUABLE EVENT is highly inverse correlated with the symptoms linked to adrenal insufficiency. OSTEONECROSIS OF JAW, on the other hand, obtained a score of 974 in our adrenal insufficiency dataset, and a score of only 53 in the UNEVALUABLE EVENT subgroup. Other disorders related to jaw and also to bone, more generally, were similarly skewed towards adrenal insufficiency and away from UNEVALUABLE EVENT. Conditions related to the lung were highly over-represented in association with adrenal insufficiency and highly under-represented with UNEVALUABLE EVENT. Brain disorders such as dementia, Parkinson's disease, depression, and attention deficit hyperactivity disorder were all strongly over-represented in the adrenal insufficiency data set.

The most highly linked symptom to UNEVALUABLE EVENT was RENAL INJURY. MULTI-ORGAN FAILURE also scored very highly, along with MULTIPLE INJURIES and RENAL IMPAIRMENT. Symptoms related to brain stem disorder include FEAR, ANHEDONIA, TARDIVE DYSKINESIA, EXTRAPYRAMIDAL DISORDER, and EMOTIONAL DISTRESS. DEATH is also highly correlated with UNEVALUABLE EVENT, with 8421 cases and a score of 941.

Since we have reached the working hypothesis that Trasylol® is the most potent of our HDA DRUGS, and that UNEVALUABLE EVENT best characterizes an acute reaction to glyphosate, we decided to use the subset of our database where both of these were present along with DEATH as a side effect to characterize trends over time of DEATH as a side effect. The results are shown in **Table 12**. As might be expected if glyphosate contamination is increasing over time, the death toll steadily rises until 2008, when Trasylol® was temporarily removed from the market. However, by 2010, the number of DEATHS recorded had risen to surpass the highest count before 2010.

4. Discussion

"Death" as a drug side effect listed in the FAERS database represents a unique opportunity to investigate acute and unusual drug reactions. In many of the reports culminating in death, it is likely that the patient already had a

Table 11. Comparison of typical symptoms linked to UNEVALUABLE EVENT contrasted with those of the adrenal insufficiency dataset. See text for discussion.

UNEVALUABLE EVENT			
renal injury	multi-organ failure	multiple injuries	renal impairment
fear	anhedonia	emotional distress	extrapyramidal disorder
stress	tardive dyskinesia	death	
ADRENAL INSUFFICIENCY			
skin disorders	lung disorders	bone disorders	gastrointestinal disorders
oedema	bacterial infections	hypotension	hyperparathyroidism
mineral imbalances	thyroid disorder	pancreatitis	arthritis
dementia	Parkinson's	ADHD	major depression

Table 12. Number of events where DEATH and UNEVALUABLE EVENT were both listed as side effects, and TRASYLOL was the only one of the HDA DRUGS that was administered.

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010
Count	212	344	416	561	654	740	521	524	777

life-threatening disease such as cancer or renal failure. However, the fact that "death" was recorded as an adverse reaction implies that the circumstances surrounding the death were unexpected in the context of the disease. The fact that "UNEVALUABLE EVENT" as a side effect is strongly linked to DEATH supports this contention. Our investigation into the specific drugs and other side effects that co-occur with death have led to a novel hypothesis that, in some cases, an acute reaction to an unintended contaminant in the drug may explain death as an outcome. We hypothesize, based on its pervasiveness, that this contaminant is usually glyphosate.

Our investigations focused mainly on comparisons among two pairs of datasets. The first pair is contrastive for HDA DRUGS among the listed side effects, which we subdivided into two groups: one that includes death as a side effect and one that does not. The second pair concerns only the subset where renal failure was a side effect, divided into two groups reflecting a distinction we have related to the presence or absence of adrenal insufficiency and associated symptoms. Within this second set, DEATH as a side effect and TRASYLOL or PROTAMINE SULFATE as a drug all linked strongly to the set without adrenal insufficiency. We propose that renal failure with adrenal insufficiency captures chronic renal failure and associated symptoms due to chronic glyphosate exposure from food, and that the TRASYLOL-associated renal failure subset is far more likely to reflect glyphosate contamination in the drug, especially when the drug in question (TRASYLOL and PROTAMINE SULFATE) protects from haemorrhage.

The symptoms derived from the research literature involving glyphosate poisoning through suicide attempts [27] and a rare but unusual reaction to protamine sulfate [25] are over-represented in the HDA DRUGS data set. We propose that these are associated with acute glyphosate poisoning. The list of symptoms associated with the diseases and conditions that have been found to be rising in frequency in step with glyphosate usage on corn and soy crops [32] are significantly over-represented in the adrenal insufficiency subset of the renal failure database. It is instructive to compare the scores for these symptoms to those in the HDA DRUGS dataset. In the case of Swanson *et al*. [32], the conditions with weak support in the HDA DRUGS dataset are multiple sclerosis, Parkinson's disease, inflammatory bowel disease and viral infection.

