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Review

Incidence of Photosensitization in Husbandry Animals: A Meta-Study on the Effects of Feed Diversity and Feed Choice

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Abstract: As this is a meta-study, we examined whether plant species diversity in the feed and the possibility of feed choice would influence the number of cases of photosensitization in farm animals. We evaluated 110 scientific references which described 172 cases of photosensitization worldwide, mainly in husbandry animals between 1926 and 2022. More than 50% of the cases occurred in South America and Australia. Among the animal species, sheep and cattle were statistically overrepresented. A total of 35 organisms were revealed to be phototoxic: 24 herbs, 2 grasses, 7 woody species, and 2 kinds of fungi. Animals developed mainly secondary photosensitization due to fresh feed (71.8%) of normal quality (88.1%), indicating that the phototoxic agents are from liver-toxic plants such as the grass *Brachiaria* and the herb *Froelichia*. Horses fell ill chiefly with primary photosensitization due to directly acting phototoxic agents of plant species such as the herbs *Medicago* and *Pastinaca*, both in fresh and conserved feed. Goats manage to avoid phototoxic plants under both high and low feed diversity if they still have free choice between plant species. High feed diversity reduced the incidence 2.4-fold, while enabled selection possibility even reduced it 7.5-fold. Since the lack of choice between forage plants was revealed to be the main cause of photosensitization, this knowledge could be used to prevent the disease in livestock.

Keywords: photosensitization; feed α-diversity; feed choice; feed quality

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1. Introduction

Cases of plant poisoning in animals are not easy to verify by tracing them back to plants because the symptoms are either unspecific [1], subtle [2], or the suspicious plants ingested are simply not visible any more [3]. Moreover, signs of grazing are inconspicuous and thus often overlooked [4]. One exception in plant poisoning is photosensitization, caused by some 250 phototoxic plant species worldwide [5] and the fungus *Pithomyces chartarum* [6]. The alimentary-induced disease is manifested in four variants, primary, secondary, endogenous, and idiopathic photosensitization [7,8] while *Pithomyces* causes exclusively secondary photosensitization [9]. In any case, symptoms are external, prominent, and resemble human photodermatitis ("sunburn"). This might be the reason why these organisms are generally well-known to animal keepers too. Although photosensitization can be confused with similar-looking contact eczema, a differential diagnosis is facilitated if phototoxic plant species (or fungi) appear between (or on) feed stuff or in pastures. Moreover, an unambiguous classification system of photosensitization is available [7,8]. Prominent examples of phototoxic plants are the genera *Heracleum* and *Hypericum*. Their compounds coumarin and hypericin accumulate in the skin and interact with sunlight, causing primary phototoxicity on the skin [10,11]. Except in a few cases in birds, white-colored mammals are most often affected, although symptoms can be observed in all kinds of colored mammals. Since the etiology of plant-born photosensitization is well-known, so are the phototoxic plant species [5]. The question therefore arose as to why farm animals are still being poisoned with phototoxic plants. This question is of special interest since in times of global change the incidence of this disease might be increase [12]. Here, we address the two key variables concerned with plant poisoning of husbandry animals in general [13]: (1) the extent of possibility of feed choice, and (2) the number of plant species in the feed, the so-called α-diversity [14]. Both variables have been widely discussed with regard to animal welfare [15] and nutritional ecology [16–18]; however, in the modern farm feeding regime [19] they are neglected [15]. The goal of this meta-study was to investigate whether the level of plant diversity in the feed or the extent of feed choice influences the number of cases of photosensitization in farm animals.

2. Materials and Methods

2.1. Search for Case Reports

We reviewed references of reported cases of photosensitization caused by potential phototoxic organisms from as early as 1926 up to today, using electronic databases such as Web of Science, CAB Abstracts, and VetSearch. Among the publication formats there were case reports, brief communications, and reviews, independent of being peer-reviewed or not. To ensure we could rely on the data, both the material and methods of the evaluated references were checked. We distinguished, too, whether the author proved or only suspected a connection with a certain phototoxic organism. In addition, the author's indication of the phototoxic potential of the organism was checked in a second source. This source was the most modern accessible publication, such as a paper or textbook, that deals with the corresponding chemistry and phototoxic agents of the organism mentioned in a case.

Non-German and non-English papers were considered if the English abstract contained the raw data mentioned above. Numerous non-English publications did not present an English abstract and were dismissed. Case collections counted as one case if the data did not allow several cases to be differentiated from each other. If the disease was a secondary finding of studies with another research focus (e.g., [20]), it counted as a case as well. However, experimentally induced photosensitization was excluded. Furthermore, publications with a non-alimentary background for hepatogenous photosensitization, such as liver-migrating endoparasites (e.g., [21]), were not part of this meta-study.

