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Original Research

Incidence of Spontaneous Ocular Lesions in Laboratory Rabbits

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Laboratory rabbits are commonly used for ocular drug and device studies. The purpose of this study was to determine the incidence of spontaneous ocular lesions in laboratory rabbits with respect to sex, breed, and supplier. We retrospectively evaluated ophthalmic examination records of rabbits screened between April 2008 and April 2010. These 1840 records represented 572 black Dutch belted (DB), 1022 New Zealand white (NZW), and 246 NZW × New Zealand red F_1 crosses (WRF1). Rabbits were between 6 and 16 wk of age and had been received from 5 suppliers. Ocular structures evaluated were the cornea, lens, iris and vitreous with respect to sex, breed and supplier. A total of 177 rabbits (9.6%) and 233 eyes (6.3%) were effected. Of total rabbits, 15.3% males and 7.3% females were affected. The most common structure affected was the cornea in 5.7% of rabbits, (DB 11.7%, NZW 3.0%, and NZR 3.3%). The lens at 3.6% was second most common (DB 2.1%, NZW 4.6%, and NZR 3.3%). Both iris (0.2%) and vitreous (0.3%) were not significantly affected. Significant sex-breeder-supplier combinations were: cornea DB supplier D, supplier D females, supplier D males, DB males and NZR females; and lens: NZW females; and at least one affected ocular structure: NZW supplier D, supplier D females, DB males, NZW females, and NZR females. Breed, sex, and supplier were significant variables of ocular lesions in laboratory rabbits. Investigators should consider each of these variables when choosing rabbits for ocular studies.

Abbreviations: DB, Dutch belted; NZW, New Zealand white; WRF1, New Zealand white × New Zealand red F_1 crossed.

Rabbits are used widely for ocular toxicology, device, and drug studies due to the availability of normative data, their large eyes, and their relatively low cost compared with other laboratory animals.[13,15] Ocular prescreening is performed to identify rabbits with any ocular lesions to determine whether individual animals should be placed into a study. This prescreening is important, because including a rabbit with an ocular defect might adversely affect a study's results. Specifically, ocular abnormalities that are present at the start of a study may be reported as study-related findings, and histopathologic abnormalities may be interpreted as resulting from the device or drug therapy.

Complete ocular prescreening examinations include external examination of the lids and slit-lamp biomicroscopy, with or without indirect ophthalmoscopy. Common conditions to rule out include inflammation, cataracts, and corneal defects. Rabbits affected by one or more of these conditions should not be placed in a study involving ocular observations. In our experience, when breeders ship only rabbits that pass ocular prescreenings, fewer rabbits are rejected at the testing facility. In addition, facilities that eliminate rabbits with ocular lesions from the facility's breeding program can decrease the incidence of spontaneous ocular lesions, because many defects are congenital.[2,3,6,9-12] Lesions may develop during shipment from trauma or aging, necessitating a second examination at the testing facility.[1] We have found that screening rabbits earlier than 1 wk prior to the intended start of a study may miss lesions, because lesions can develop over time, as a rabbit ages or with a new incidence of trauma.

We found only 1 report[11] that evaluated the incidence of ocular lesions in laboratory rabbits. This retrospective study to determine incidence of cataracts in laboratory rabbits was limited in that the only ocular structure evaluated was the lens. In addition, only 2 breeds, New Zealand whites (NZW) and New Zealand reds (WRF1), were assessed.[11]

Regular ocular screenings of rabbit breeding colonies allow vendors to remove affected animals from the breeding program, given that defects like corneal dystrophy are heritable.[10] Previous studies assessing individual structures of the rabbit eye have been limited by small sample size,[11] and a comprehensive study evaluating all structures has not been reported. In addition, we found no previous studies that compared the incidences of ocular lesions in laboratory rabbits between vendors. Therefore, the purpose of the present study was to determine the occurrence and incidence of spontaneous ocular lesions in laboratory rabbits, evaluating sex–breed–supplier combinations. We hypothesize that both the breed and sex of the rabbit and the individual supplier will influence the rate of incidence of ocular lesions in laboratory rabbits.