We propose that these conditions, all of which are well supported in the adrenal insufficiency dataset, are linked to chronic exposure of the gut microbiome to glyphosate via an oral delivery pathway, whereas intravenous administration of glyphosate through drug contamination would by-pass the gut. For instance, in [41], it was proposed that glyphosate could be causal in Parkinson's disease through manganese toxicity in the brain stem, consequential to manganese accumulation in the liver through disrupted bile flow. Manganese then traverses the vagus nerve to accumulate in the brain stem.

In two independent life-long rat studies, liver and kidney disease are strongly linked to chronic exposure to Roundup® in small environmentally plausible doses [42] [43]. Mesnage *et al*. [42] identified over 4000 genes related to liver and kidney function whose expression rates were significantly altered, and this was consistent with anatomical and histological changes as well as blood and urine biochemical pathologies identified by Séralini*et al*. for rats similarly exposed [43]. Mesnage *et al*. [42] wrote in the abstract: "Observed alterations in gene expression were consistent with fibrosis, necrosis, phospholipidosis, mitochondrial membrane dysfunction and ischemia."

UNEVALUABLE EVENT: We hypothesize that the most common situation where UNEVALUABLE EVENT occurs is in cardiac surgery relating to heart disease and heart failure, where drugs are administered to protect from haemorrhage. This leads to an increased risk to death consequential to glyphosate contamination in the administered biologicals, in part due to an inability to flush the toxic chemical out of the blood into the tissues. This results in kidney toxicity due to the large concentration of glyphosate that reaches the kidney, and to increased exposure in the brainstem, which, like the kidney, is a highly perfused terminal watershed area. Thus, we are hypothesizing synergistic action between glyphosate and drugs used to prevent haemorrhage, which results in an inability to reduce the toxic burden in the vasculature.

The side effect, FEAR is significant, and it suggests excitation of the NMDA receptors in the amygdala [44] [45]. FEAR was hugely overexpressed in association with UNEVALUABLE EVENT, as it was listed as a side effect in over half of the events, with over 15,000 cases and a score of 978. NMDA receptors respond to simultaneous presence of glutamate and glycine ligands [46]. Studies on rats exposed to glyphosate have shown that its mechanism of action in the hippocampus is over-stimulation of NMDA receptors [47], likely due to glyphosate's chelation of manganese interfering with glutamate recycling [48] coordinated with its direct action as a glycine mimetic to act as the second ligand.

A Role for Toxic Metals? Toxic metals such as aluminum and cadmium may also play a role in the drug

reactions investigated here. Albumin and heparin are especially effective at extracting aluminum from glass, and this has brought up a concern for aluminum toxicity in these products following a long storage time in a glass vial [49]. It has been proposed that aluminum may be synergistically toxic with glyphosate [50], and this would be particularly true under conditions of kidney failure when aluminum tends to be stored in the body due to failed kidney function [51]. Parathyroid hormone dramatically increases the retention of aluminum in the brain of rats fed dietary aluminum [52]. Elevated PTH through secondary hyperparathyroidism is a common feature of renal failure [53]. This is supported by the adrenal insufficiency analysis, where there were five side effects related to elevated parathyroid, and they scored in the range from 814 to 957.

It is plausible that these biological pharmaceuticals could also extract cadmium from glass, as cadmium can be leached from glass in acidic environments [54]. Glyphosate is both acidic and a strong chelating agent, so its presence could compound the problem. Both arsenic [28] and cadmium [55] have been proposed as possible causes of chronic kidney disease. Cadmium exposure is a growing problem, and studies on children have shown that it is linked to impaired bone mineralization [56], which is a key feature of our adrenal insufficiency profile. It was hypothesized in [28] that arsenic is synergistically toxic with glyphosate due to glyphosate's action as a chelating agent. Glyphosate could be expected to unload its arsenic cargo in the acidic environment of the terminal watershed in the kidney. Thus it is possible that glyphosate contamination in a biological drug such as heparin could enhance the effectiveness in extracting toxic metals from the vial and then carrying them to the terminal watershed areas of the kidneys and brain stem nuclei to cause harm.

A high rate of kidney failure was reported in a small agricultural community in India which was linked to toxic metal contamination, mainly cadmium and lead, in the soil [57]. Symptoms included oedema, anemia, proteinuria, anorexia, hypertension, glycosuria, haematuria and renal calculi. All of these symptoms were over-represented in our adrenal insufficiency dataset.

Glyphosate Formulations: Glyphosate formulations generally contain buffering salts such as isopropylamine salt to increase glyphosate's solubility in water. Furthermore, a surfactant is added such as polyoxyethyleneamine (POEA) to increase uptake of glyphosate into the cells of the weeds, and POEA is itself also highly toxic [58]. In fact, glyphosate formulations have been found to be up to 125 times more toxic to animals than glyphosate by itself [59].