2.2. Variables of Evaluation Case Reports

Along with certain raw data selected from the references, such as the kind of phototoxic organism or the kind of feed, additional data were extracted from the sources such as α-diversity and feed quality that were not explicitly addressed by the authors but mentioned anyway. In total, the cases of photosensitization evaluated included the following seven principal variables along with the two key variables: (1) level of feed examination, (2) kind of phototoxic organism, (3) type of photosensitization, (4) animal species, (5) kind and quality of feed, (6) plant species diversity of feed (first key variable), and (7) possibility of feed choice (second key variable; Figure 1).

2.2.1. Level of Feed Examination

The first principal variable "level of feed examination" was determined by asking if the authors examined the quality and botanical composition of the feed (1) completely, (2), partly, or (3) whether it was unknown.

The feed was considered as completely examined if the authors (a) inspected the pasture and indicated the presence of plant species other than the already identified phototoxic ones, (b) stated that no other phototoxic plants were growing there, (c) noted that a phototoxic plant species was found in large quantities, (d) counted fungi spores in the feed (e.g., [22]), (e) analyzed the feed botanically, (f) stated that no phototoxic plants were found, or (g) named both main plant species and those with a mass portion of less than 5%.

The feed was taken as partly examined if authors (a) searched for the presence or absence of phototoxic plants, (b) stated simply that no other phototoxic plants were present, and (c) indicated the presence of "many" species with no further information.

On the other hand, if there was no information regarding the level of feed examination in the reviewed references or if the authors gave no hints about feed examination, the level of feed examination was considered unknown.

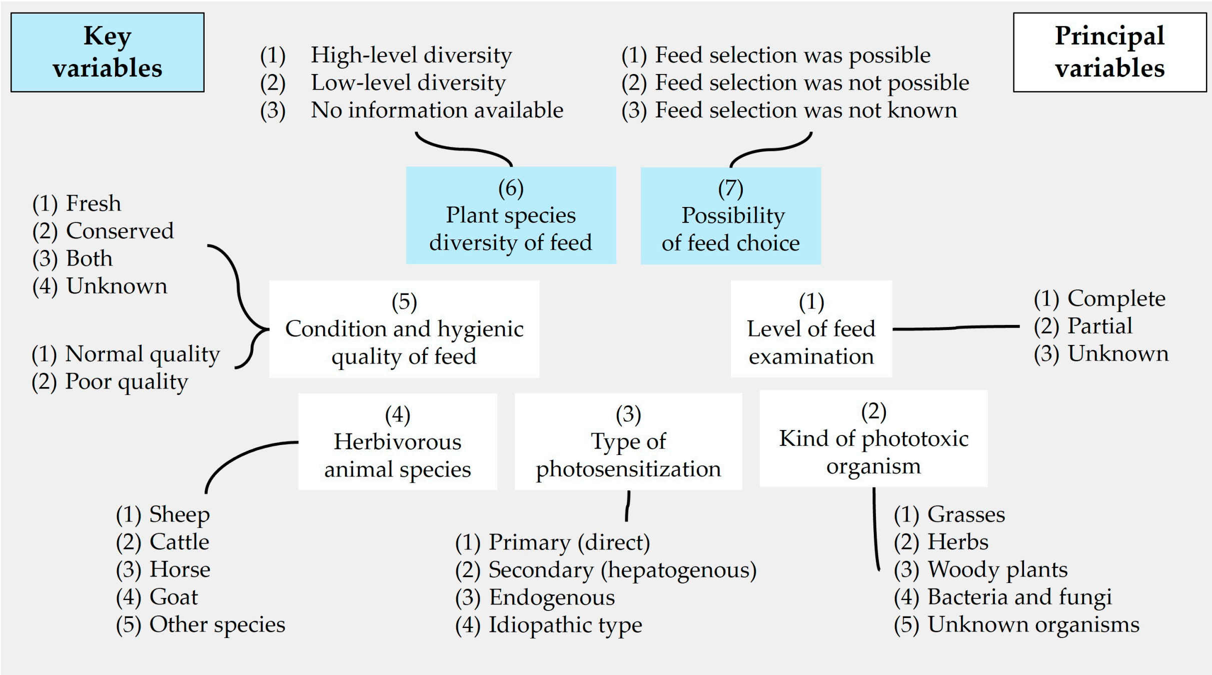

Figure 1. Key variables, principal variables, and subvariables used for data analysis.