Materials and Methods

Humane care and use of animals. Animals were housed in an AAALAC-accredited laboratory animal facility that was in compliance with the *Guide for the Care and Use of Laboratory Animals*.[7] All examinations involving animals were approved by the

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IACUC at the Biological Test Center, a contract research organization registered with the US Department of Agriculture.

Animals. Data were obtained from 1840 prestudy ophthalmic examinations conducted on rabbits by 3 veterinarians over a 2-y period. Breeds examined included NZW, NZW × New Zealand red F_1 crosses (WRF1), and black Dutch belted (DB). Animals were obtained in 50 shipments from 5 suppliers (suppliers A, B, C, D, and E). Rabbits ranged in age from 6 to 16 wk at time of ocular examination. Each animal was housed in individual, hanging, stainless-steel cages in a room with controlled environmental conditions (16 to 22 °C; 30% to 70% relative humidity; 10 to 15 air changes per hour; and a 12:12-h light:dark cycle). All rabbits were clinically healthy and acclimated to facility conditions for a minimum of 7 d prior to ocular examinations.

Records examined. Records were reviewed between April 2008 and April 2010. Animals with abnormalities that did not involve the globe (for example, lid defects) were excluded from the study. Each rabbit underwent a complete ophthalmologic examination including slit-lamp biomicroscopy (LS15, Kowa Optimed, Torrance, CA). Direct pupillary light reflexes were examined before induction of mydriasis with topical 0.5% tropicamide solution (Mydriacyl, Alcon Pharmaceuticals, Ft Wayne, TX). Observations of the cornea, lens, iris, and vitreous were performed according to an ocular observation scoring system.[8] For the cornea: 0, normal; 1, some loss of transparency in epithelium only; 2, moderate loss of transparency, with cloudiness all the way to endothelium; 3, entire thickness of the corneal stroma was involved, and diffuse illumination rendered underlying structures barely visible; 4, entire thickness of the corneal stroma was involved, underlying structures cannot be seen by using diffuse illumination. The lens received a score of 0 if it was clear; otherwise, scores were based on the anatomic location of any lesion: 1, anterior cortex or capsule; 2, nuclear lesion; 3, posterior cortex or capsule; and 4, equatorial lesion. The iris was scored as follows: 0, normal iris without hyperemia; 1, minimal injection of secondary vessels; 2, minimal injection of tertiary vessels with moderate injection secondary vessels; 3, moderate injection of secondary and tertiary vessels with slight swelling of iris stroma; and 4, marked injection of secondary and tertiary vessels with marked swelling of iris stroma. The vitreous received scores as follows: 0, clear; 1, a few scattered opacities present, and fundus was unimpaired; 2, moderate scattered opacities, details of fundus somewhat obscured; 3, many opacities, marked blurring of fundus details; and 4, dense opacities, no view of fundus.[8] Examiners did not diagnose specific diseases but rather rated their influence on ocular structures by using the scoring system. Examinations were considered negative (score of 0) or positive (score, 1 or greater), thereby removing subjective staging of lesions, so that our study was not affected by having 3 different examiners.

Statistical analysis. The software program used for analysis was SAS version 9 (SAS Institute, Cary, NC). Analyses were performed by using a series of Fisher Exact Tests, evaluating the incidence of ocular abnormality in relation to each of the variables sex, breed, and rabbit supplier while holding the remaining variables constant. For example, analysis was done for the variable sex for each combination of breed and supplier. Because of the large number of tests and multiple outcomes, differences were considered to be statistically significant when the P value was less than 0.01.