A study in Korea from 2010 involving 76 patients who ingested glyphosate formulations revealed respiratory failure, hypotension, acute pancreatitis, acute kidney injury, hyperkalemia and seizures as common symptoms [60]. A study involving over 600 patients with acute poisoning from glyphosate-containing herbicides in two hospitals in Sri Lanka between 2002 and 2007 found a 3.2% fatality rate, with a median time to death of 20 hours [61]. Symptoms linked to death included gastrointestinal symptoms, respiratory distress, hypotension, altered level of consciousness, and oliguria. Plasma levels of glyphosate above 734 μg/mL were detected. All of the symptoms listed above for both studies were significantly over-represented in our adrenal insufficiency dataset.

A study on piglets is especially relevant to our results because it examined the effects of glyphosate infusion as well as the infusion of the isopropylamine salt of glyphosate (IPAG) and the commonly used surfactant, POEA [26]. The latter two were found to be much more toxic than glyphosate alone. A 35 minute intravenous infusion of IPAG resulted in a precipitous drop in blood pressure, over the course of about an hour, highly reminescent of the rare and unusual reaction to protamine sulfate described earlier [25]. Half of the 6 piglets died immediately following the blood pressure drop, along with indications of ventricular arrhythmia. This was associated with lowered cardiac contractility and heart failure. Only 2 of the 6 piglets recovered, with a mortality rate therefore of 66.7%. POEA was also found to be toxic, causing metabolic acidosis, pulmonary vasoconstriction, left ventricular dysfunction and circulatory collapse, ultimately leading to death within a few hours of exposure for all 6 exposed piglets. A woman who drank a formulation containing glyphosate and POEA developed acute respiratory distress with circulatory collapse, renal failure, disseminated intravascular coagulopathy and aseptic meningitis, suggesting brain involvement [62].

The symptoms of both IPAG and POEA exposure are strongly linked to the HDA DRUGS dataset, with consistently high scores for HYPOTENSION (770) VENTRICULAR ARRHYTHMIA (747), LEFT VENTRICULAR FAILURE (812), METABOLIC ACIDOSIS (709), CIRCULATORY COLLAPSE (712), PULMONARY VASCULAR DISORDER (872), RESPIRATORY DISTRESS (793), DISSEMINATED INTRAVASCULAR COAGULATION (723) and DEATH (933). This might suggest that the additional components of glyphosate formulations could also be present in the administered biological drugs.

Remarkably, there was only one case of "ARRHYTHMIA" of any sort in the kidney failure set without adrenal insufficiency, while there were 2382 cases reported in the adrenal insufficiency subset of the kidney failure database. HYPOTENSION was also strongly linked to adrenal insufficiency (785) as well as CIRCULATORY COLLAPSE (756). Patients with adrenal insufficiency have been shown to be at increased risk to lethal arrhythmias when exposed to excessive stress [63].

OSTEONECROSIS OF JAW: OSTEONECROSIS OF JAW is an unusual side effect highly correlated with DEATH in our analysis (see **Table 5**). Furthermore, the kidney failure set with adrenal insufficiency had 2199 cases where OSTEONECROSIS OF JAW was a listed side effect, as compared to only 140 in the comparison set of kidney failure without adrenal insufficiency. There were no cases of OSTEONECROSIS OF JAW when TRASYLOL was a listed drug and none of the other HDA DRUGS were present. This type of event (TRASYLOL only) was not uncommon, with over 11,000 cases listed, so it is quite striking that none included OSTEONECROSIS OF JAW.

OSTEONECROSIS OF JAW may seem at first glance unrelated to glyphosate exposure, and certainly there are other known risk factors, including tooth removal, bisphosphonates, chemotherapy, multiple myeloma, low blood protein levels, and renal impairment [64]. Avascular necrosis of the jaw [64] is associated with persistent bacterial infection (generally Actinomyces colonization) and increased oxidative stress and glutathione depletion [65]. Glyphosate both decreases glutathione and increases oxidative stress. In addition, many items on this list can plausibly be linked to glyphosate. A complex formed by two glyphosate molecules chelating aluminum [50] may behave much like a bisphosphonate to interfere with pyrophosphate-based activities in the cell [66]. Such a complex would be very similar to bisphosphonates in that both molecules contain two phosphonyl groups. Glyphosate has been linked to multiple myeloma [67] and to multiple other cancers and therefore to chemotherapy [33] [34], and there is strong support in the literature for glyphosate causing renal impairment [28] [43]. Low plasma proteins, such as serum albumin and transferrin, are associated with pulmonary vascular permeability [68]. A good indicator of systemic transvascular leaks is microalbuminurea [69], and it is also linked with chronic kidney disease [70].