2.2.2. Kind of Phototoxic Organism

Five kinds of phototoxic organisms, (1) grasses, (2) herbs, (3) woody plants, (4) bacteria and fungi, and (5) unknown organisms, were assessed in this study.

2.2.3. Type of Photosensitization

The third principal variable manifested itself in four types: (1) primary (direct), (2) secondary (hepatogenous), (3) endogenous, and (4) idiopathic type [7,8].

The first type, primary photosensitization, occurs when phototoxic components of plants are taken up through ingestion and arrive in the skin unchanged or through direct skin contact [23]. This kind of the disease appears within hours of the ingestion or contact [23]. In contrast, the delayed onset of the disease in other types makes it more difficult to identify the trigger.

The second type, hepatogenous photosensitization, is a consequence of liver diseases caused through liver-toxic plant components [24] or fungi [25]. The damaged liver can no longer excrete photoactive phylloerythrin, a by-product of bacterial digestion of chlorophyll, through the bile [26]. Instead, it accumulates in blood and skin where it causes a range of typical photosensitization symptoms [2].

The third type, endogenous photosensitization, is a metabolic effect inherited in cattle and therefore was not relevant for this study [27].

The fourth type, idiopathic photosensitization, includes cases in which the cause of the disease is not known so far.

2.2.4. Animal Species

The fourth principal variable concerned all mammal herbivorous animal species that appeared in the references considered.

2.2.5. Kind and Quality of Feed

The kind of feed was expressed as (1) "fresh", in the case of ingestion of living plants either provided on pasture or after being recently harvested in a manger; (2) "conserved", in the case of hay, silage, or pellets; (3) "both", if animals had access to both kinds of feed; and finally, (4) "unknown", if no information about the kind of feed was given by the authors.

The feed was considered of (1) normal quality if there were neither direct nor indirect hints on quality deficiencies apparent in the reference. In the case of (2) poor quality, the authors stated that there was either (a) *Pithomyces chartarum* on pasture grass or bacteria and fungi (mold) in conserved feed stuff or (b) moisture in the case of hay, the latter according to the criteria described in [28].

2.2.6. Plant Species Diversity

The sixth principal variable (or first key variable) was related to a feed sample or a pasture and thus represented α-diversity, defined as the number of species within a certain unit [14]. α-diversity in our study comprised three subvariables: (1) high-level diversity, (2) low-level diversity, and (3) no information available.

The feed was assumed to be (1) highly diverse if authors (a) stated that there were various weeds present, or (b) found several plants growing on the property or in conserved feed, or (c) mentioned certain key words such as "native vegetation" or "fallow", or noted plants that are indicator species for a low soil nitrogen level, which means that the α-diversity on grasslands is higher than on intensively fertilized land [29], or if authors (d) listed at least four plant species without stating that one was dominant, the minimum number of species in species-rich meadows in Middle Europe [30].

Low-level diversity (2) was recognized if (a) the pasture or conserved feed consisted of fewer than four plant species, or (b) conserved or fresh feed was stated by the researchers to be dominated or massively invaded by one plant, or (c) animals received pellets only.

In the case of (3) no information available, the authors did not mention any details on botanical α-diversity of feed or pastures.

2.2.7. Possibility of Feed Choice

As for the seventh variable (or second key variable), we discerned three subvariables: (1) feed selection was possible; (2) feed selection was not possible; and (3) feed selection was not known.

Feed selection was considered possible if there were (a) various kinds of feedstuff that were given simultaneously or shortly one after the other, or (b) the pasture or conserved feed possessed a high diversity, as defined in the previous section.

In contrast, feed selection was considered not possible if (a) a pasture was contaminated with fungi such as *Pithomyces chartarum*, or (b) animals received only pellets, or (c) the pasture vegetation was completely dried out, even if biodiversity was high.

If any relevant information was missing, the possibility for feed selection was regarded as unknown.

2.3. Data Analysis

Most of the data were analyzed descriptively, counting the presence or absence of defined traits corresponding to the above-mentioned variables. In addition, the Pearson correlation coefficient *r* was calculated using Microsoft Excel© 2013 on the basis of the number of animal nominations for the key variables "plant species diversity of feed" and "possibility of feed choice". The level of significance was extracted from tables of critical values of the correlation coefficient r in Cann (2004) [31], based on a one-sided test.

3. Results

3.1. Overview of All Variables

The level of feed examination was for the most part either partly or completely carried out (Figure 2). The most abundant kind of phototoxic organism was herbs. Secondary photosensitization turned out to be the predominant type of this disease, with sheep the mainly affected animal species. The feed was largely both of normal quality and fresh. Regarding the key variables, the level of diversity in the feed proved to be mostly low, without the possibility of feed selection.