Results

Incidence of spontaneous ocular lesions. A total of 1840 (529 male and 1311 female) rabbits were examined, comprising 572 (185 female, 387 male) DB; 1022 (880 female, 142 male) NZW; and 246 (246 female, 0 male) WRF1 rabbits (Table 1). Of the 1840 rabbits examined, 177 (9.6%) had ocular lesions that excluded the animals from placement on an ocular study, with 233 (6.3%) eyes being affected. Both eyes were affected in 54 (30.5%) of the 177 affected rabbits; only 2 of the 54 rabbits had 2 ocular structures involved in the same eye. Therefore, the most common outcome in eyes with lesions was that a singular structure was involved. The number of rabbits affected with respect to each structure relative to all rabbits evaluated was: cornea, 104 (5.7%); lens, 67 (3.6%); iris 3 (0.2%); and vitreous, 5 (0.3%; Table 2). Overall, the incidence of structure involved relative to affected animals was: cornea, 58.8%; lens, 37.9%; iris, 1.7%; and vitreous, 2.8% (total percentage exceeds 100% because of the 2 rabbits with 2 ocular structures affected). Among all rabbits examined, the incidence of bilateral involvement according to structure was: cornea, 34 (1.8%); lens, 17 (0.9%); iris, 2 (0.1%); and vitreous, 1 (0.1%). Of affected rabbits, the incidence of those with bilateral disease based on structure was: cornea, 32.7%; lens, 25.4%; iris, 66.7%; and vitreous, 20%.

Spontaneous ocular lesions by sex. The incidences of corneal, lens, iris, and vitreous lesions were compared between sexes, relative to breed and supplier (Table 2). Total affected rabbits were 81 male (15.3% of the 1840 rabbits examined) and 96 female (7.3%). In male rabbits, ocular lesions occurred more often in DB (16.5%) than NZW (4.2%); however, ocular lesions in female rabbits occurred more often in NZW and WRF1 (8.8 and 6.9%, respectively) than DB rabbits (3.2%). Statistical analysis revealed that female NZW rabbits from supplier D experienced significantly more ocular lesions of any structure than did male rabbits (12.8% compared with 4.4%, respectively; $P = 0.01$).

Ocular structures commonly affected were the cornea and lens for both male and female rabbits. The cornea was affected more often in male (12.7%) than female (2.8%) rabbits. Corneal lesions occurred more frequently in male DB (14.2%) compared with NZW (0.7%) rabbits, whereas corneal lesions in female rabbits were less frequent in DB (0.5%) than either NZW (3.2%) or WRF1 (3.3%) rabbits. The incidence of corneal lesions in DB rabbits from supplier D differed significantly ($P = 0.003$) between male (6.3%) and female (0.5%) rabbits.

Lenticular lesions were more frequent in female (4.1%) than male (2.5%) rabbits. Male and females had almost identical incidence of lens lesions in DB (2.1% compared with 2.2%), and less frequently in both NZW (male, 3.5%; female, 5.0%) and WRF1 (female 3.3%). Conversely, iris and vitreous lesions were uncommon in both sexes. Lesions of the iris affected male and female rabbits equivalently, regardless of breed (male rabbits: DB, 0.3%; NZW, 0%; female rabbits: DB, 0%; NZW, 0.2%; WRF1, 0%). Lesions of the vitreous occurred only in female rabbits (overall, 0.4%; DB, 0.5%; NZW, 0.2%; WRF1, 0.4%).

Spontaneous ocular lesions by breed. The incidence of ocular lesions varied significantly according to breed (Table 2). The incidence of corneal lesions in female and male rabbits from supplier D differed significantly among breeds (female rabbits: WRF1, 7.6%; NZW, 3.8%; DB, 0.5%; $P = 0.039$; male rabbits: DB, 6.3%; NZW, 0.7%; $P = 0.0098$). The incidence of ocular lesions (in any structure) in female rabbits from supplier D varied significantly

Table 1. Number of rabbits from each supplier

	Dutch belted		New Zealand white		New Zealand red		Total
Supplier	Female	Male	Female	Male	Female	Male	rabbits
A	0	0	386	0	0	0	386
B	0	197	14	0	154	0	365
C	0	0	66	0	0	0	66
D	185	190	234	136	92	0	837
E	0	0	180	6	0	0	186
Total	185	387	880	142	246	0	1840

Table 2. Incidence (%) of rabbits with at least one eye with affected ocular structure

Group	Cornea	Lens	Iris	Vitreous
All rabbits	5.7%	3.6%	0.2%	0.3%
Dutch belted	11.7%	2.1%	0.2%	0.2%
New Zealand white	3.0%	4.6%	0.2%	0.3%
New Zealand red	3.3%	3.3%	0%	0.4%
Supplier A	4.7%	5.2%	0.3%	0.3%
Supplier B	15.1%	1.4%	0.3%	0.3%
Supplier C	0%	0%	0%	0%
Supplier D	3.6%	4.8%	0.1%	0.4%
Supplier E	0.5%	1.1%	0%	0%

($P = 4.1 \times 10^{-4}$) among the different breeds (WRF1, 14.1%; NZW, 12.8%; DB, 3.2%).