There is a plausible link among jaw necrosis, pancreatitis, and adrenal insufficiency. Salivary albumin levels are elevated in association with frailty in the elderly [71], and this suggests loss of albumin through vascular leakage eventually terminating in the saliva (as a mechanism to export the toxic chemicals bound to albumin?). Autoimmune chronic pancreatitis is associated with impaired biliary flow and salivary gland dysfunction, and is treatable with corticosteroids, suggesting a role for adrenal insufficiency [72]. Adrenal insufficiency is also common in association with acute pancreatitis [73] [74]. In a prospective cohort study on patients with biliary pancreatitis, insufficient adrenal cortisol secretion, *i.e.*, primary adrenal insufficiency, in response to a corticotropin stimulus was strongly correlated with severity of disease and mortality risk [75]. One third of the patients in the study suffered from adrenal insufficiency.

In vitro studies have suggested that glyphosate binds to serum albumin [76], and so albumin lost from the blood through vascular leakage may be carrying glyphosate out of the vasculature into the tissues, including the salivary glands, where it could gain access to and harm the jaw, perhaps through a bisphosphonate-like mechanism. SALIVARY GLAND DISORDER was highly over-represented in the adrenal insufficiency dataset, with a score of 958. Glyphosate exposure has been shown to negatively impact the salivary glands. In a study where mice were exposed to glyphosate via their feed, the weight of the salivary glands, especially the parotid gland, increased significantly following exposure to glyphosate, and this was associated with cytoplasmic changes of acinar cells (basophilic change, fine vacuolation, swelling, and loss of the normal periodic acid-Schiff (PAS)-positive reactivity of the secretory granules) [77]. Industry-sponsored toxicology reports for glyphosate often mention salivary problems. These include excess and/or foamy salivation; cellular alterations, lesions, and enlargement of the salivary gland; ulceration of the tongue and oral mucosa [78].

Acinar cells are also implicated in pancreatic toxicity due to glyphosate. Diseases of the pancreas were highly over-represented in the adrenal insufficiency subset of the kidney failure dataset, including CHRONIC PANCREATITIS (820) and PANCREATIC CARCINOMA (833). Excessive stimulation of pancreatic acinar cells activates trypsin synthesis and the production of cytokines, both of which result in cellular damage [79]. Acinar cell damage has been implicated in glyphosate exposure in multiple studies involving rodents [80], and acinar cell carcinoma is the second most common type of pancreatic cancer [81]. The incidence of pancreatic cancer is sharply on the rise in step with glyphosate usage on corn and soy crops ($R = 0.918$, $p < 4.6E{-}7$) [32]. Glyphosate, in a monotonic dose-response relationship, substantially increased the levels of digestive enzymes,

including trypsin, chymotrypsin, amylase and acid protease, in the gut of fish exposed to low doses [82].

4.1. Evidence of Glyphosate Contamination in Specific HDA DRUGS

RED BLOOD CELLS, PLATELETS, SERUM ALBUMIN, PLASMA: Glyphosate contamination in blood products is plausible. There is no question that ingested glyphosate can cross the gut barrier. A study of 13 cases of acute glyphosate toxicity in humans confirmed that ingested glyphosate penetrates past the gut barrier and infiltrates the blood. Glyphosate was found present in the blood in all 13 cases, with the highest detected level being 7480 mg/L for one of the fatal cases [83]. A study by Krüger *et al*. in 2014 showed that humans in Europe have detectable amounts of glyphosate in their urine, and those consuming an organic diet had less than those eating conventional food [9]. Since red blood cells, platelets and serum albumin are all blood products, they can be expected to sometimes be contaminated with glyphosate, given its pervasiveness in our food supply. Studies have shown that glyphosate likely binds to serum albumin [76].

There are many different potential adverse reactions to transfusion, most of which probably have nothing to do with glyphosate contamination. However, one that is of special interest to us in the context of our studies is acute hypotensive transfusion reaction (AHTR). It is characterized by an abrupt drop in blood pressure along with haemolysis and acute lung injury. Sometimes, hypotension is the only manifestation. Angiotensin-converting enzyme inhibitors (ACE inhibitors) may have a synergistic role, likely because they also reduce blood volume [84]. In a typical case study of a 12 year-old girl, blood pressure began to drop during the transfusion, and an increase in the rate of transfusion to try to maintain blood pressure only made the situation worse. Brain swelling and diffuse oozing followed, with red blood cells appearing in the urine 30 minutes later. It was confirmed that there were no blood incompatibilities. [85].

Up to half of the critically ill children in pediatric intensive care units receive at least one red blood cell transfusion, often due to severe anaemia. Low serum transferrin levels are especially problematic when packed RBC units are delivered intravenously, especially in the case of premature babies, and particularly following long-term storage [86]-[88], Oxidized free heme accumulates in the extracellular fluid of aged packed RBC units, while at the same time antioxidant defenses such as vitamin C and glutathione become depleted. The preparation process of these units involves the removal of most plasma proteins that could bind and sequester iron, such as transferrin and albumin.