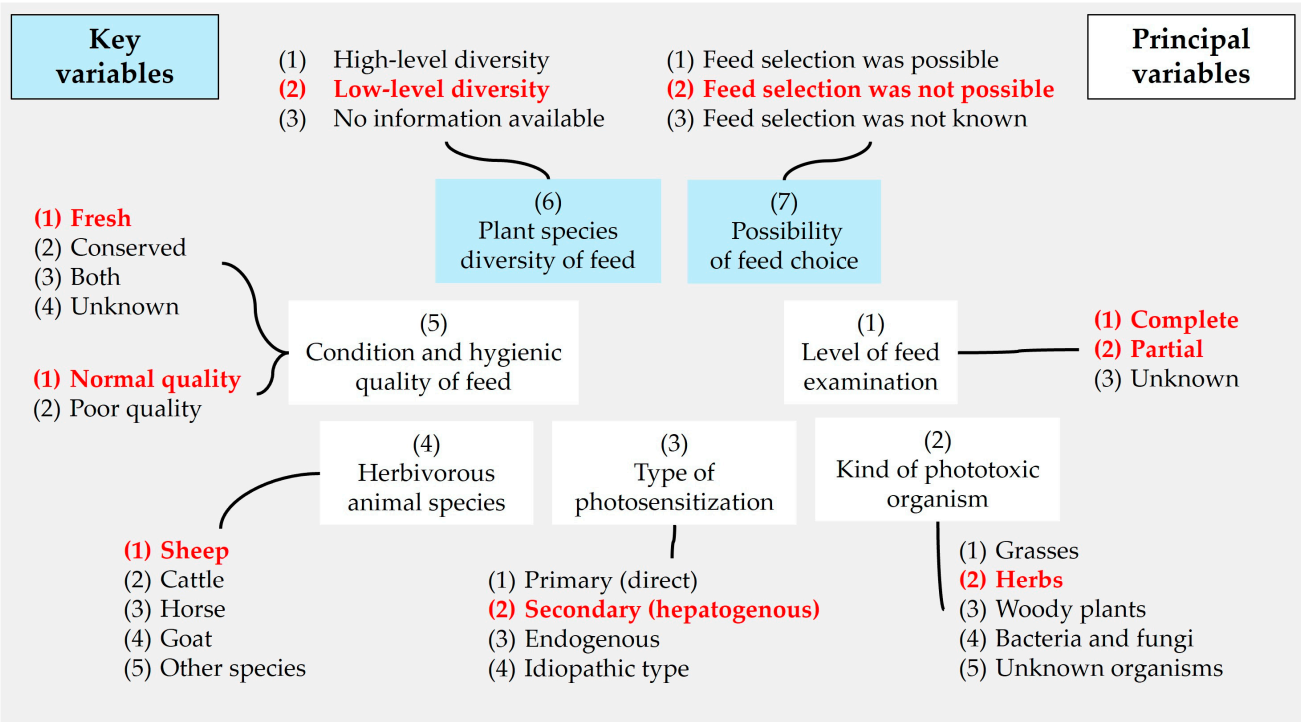

Figure 2. Key and principal variables and the most important subvariables, marked in red.

3.2. Botanical Data Basis

A total of 172 cases of photosensitization were obtained from 110 publications from six continents, mostly from South America (31.4%) (Table 1). Twenty references (18.2%) written in a language other than English but with an abstract in English were evaluated in this study.

Table 1. Case reports (n) and their origin, and level of feed examination.

Continent	Cases (n)	Portion (%)	Feed Examination by Authors		
			Completely	Partly	Unknown
South America	54	31.4	31	13	10
Australia	38	22.1	14	20	4
North America	33	19.2	18	10	5
Europe	14	8.1	2	9	3
Asia	12	7.0	3	5	4
New Zealand	11	6.4	3	4	4
Africa	8	4.7	1	6	1
India	2	1.2	0	0	2
Sum (n)	172	-	72	67	33
Portion (%)	-	100	41.9	39.0	19.2

The authors mainly fulfilled the precondition for an estimation of diversity because the feed was completely (41.9%) and partly (39.0%) examined botanically, whereas only in a minority of cases it remained unknown (19.2%).

A total of 43 out of 110 references and thus 82 out of 172 cases (39% and 47.6%) were peer-reviewed, while in the rest (61% and 52.3%) this remained unknown (Figure 3).