Spontaneous ocular lesions by supplier. Incidence of ocular lesions was highly dependent on supplier (Table 2). Furthermore, corneal lesions were significantly ($P = 2.7 \times 10^{-8}$) more numerous in DB male rabbits from supplier B (27.4%) compared with supplier D (6.3%), whereas WRF1 female rabbits from supplier D experienced significantly ($P = 0.0049$) more corneal lesions than did those from supplier B (7.6% compared with 0.6%, respectively). Regarding lenticular lesions, we observed a significant ($P = 0.0016$) difference in incidence between suppliers of NZW females: D, 8.5%; A, 5.2%; E, 1.1%; B, 0%; and C, 0%. Comparing the incidence of ocular lesions (any structure) by supplier revealed significantly ($P = 3.2E-07$) greater incidence in DB male rabbits from supplier B (29.4%) than from supplier D (8.9%). The overall incidence of ocular lesions in NZW female rabbits was significant ($P = 2.8 \times 10^{-6}$) among suppliers: D, 12.8%; A, 10.4%; E, 1.7%; B, 0%; and C, 0%. WRF1 female rabbits from supplier D had a higher ($P = 0.0011$) incidence of ocular lesions than did those from supplier B (14.1% and 2.6%, respectively).

Discussion

Rabbits are used frequently in studies on ophthalmic drugs and devices and in toxicologic studies, yet available data on the rates of incidence of spontaneous ocular lesions in the rabbit are limited.[11] Ocular studies in rabbits use specific breeds: NZW rabbits have relatively large unpigmented eyes that are sensitive for toxicologic studies, whereas DB and WRF1 rabbits have pigmented eyes. However, information on the incidence of ocular lesions according to breed also is limited.[11] In addition, DB rabbits are smaller than are other breeds and therefore are a good choice for ocular toxicity and pharmacokinetics studies when test article is limited.[15] Research facilities often acquire rabbits from various vendors on the basis of personal experience and the availability of rabbits of a particular breed and sex. Rabbits acquired from a supplier with a high incidence of spontaneous lesions among their animals cost research facilities in terms of resources, because affected rabbits cannot be placed on an ocular study, and time, because of delay due to inadequate numbers of rabbits free of ocular lesions. Although our facility can place rabbits excluded from ocular research protocols in nonocular studies, not every facility may have this option. Therefore, a facility should limit the number of rabbits received with spontaneous ocular lesions. This restriction can be achieved by selecting the breed, sex, and supplier most appropriate for a given study.

Corneal lesions are common in rabbits because of their environment, diet, lid abnormalities, and heritability.[1,2,5,6-12,14] In our experience, nesting material and fighting between rabbits in different cages largely contribute to the traumatic corneal lesions that occur prior to arrival (before or during shipment). In the current study, corneal defects were present in 5.7% of all rabbits examined (1.9% bilaterally affected). The cornea was affected more often in male (15.3%) than female (2.8%) rabbits. This finding supports the notion that various behaviors, such as fighting and playing with neighboring rabbits, contributes to ocular trauma. DB rabbits had the highest incidence of corneal lesions (11.7%), whereas incidences in NZW (3.0%) and WRF1 (3.3%) rabbits were considerably lower. Based on the author's experience, DB rabbits tend to be more aggressive and fight more often with each other than NZW or WRF1 rabbits, perhaps accounting for a high incidence of traumatic corneal lesions in this breed, as roughly two thirds of our DB rabbits were male.