However, RBC transfusions can also cause an acute reaction independent of storage time. A study by Reddy *et al*. in 2011 of 100 critically ill pediatric patients found that 20% of those administered red blood cells experienced an adverse reaction resulting in extravascular haemolysis, linked to an increase in the acute phase response, along with excess free (non-transferrin-bound) iron associated with high serum bilirubin, indicative of haemolysis [89]. They tested for and ruled out any relationship with the length of storage of the transfusion [89]. Hyperbilirubinemia was strongly correlated with the HDA DRUGS in our analysis, suggesting that red blood cells are incurring damage. Glyphosate has been shown to cause severe damage to exposed red blood cells, both in in vivo studies on fish [90] and in vitro studies on human red blood cells [91]. Red blood cells depend on glucose-6-phosphate dehydrogenase (G6PD) to maintain the antioxidant glutathione in the reduced state, and glyphosate has been shown to suppress G6PD activity in experiments on E. coli [92] and on goldfish [93]. Glyphosate can be expected to lead to free serum iron and depleted antioxidant proteins due in part to its destructive effect on red blood cells [90] and human cell membranes [94].

Sickle cell disease (SCD) is the most prevalent inherited disorder in African Americans [95]. RBC transfusion is the cornerstone treatment for complications of SCD [96], and most patients require blood transfusions starting in early childhood [97]. Fatal pulmonary complications, including interstitial abnormalities, impaired pulmonary function, and pulmonary hypertension, are a significant cause of mortality associated with SCD [98] [99]. The mechanism leading to pulmonary hypertension is unknown and typically explained as “multifactorial” [100]. In a study in a single hospital in the U.S. of 141 patient deaths from SCD between 1976 and 2001, it was noted that pulmonary hypertension as cause of death was more than twice as common after 1992 (36.2%) compared to before 1992 (16.6%) ($P < 0.01$) [95]. This temporal increase could be explained by increased glyphosate residue in the transfusions. INTERSTITIAL LUNG DISEASE (736), PULMONARY OEDEMA (769) and PULMONARY HYPERTENSION (854) were all significantly over-represented in the adrenal insufficiency dataset.

HEPARIN and TRASYLOL: Pharmaceutical-grade heparin is derived from mucosal tissues of slaughtered animals such as pig intestines and bovine lungs [37]. Both pigs and cattle are typically fed genetically engi-

neered RR corn and soy feed, particularly in the US. Studies on glyphosate contamination in chickens found the highest concentrations in the gut, as might be expected given the oral source. But the second-highest levels were found in the lungs [101]. Interestingly, a study on cows in Germany and Denmark found the highest levels in the lungs, with glyphosate showing up in all the organs tested [9]. Monsanto's own studies showed that radioactively labelled carbon in orally administered glyphosate can be recovered from carbon dioxide in the expelled breath [102]. We hypothesize that the high scores for multiple lung disorders associated with the adrenal insufficiency subset links to chronic glyphosate poisoning in the lungs. Heparin is a highly cationic peptide, which increases its likelihood of electrostatic binding to the negatively charged molecule, glyphosate.

Trasylol® (aprotinin) is a natural protease inhibitor obtained from bovine lung, administered intravenously. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5 - 6.5. These buffering agents will increase the solubility of glyphosate, increasing the likelihood of its contamination due to glyphosate residues in the lung tissues. It is even likely that aprotinin expression is stimulated in the cow in the context of glyphosate exposure, due to the release of trypsin by the pancreas and its escape into the lung tissue following vascular leaks, as will be more fully discussed later in this paper.

PROTAMINE SULFATE: Protamine is used increasingly to reverse heparin anticoagulation during cardiac catheterization, vascular surgery procedures, dialysis, and leukapheresis. Protamine sulfate is a basic protein extracted from fish sperm heads, mainly sturgeon and salmon [103], although in recent years recombinant technology through microbial cultures such as E. coli is increasingly being used [104] [105]. We discussed in the introduction studies showing anomalous reactions to protamine sulfate therapy involving lung complications and a high risk of death [24] [25].

Iran has been the second-highest producer of sturgeon-derived products, coming mainly from fish living in the Caspian Sea. However, the native sturgeon population has declined by 90% over the past three decades, and all sturgeon species in the Caspian Sea are now critically endangered. Coastal habitats are being widely exposed to herbicides, especially glyphosate, from large farms and paddy fields nearby [106]. Glyphosate is acutely toxic to fish [107]. Reproductive failure due to glyphosate exposure is hypothesized to be an important contributor to their decline in the Caspian Sea [106]. It is therefore not unreasonable to suppose that products derived from sturgeon testes might be contaminated with glyphosate.