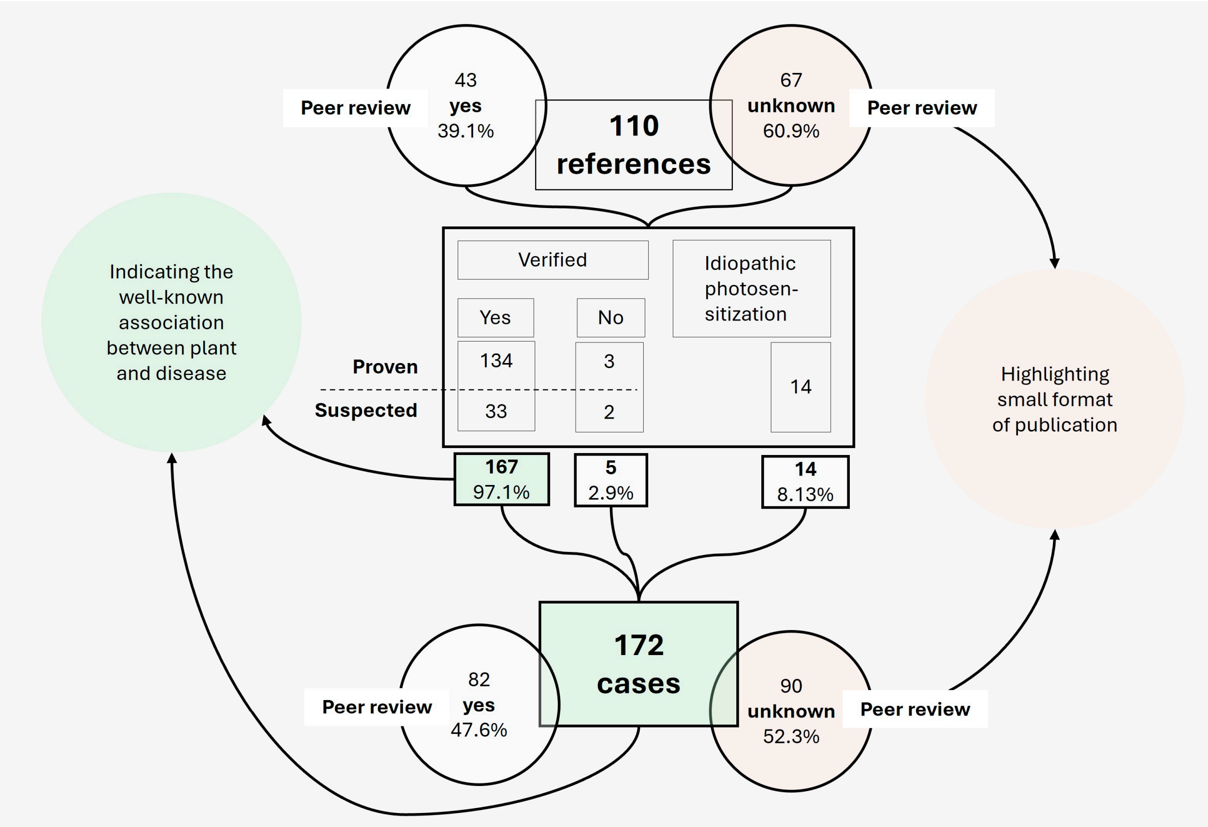

Figure 3. Composition of the data material. "Proven" means that the author proved the identity of the phototoxic organism. "Suspected" means that the author suspected the identity of the phototoxic organism. "Verified" means that the author's indication of the phototoxic potential of the respective organism was checked in the present study by a second source.

Apart from 14 cases of idiopathic photosensitization (8.1%), there were 33 cases (19.2%) in which the authors failed to prove the phototoxic agent. In only 5 cases (2.9%) the data were not evidence-based, and concerned cyanobacteria (3 cases) as well as a grass and a herb (1 case each). As for the cyanobacteria, no evidence of their phototoxicity was provided according to a review article [32]. As for the grass (*Alopecurus*), it was rather a plant-colonizing fungus that was the causative organism according to [33]. As for the herb (*Ranunculus*), its blister-generating compounds [34] probably caused symptoms of contact dermatitis that strongly resembles photosensitization.