In addition, superficial corneal dystrophy, a familial disease, occurs in DB rabbits,[10] including those at our facility. DB rabbits from supplier D were more likely to have corneal lesions in male (6.3%) than female (0.5%) rabbits. We were unable to determine whether male rabbits overall are more likely to develop corneal lesions than are female, because we obtained only male rabbits from the only other supplier of DB animals (B). When rates of lesions were compared by breed, corneal lesions occurred significantly more often in female WRF1 rabbits from supplier D (7.6%) than in both NZW (3.8%) and DB (0.5%) female rabbits from the same supplier and in male DB rabbits from supplier D (6.3%) compared with both NZW (0.7%) and WRF1 (0%) male rabbits from that supplier. We were unable to compare the incidence of corneal lesions among male rabbits from supplier B between DB and other breeds, because the only breed represented among male rabbits from supplier B was DB. However, 27.4% of all male DB supplier B rabbits had corneal lesions in at least one eye compared with 6.3% of male DB supplier D rabbits.

Various spontaneous lens defects in rabbits occur due to infectious, environmental, or genetic causes. Pathologies of the lens can result from a lens-induced uveitis due to *Encephalitozoa cuniculi*.[4,17] Only 1 of our 5 vendors has a history of being positive for *E. cuniculi*. Cataracts have been described as idiopathic findings of older rabbits and due to incidental or familial (consistent with an autosomal recessive mode of inheritance) causes in young animals.[11] We found the lens to be the second most commonly affected ocular structure, with an incidence of 3.6% among all rabbits examined. The incidence of lenticular lesions in NZW rabbits in our current study (4.6%) is similar to that reported in the literature (5.7%).[10] However, we noted a greater incidence in WRF1 (3.3%) than previously reported (1.1%).[11] This difference is likely due to the relatively small numbers of WRF1 used in both our current study (n = 246) and that previously reported (n = 276).[13] Much larger numbers of NZW were evaluated in both our current study (n = 1022) and that previously reported (n = 670), likely giving us a better representation of lenticular lesions in rabbits than was found by using WRF1. In our study, DB rabbits had the lowest incidence of lenses affected (2.1%); no published data on affected lenses in DB rabbits were available for comparison. In addition, the incidence of lens lesions in female NZW rabbits varied significantly depending on supplier, with rabbits from suppliers D (8.5%) and A (5.2%) more likely to have lens lesions than those from suppliers E (1.1%), B (0%), and C (0%). No significant differences occurred when comparing rates of lens lesions in rabbits for breed–supplier or sex–supplier combinations.

Spontaneously occurring ocular lesions in both the iris (0.2%) and vitreous (0.3%) of our rabbits, but the rates of incidence for lesions in these ocular structures did not vary depending on the sex, breed, or supplier of the animals. One can conclude that the sex, breed, and supplier of the rabbits are less important factors for studies of the iris or vitreous than for studies of the cornea or lens.

Suppliers of rabbits played a significant role in rates of lesions in our rabbits for both sex and breed. Corneal lesions appeared significantly more often in both DB male rabbits from supplier B (27.4%) compared with supplier D (6.3%) and in WRF1 female rabbits from supplier D (7.6%) compared with supplier B (0.6%). Various environmental factors can account for differences between suppliers, including nesting materials and shipping containers. If the lesions we observed were heritable, however, this factor becomes an issue when deciding on which vendor to use if the vendor keeps closed breeding colonies. Regarding lesions of the lens, NZW female rabbits from supplier D were more likely to have lesions than those from supplier A (8.5% versus 5.2%, respectively); however, rabbits from both suppliers D and A were more likely to have lenticular lesions than were those from suppliers E (1.1%), C (0%), and B (0%). However, limitations were present when we evaluated the incidence ocular lesions based on supplier. Not all rates could be determined for every supplier–sex–breed combination, because not every sex and breed was obtained from each supplier. In fact, our study only includes data for all 3 breeds of the same sex (female) for 1 supplier (supplier D); therefore, we only have one supplier–sex combination for which we can compare all 3 breeds. In addition, total numbers of rabbits varied significantly between all 5 suppliers. Rabbits from supplier C had no spontaneous ocular lesions, but we obtained only 66 rabbits from this supplier. In contrast, suppliers B and D accounted for the most ocular lesions, and these vendors supplied the largest numbers of animals (n = 730 and 1674, respectively). This bias also holds for breed, in that we had many more NZW rabbits (n = 1022) than both WRF1 and DB (n = 246 and 572, respectively). In fact, as we compared each sex–breed–supplier combination, total numbers ranged between 66 and 386 rabbits only. Because the numbers of subjects are so small, even one shipment that contains large numbers of affected rabbits will affect greatly the incidence data we obtain. This association is especially true regarding familial traits, because each shipment contains rabbits with the same birth date, which therefore are likely to be related.