Recombinant methods are also not necessarily free from glyphosate contamination. There is no awareness that glyphosate might be an issue, and so it remains an open question as to whether the medium on which the microbes are grown might contain glyphosate. A highly productive choice for nutrition for the microbes to induce high yield of the recombinant protein is a mixture of glucose, lactose and glycerol [104] [105]. Glucose could be obtained from GM RR sugar beets, or sugar cane sprayed with Roundup® right before the harvest, or from high fructose corn syrup derived from RR corn. Lactose is derived from milk, likely produced by cows exposed to high doses of glyphosate in their GM corn and soy feed. Glycerol is now a major by-product of the production of biofuel from soybeans, and most of the soybeans grown in the US are genetically engineered to be glyphosate resistant, and therefore highly exposed to glyphosate.

NITROGLYCERIN and VANCOMYCIN: Nitroglycerin and vancomycin were the weakest of the HDA DRUGS in terms of their score for association with death. Nitroglycerin is administered in multiple ways, including as an intravenous solution, a transdermal patch, and sublingual sprays and tablets. Vancomycin must be given intravenously for systemic therapy, since it is not absorbed from the intestine. Nitroglycerin is an antihypertensive agent that releases nitric oxide, a vasoactive gas that relaxes the vessel wall. An antihypertensive agent might work synergistically with glyphosate to increase risk in a situation where blood pressure is dropping precipitously.

Vancomycin is a popular antibiotic that's most effective against gram-positive bacteria. A known adverse effect of vancomycin, in less than 1% of patients, is thrombocytopenia. Confirming this adverse reaction, we obtained highly significant scores of 762 for THROMBOCYTOPENIA and 916 for ESSENTIAL THROMBOCYTHAEMIA, when comparing a subset of our HDA DRUGS dataset where vancomycin was the ONLY HDA DRUG present to the opposing set where vancomycin was not among the HDA DRUGS. Nephrotoxicity is another issue with VANCOMYCIN, and we obtained a score of 908 for "NEPHROPATHY TOXIC" when comparing these two sets.

Since it is not obvious how these two drugs might be contaminated with glyphosate, we hypothesize that their link to DEATH may be through other mechanisms directly linked to the drug's biological effects. However, the highly significant scores for the known side effects of these drugs show that our method has merit.

VERSED: VERSED, a benzadiazepine, is a low-toxicity drug, and it is therefore anomalous on the HDA DRUGS list. It is often used as a premedication for sedation, and it is likely that surgery is commonly associated with "DEATH" as an outcome. Therefore, it may be "guilty by association" with the other death-related drugs. We can easily test this by separating out those events where VERSED, but none of the other HDA DRUGS, was administered. This occurred in only 399 of the HDA DRUG events (out of 43,434) (fewer than 1%). When these 399 events are compared with the remainder of the HDA DRUG events, all of the side effects that were linked to death (see **Table 3**) get a score < 500, meaning that they are under-represented in association with VERSED only. Therefore, we highly suspect that VERSED is anomalously tagged as an HDA DRUG. It is probably highly significant that "UNEVALUABLE EVENT" was hugely under-represented with VERSED only: the number of cases was more than 12-fold fewer than would be predicted based on the frequency in the other HDA DRUG events.

4.2. Possible Biological Mechanisms

It should be clear by now that we are proposing two ideas in this paper: (1) People are chronically exposed to glyphosate in their food and water, and this is leading to a disease profile that is captured in our adrenal insufficiency dataset linked to kidney failure, and (2) Certain biological pharmaceuticals may be contaminated with glyphosate which is inadvertently administered intravenously, leading to an acute symptom profile that is quite distinct from the one resulting from chronic glyphosate exposure.

Our research has led us to propose a hypothesis for a systemic reaction to chronic glyphosate exposure from food and water. This reaction likely initiates with pancreatitis, leading to a leaky vasculature due in part to increased trypsin synthesis, resulting in the escape of blood plasma along with trypsin and glyphosate, likely bound to serum albumin, into the extracellular space. This causes chronic damage to multiple organs, but spares the vasculature and the kidneys. It follows that death as a side effect is more likely when glyphosate exposure is concurrent with drugs that protect from haemorrhage, such as Trasylol® and protamine sulfate, due to the fact that glyphosate stays in the blood and fatally damages the kidneys.

GGT, Adrenal Insufficiency, Vitamin C Deficiency and Pancreatitis: Multiple studies on plants have demonstrated that glyphosate induces glutathione-S-transferase activity [108]-[110]. It is not clear that glyphosate itself is detoxified through glutathionylation, but, rather, it is perhaps more likely that glyphosate interferes with other conjugations of xenobiotics in general, such as with sulfate or glucuronate, that depend on CYP enzymes, leaving glutathionylation as the preferred pathway for detoxification when CYP enzymes are suppressed. This will also lead over time to a depletion of glutathione bioavailability in the liver, a source of oxidative stress.