3.3. Phototoxic Organisms

Herbs turned out to be the largest class of phototoxic organisms. In total, 35 phototoxic organisms were involved in the 172 cases. The most frequent phototoxic organism was signal grass (*Brachiaria decumbens*, *Poaceae*, 15 cases), followed by the herbaceous cottonweed (*Chamaecrista*, *Fabaceae*, 13 cases). Represented by 24 genera (*Froelichia*, *Chamaecrista*, *Medicago*, *Tribulus*, *Hypericum*, *Biserrula*, *Pastinaca*, *Ammi*, *Brassica*, *Trifolium*, *Lotus*, *Narthecium*, *Senecio*, *Cynoglossum*, *Heliotropium*, *Persicaria*, *Alternanthera*, *Crotalaria*, *Erodium*, *Lantana*, *Petroselinum*, *Heracleum*, *Tanacetum*, and *Thamnosma*), herbs were the most diverse functional group among phototoxic organisms and made up the largest proportion of case reports with 106 cases (Figure 4).

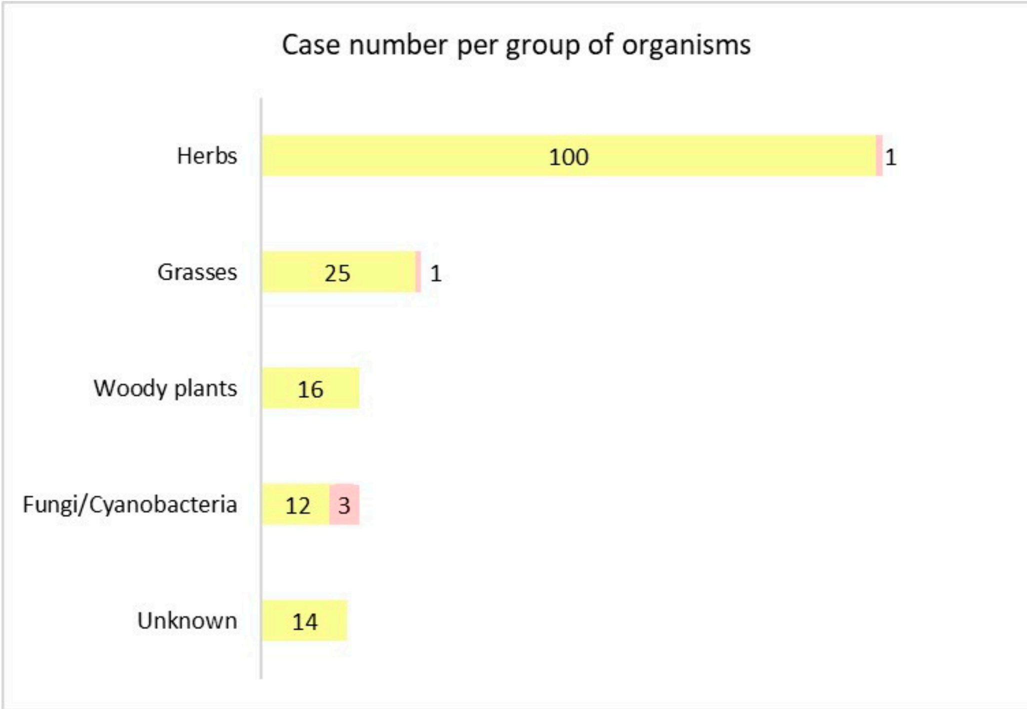

Figure 4. Case reports (n) differentiated according to the phototoxic organisms. Yellow: verified cases. Red: non-verified cases. N_{total} = 172.

There were seven woody plants (*Enterolobium*, *Myoporum*, *Stryphnodendron*, *Heterophyllaea*, *Holocalyx*, *Malachra*, and *Phytolacca*) that caused 16 cases, and only two grasses (*Brachiaria* and *Panicum*) that were involved in 25 cases. *Pithomyces chartarum* and mold species caused about 12 cases.

3.4. Animal Species, General Feed Characteristics, and Type of Photosensitization

Sheep (n = 69 animals) and cattle (n = 55) accounted for most cases (39.0% and 31.1%; Table 2) because they are commonly kept in large flocks [11] and thus were statistically overrepresented here. Animals received more feed of normal quality (89.3%) than of poor quality (10.7%).

Table 2. Effect of different feed qualities on incidence of photosensitization in different animal species.

Animal Species	Normal Feed Quality	Poor Feed Quality	Total
Sheep	60	9	69
Cattle	45	10	55
Horse	30	1	31
Goat	11	0	11
Other animals [2]	10	1	11
Sum (n)	156	21	177 [1]
Portion (%)	88.1	11.9	100

[1] The authors of four publications ([35–38]; described cases in which more than one animal species was involved, resulting in slightly higher number of animals (n = 177) than case reports (n = 172). [2] Identifications in the category "other animals" consisted of nine species, four domestic ones (pig, donkey, water buffalo, and buffalo) and five wild ones (fallow deer, gray and red kangaroo, hairy-nosed wombat, and llama).