Data were evaluated to determine the overall incidence of ocular lesions in any structure by comparing sex, breed, and supplier. Of all affected rabbits, the cornea accounted for 58.8% of lesions, whereas the lens, vitreous, and iris were affected at rates of 37.9%, 1.7%, and 2.8%, respectively. We therefore conclude that, when evaluating rabbits for any type of ocular lesion, the cornea is the most significant component, with some contribution from the lens. This pattern is true in our data in that the cornea was the ocular structure involved in every significant breed–sex–supplier combination with one exception, which involved the lens (NZW female rabbits). In fact, almost every time that the cornea or lens was significant for a particular breed–sex–supplier combination, significance also was found for ocular lesions of any structure for the same breed–sex–supplier combination (cornea: supplier D female rabbits; DB male rabbits; and WRF1 female rabbits; and lens: NZW female rabbits). The only instances in which significance did not mimic that for lens or cornea combinations were for lesions for DB supplier D rabbits and sex (significant for corneal but not overall ocular lesions), NZW supplier D and sex (significant for overall but not for corneal or lenticular lesions), and supplier D male rabbits (significant for corneal but not overall lesions).

Ocular studies sometimes will include rabbits with spontaneous ocular lesions among the test population. Investigators may choose to use the lesioned eye as the control, while using the eye with no lesions as the test eye. Alternatively, investigators may choose to use rabbits with bilaterally affected eyes that do not involve the structures that are the focus of the study, monitoring progression by comparing the test eye with the control. Among our rabbits with lesions, the proportions for which both eyes were affected were: cornea, 32.7%; lens, 25.4%; iris, 66.7%; and vitreous, 20%. Although bilateral involvement appears high in the iris, only 3 rabbits examined had this lesion. More interesting is the fact that almost one third of rabbits with corneal lesions had both eyes affected. These rates must be considered when considering whether a rabbit with an ocular defect can be included in a study.

Our study has several limitations. Three veterinarians, none of whom was a board-certified veterinary ophthalmologist, performed the examinations. Because the MacDonald–Shadduck scoring system[8] was used for evaluation, we can only differentiate lesions based on structure involved rather than on diagnosis. In addition, only 4 ocular structures, rather than the entire eye, were evaluated in our study. Because not every rabbit had an indirect examination, we did not include structures in the back of the eye specifically the fundus and optic nerve head, in our study. Glaucoma due to goniodysgenesis of the trabecular meshwork and pectinate ligaments has been documented in NZW rabbits.[9,16] Rabbits appear normal at birth, but ocular pressure rises to 26 to 48 mm Hg after the first 1 to 3 mo. The classic presentation is buphthalmia, opaque corneas, and loss of vision.[9,16] In addition,

we only examined rabbits whose age at presentation was between 6 and 16 wk. Changes due to glaucoma and other hereditary conditions, including corneal dystrophy and cataracts, tend to develop with age, and therefore the inclusion of older rabbits in our study likely would have increased the incidence of ocular lesions. From our experience, young rabbits typically are used in ocular studies; we chose to evaluate the typical ages used at our facility. Finally, only female WRF1 were evaluated in the current study, and therefore our observations regarding this breed are limited.

Sex, breed, and supplier significantly influenced the incidence and type of spontaneous ocular lesions in the rabbits evaluated in the current study. Investigators should consider these factors when choosing rabbits for use in ophthalmic studies.

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