Gamma glutamyltransferase (GGT) is a widely expressed enzyme, especially in the liver. Since GGT is needed to break down glutathionylated xenobiotics, such as polycyclic aromatic hydrocarbons [111], it can be expected to be induced in the presence of glutathionylated xenobiotics. Increased GGT expression is linked to glyphosate through multiple animal studies. Its over-expression is associated with many diseases related to hepatobiliary and pancreatic disorders [112]-[114]. Kids born from goats fed GM RR soy had elevated liver expression of GGT [115]. GGT was found to be enhanced up to 5.4-fold in the liver in Séralini *et al.*'s long-term study of rats exposed to GMO's plus Roundup® [43]. Lum and Gambino found extremely high levels of GGT in cases of acute pancreatitis, primary carcinoma of the head of the pancreas, and adenocarcinoma of the bile duct [113]. GGT levels were higher than the upper limit of normal for 100% of cases of pancreatitis, with an average value of ten times the upper limit. A retrospective study on over half a million hospitalized cancer patients, between 1995 and 2003, showed that the administration of both red blood cells and platelets led to increased risk to thrombosis and death compared to no transfusion [116]. It was proposed that a factor could be the presence of redox-active iron in the transfusion, leading to an increase in iron-catalyzed free radical-mediated oxidative stress [117]. Elevated GGT would greatly enhance this effect, because GGT has a pro-oxidant effect by promoting iron reduction and the peroxidation of lipids [118] [119].

21-Hydroxylase is a CYP enzyme that catalyzes the synthesis of cortisol and aldosterone in the adrenal glands. Women with adrenal insufficiency due to 21-hydroxylase deficiency generally have elevated expression of GGT, along with increased risk to non-alcoholic fatty liver disease [120]. This may be linked to a deficiency in ascorbate. The adrenal glands have an unusually high concentration of ascorbate, which is a cofactor both in catecholamine biosynthesis and in steroidogenesis [121]. It also plays an essential role in protecting them from oxidative damage. Red blood cells use a glutathione-dependent dehydroascorbate reductase to maintain vitamin C in

the reduced state in the vasculature, and this function could be impaired in the presence of glyphosate, due to both glutathione depletion and oxidative stress. Furthermore, the suppression of G6PD by glyphosate impairs the glucose-mediated reducing capacity of RBCs [92] [93]. The liver also reduces dehydroascorbate to ascorbate, but this burden induces loss of glutathione and oxidative stress as well [122].

The symptoms of severe vitamin C deficiency (scurvy) were listed in [123] as "anorexia, anaemia, arthralgia, bleeding gums, coiled hair, depression, dry eyes and mouth (Sjögren's Syndrome), ecchymosis, follicular hyperkeratosis, fatigue, frequent infections, impaired wound healing, inflamed gums, joint effusions, myalgia, muscle weakness, perifollicular hemorrhages, and petechiae." We found 51 side effects that were highly over-repre- sented in the adrenal insufficiency dataset which collectively matched with all of the above symptoms except coiled hair: scores for all but 5 of them were above 900, and those 5 were all above 800.

Pancreatitis and Trypsin: Acute pancreatitis has been observed in a case study of a reaction to glyphosate exposure through a suicide attempt [124]. Pancreatitis on the first day was followed by chemical pneumonitis and respiratory failure, likely due in part to the release of glyphosate into the pleural cavity, along with blood plasma and serum proteins. Acute haemorrhagic pancreatitis induces increased lung vascular permeability, an effect that is linked to overexpression of proteases such as trypsin [125]. Trypsin induces platelet activation [126], and platelet-rich blood clots release cytokines and inflammatory mediators such as vascular endothelial growth factor, which can increase capillary permeability leading to exudative pleural effusion [127]. The cytokines, interleukin-1β (IL-1β) and interferon γ (IFN-γ) have been shown to significantly increase vascular permeability, allowing neutrophils to penetrate the endothelial layer [128].

Pretreatment with Trasylol® protects from this effect of trypsin [125] [129], making it attractive in the context of open heart surgery. Tahamont *et al*. [129] proposed that the increases in pulmonary lymph flow and transvascular protein clearance after pancreatitis is the result of the release of proteases such as trypsin. They wrote: "The release of proteases into the circulation after acute pancreatitis may be the initiating event mediating the pulmonary vascular injury" ([129], p. 15). Trasylol® protects more generally from exudative pleural effusion. In a study on dogs with experimentally induced myocardial infarction, it was demonstrated that Trasylol® administered 30 minutes after ligation with cobra venom factor significantly reduces the inflammatory response and tissue exudate in the myocardium [130] [131].