As known from earlier studies (for example [39]), secondary photosensitization happens more frequently (55.4% versus 33.3%; Table 3), with liver-toxic plants as the cause of the disease. In horses, however, the incidence of primary photosensitization was revealed to be higher (18 versus 10 animals).

Table 3. Incidence of distinct kinds of photosensitization in different animal species.

Animal Species	Primary Photosensitization	Secondary Photosensitization	Unknown Kind of Photosensitization	Total
Sheep	22	44	3	69
Cattle	13	29	13	55
Horse	18	10	3	31
Goat	4	7	0	11
Other animals	2	8	1	11
Sum (n)	59	98	20	177
Portion (%)	33.3	55.4	11.3	100

Fresh feed represented the largest portion among the kinds of feed stuff (Table 4). Most of affected animal individuals (71.8%) went back to fresh feed consisting of whole plants with their complete composition and concentration of secondary metabolites. The few existing cases related to conserved feed (n = 25; 14.1%) may be attributed to phototoxic compounds still being present, yet these are at least partly decomposed during any conservation process. For example Araya and Ford (1981) showed that 80% of the hypericin content was lost when St. John's Wort (*Hypericum perforatum*) was dried in the sun [40]. This had been shown for the coumarins in *Pastinaca* [41] and an unknown component in *Medicago* [42] too.

Table 4. Effect of different kinds of feed on incidence of photosensitization in different animal species.

Animal Species	Kind of Feed				Sum (n)
	Fresh	Conserved	Both	Unknown	
Sheep	59	4	3	3	69
Cattle	39	7	5	4	55
Horse	13	13	3	2	31
Goat	9	0	0	2	11
Other animals	7	1	3	0	11
Sum (n)	127	25	14	11	177
Portion (%)	71.8	14.1	7.9	6.2	100

3.5. Feed Diversity and Feed Choice

Freshly harvested or still growing phototoxic plants are more effective (n = 127) than their dried or conserved counterparts (n = 25; Table 5), a finding confirmed by [43].

Table 5. Effect of plant diversity and feed choice on incidence of photosensitization per kind of feed.

Feedstuff	High Diversity	Low Diversity	Unknown Level of Diversity	Sum of Animals (n)	Feed Choice	No Feed Choice	Unknown Possibility of Feed Choice	Sum of Animals (n)
Fresh feed	21	56	50	127	8	83	36	127
Conserved feed	5	12	8	25	3	22	0	25
Fresh and conserved feed	6	5	3	14	4	6	4	14
Unknown feed condition	0	4	7	11	0	2	9	11
Sum (n)	32	77	68	177	15	113	49	177
(%)	18.1	43.5	38.4	100	8.5	63.8	27.7	100

High feed diversity reduced the incidence 2.4-fold (32 versus 77 animals) while selection possibility even reduced it 7.5-fold (15 versus 113 animals), confirming that "selection behaviour has such high importance for the cognitive well-being of ruminants and access to feed diversity should be a compulsory criterion of welfare" [44]. In this context, it was interesting that goats were the only species that did not fall ill if they had any choice to select plant species (incidence = 0) (Table 6).

Table 6. Effect of feed diversity and choice on incidence of photosensitization in different animal species.

Animal Species	High Diversity	Low Diversity	Unknown Level of Diversity	Sum	Feed Choice	No feed Choice	Unknown Possibility of Feed Choice	Sum
Sheep	8	35	26	69	8	43	18	69
Cattle	12	21	22	55	4	36	15	55
Horse	8	12	11	31	2	21	8	31
Goat	2	4	5	11	0	8	3	11
Other animals	2	5	4	11	1	5	5	11
Sum (n)	32	77	68	177	15	113	49	177
Portion (%)	18.1	43.5	38.4	100	8.5	63.8	27.7	100

The incidence of photosensitization in the case of fresh feed was 10-fold lower if selection was possible (8 versus 83 animals; see Table 5), but only 2.6-fold lower in the case of high diversity (21 versus 56 animals). Even in conserved feed, the higher ranking of feed choice was eminent: the incidence of photosensitization in the case of conserved feed was 7.3-fold lower if selection was possible (3 versus 22 animals; see Table 5), but only 2.4-fold lower in the case of high diversity (5 versus 12 animals).

4. Discussion

The introduction of two key variables served to analyze whether the number of photosensitization cases in farm animals was associated with different levels of feed plant diversity or feed choice.

4.1. Reliability of Meta-Data

The high proportion (60.9%) of references without any indication as to whether they are peer-reviewed reflects the small publication format in which case reports often appear, in particular when written decades ago. At 38.4% and 27.7%, the level of diversity and the possibility of feed choice are unknown to a significant extent. However, authors of studies that did not address these variables are not expected to have considered them relevant, probably because the feed lacks a certain species diversity or the animals were not given any feed choice. Otherwise, both variables would have been a significant observation, since dealing with phototoxic organisms presumes that the authors thoroughly look at the feed composition and choice. In conclusion, it is unlikely that unknown feed diversity and choice could be cases of high diversity or selection possibility. The data gap would rather lead to an underestimation of the effects of the two key variables. On the other hand, it was necessary to rely on the authors' statements on diversity and choice, expressed as indirect parameters. This method might be of varying accuracy and thus could weaken the results presented here.

4.2. Impact of Feed Diversity and Feed Choice on the Incidence of Photosensitization

Since only cases of disease are described in case reports, cases of healthy animals are usually missing. In other words: in our meta-study dealing only with case reports, the incidence is at least n = 1, whereas the number of control individuals is almost always n = 0. Within this database, even optimal conditions such as good quality feed with a high α-diversity and free choice lead to cases of photosensitization. With this bias, the impact of both key variables needs to be discussed. For example, there is an increased probability of the presence of poisonous plants with increasing diversity [45]. Therefore, in feeds of high α-diversity, the frequency of encounters between phototoxic plants and farm animals is increased. On the other hand, even a high diversity is prone to decrease over time under constricted conditions such as overgrazing or lack of ad libitum feeding. At this point, "plant species diversity" implies "dietary choice". Such a chronological effect of the two paired key variables might be the reason why feed diversity alone diminishes the incidence of photosensitization to a far lesser degree than selection possibility does. Against this background, feed condition plays an essential role. One would suggest that the animals would recognize the respective toxins as repellents in fresh plants and thus would refrain from eating certain species, as anticipated by Provenza et al. (1992) who assumed that an animal is capable of avoiding phototoxic plant species [46]. The tenfold lower incidence of cases in which fresh feed was eaten than in cases of preserved feed shows that successful negative selection indeed occurs, provided that the animals have a choice between feedstuffs or feed plants. α-diversity, an elementary condition for resilient grassland communities [47], is thus favorable for commercial animal nutrition as long as it is accompanied by feeding management with the possibility of feed selection.

The most interesting examples in this context are horses and goats. Horses mainly suffer from primary photosensitization because, more often than other animal species, they receive certain feed plants such as alfalfa (*Medicago*) or come into contact with weeds such as parsnip (*Pastinaca*) that cause this kind of photosensitization ([41,42], Appendix A). However, horses fall ill almost regardless of whether the feed is species-rich or not. This could mean that the choice between plants of an initially species-rich feedstuff becomes smaller over the feeding time, resulting in the dominance of phototoxic plants that no longer can be avoided. Such a situation could occur if the feed is not given ad libitum, as is usual in horse racing stables. Moreover, horses might be forced to feed on pure lucerne, a common feedstuff, dried or fresh, for horses kept for pleasure [42,48,49]. Alfalfa is known to cause photosensitization under conditions that have not yet been fully clarified [42]. In both scenarios (no ad libitum or pure alfalfa feeding), horses cannot avoid even brief physical contact with plants with phototoxic agents relevant to the type of primary photosensitization that goes back to direct skin contact of the agents [50,51]. In contrast, goats are tolerant of giant hogweed (*Heracleum mantegazzianum*), one of the most potent phototoxic plant species [52]. Moreover, according to the data here, goats manage to avoid phototoxic plants under both high and low feed diversity if they still have free choice between plant species. The finding of zero incidence in a genuine database of cases of photosensitization in an animal species known for its selective feeding behavior [53] is remarkable and underlines that feed choice is the ultimate condition for the preservation of animal health.

5. Conclusions

The results of the present meta-analysis indicate that feed choice and diversity are positively related to photosensitization. In particular, animals having low or no possibility of feed choice are more likely to be affected by photosensitization. Therefore, various kinds of feedstuff given simultaneously or the permanent existence of feed plant diversity in the pasture or in the feed trough may prevent photosensitization in farm animals.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A. Reference List of Case Reports Sorted by Animal Species

1. Cattle

- Bourke, C.A.; Rayward, D. Photosensitisation in dairy cattle grazing alligator weed (Alternanthera philoxeroides) infested pastures. Aust. Vet. J. 2003, 81, 361–362, doi:10.1111/j.1751-0813.2003.tb11515.x.
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