Astonishingly, if we compare counts for all side effects related to pancreatitis and pancreatic cancer between HDA DRUGS not including TRASYLOL and HDA DRUGS including TRASYLOL, we get a score of 994; *i.e*., pancreatic dysfunction is hugely over-represented in the HDA DRUGS when TRASYLOL is omitted. What is most interesting, however, is that TRASYLOL-containing HDA DRUG events are much more strongly linked to DEATH, with a score of 934, when compared to HDA DRUGS omitting TRASYLOL. This suggests to us that protection from vascular leakage and haemorrhage in the context of glyphosate poisoning is very risky, because it prevents the escape of glyphosate from the blood and results in kidney injury leading to death.

Pathological Sequelae Leading to Death: Thus, a story emerges from the data analysis we have performed, and it suggests that a signaling cascade launched by pancreatitis leads to pancreatic release of digestive enzymes, which then both degrade ACTH [132] and erode the vascular wall in the major vessels sufficiently to induce migration of serum and even whole blood into the pleural and abdominal cavities. The loss of ACTH can plausibly induce secondary adrenal insufficiency, whereas primary adrenal insufficiency develops in part due to Roundup®'s suppression of StAR and reduced supply of ascorbate. The intended use of the anti-trypsin agent, aprotinin (Trasylol®) is to break down trypsin only after it has breached the artery wall. This is sensible in order to prevent trypsin from digesting lung tissue and causing major damage to the lung. Administering of Trasylol® intravenously during open heart surgery has the desired effect of preventing the escape of blood into the pleural cavity during the operation by neutralizing the trypsin while it is still in the arteries, but this then does not protect the glomeruli from a high dose of the toxic chemical that launched the signaling cascade in the first place. Thus, while multiple organs, such as the lungs, the gut, the bones, the skin, the brain, the eyes, the ears, etc., are spared, the kidney suffers acute injury and the patient has a much higher chance of death as an outcome.

If we are right, then there is good news in that Trasylol® and heparin could be sourced from grass fed cows rather than cows fed GM RR corn and soy feed. Trasylol® may be an outstanding drug for protection from haemorrhage during open heart surgery if we can prevent the rare acute reaction leading to death that may in fact be largely due to a contaminant rather than to the drug itself.

We end this section with a quote from a recent paper discussing data mining from FAERS: "A report in the FAERS database is a story, sometimes only a rumor, but numerous reports can reflect reality. With larger num-

bers of faithful reports, the FAERS database and other spontaneously reported databases should help to optimize pharmacotherapy." ([133], p. 6). We hope that the analysis we report here will lead to further investigation into the theory we have presented concerning glyphosate exposure in food and drugs.

5. Conclusions

In this paper, we have presented evidence that a toxic chemical contamination might explain the high risk of death as a side effect associated with certain biologically derived drugs, including multiple blood products as well as drugs extracted from bovine lung and sturgeon testes. We theorize that the contaminant causing this acute reaction is glyphosate, the active ingredient in Roundup®. We show that events in FAERS which include drugs that are strongly linked to death exhibit side effects that are well correlated with symptoms related to glyphosate toxicity in suicide attempts as well as to a rare but unique reaction to protamine sulfate. This reaction is highly reminiscent of the reaction of piglets exposed to glyphosate salts intravenously [26]. From this we hypothesize that these biologically derived drugs may be contaminated with glyphosate and it is the glyphosate that is causing the acute reactions. We further hypothesize that glyphosate adjuvants such as POEA and various toxic metals, including iron, aluminum and cadmium, may play a synergistic role.

Based on knowledge that glyphosate is causative in kidney failure, we undertook a separate investigation into the subset of the FAERS database with renal failure as one of the symptoms. This yielded interesting insight into the underlying pathology associated with chronic kidney disease. By separating the renal failure dataset into two contrastive subgroups, we are able to show that adrenal insufficiency characterizes a chronic form of kidney failure that we believe is a reflection of chronic glyphosate exposure from food sources. Symptoms of diseases whose rising frequency over time correlates with the rising use of glyphosate on corn and soy crops were well-matched with the adrenal insufficiency dataset. We note that those side effects related to glyphosate toxicity that are under-represented in our HDA DRUGS database are linked to gut dysbiosis, and we suggest that the intravenous route rather than the oral route serves to minimize gut exposure.

We have developed a hypothesis to explain the symptom patterns observed in the context of kidney failure and adrenal insufficiency. We propose that the pancreas is highly susceptible to damage from glyphosate, and that pancreatitis induces vascular leakage mediated by trypsin over-expression and platelet activation. Vascular leakage results in a flushing of blood products, including glyphosate, into the pleural and abdominal cavities, causing conditions such as pulmonary oedema and ascites. The two drugs that were most strongly linked to death as an outcome, Trasylol® and protamine sulfate, both are administered to protect from haemorrhage. They therefore interfere with the flushing of glyphosate into the tissues, sparing the lungs, gut, skin, heart, brain and other organs from major damage, but ultimately leading to an increased risk to death due to kidney failure.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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