Preclinical Ocular Considerations in Laboratory Rabbits

Introduction / Background
Laboratory rabbits are most commonly used 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. However, spontaneous ocular lesions will occur in these animals, detrimentally affecting study results and study outcomes. Specifically, ocular abnormalities that are present but undetected at the start of a study may be reported as study-related findings, and pre-existing histopathologic abnormalities may be interpreted as resulting from the device or drug therapy. Previous research has shown that the incidence of these lesions may be tracked when interactions between sex, breed, and supplier are quantified. Incidence of Spontaneous Ocular Lesions in Laboratory Rabbits, a study performed by Dana Holve, Karen Mundwiler, and Stacy Pritt, 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 F1 crosses (WRF1).

A total of 177 rabbits (9.6%) and 233 eyes (6.3%) were affected by ocular lesions. The most common structure affected was the cornea in 5.7% of rabbits (DB 11.7%, NZW 3.0%, and NZR [New Zealand Red] 3.3%). This data suggests that lesions are more prevalent than once thought and their affluence must be addressed.

Ocular prescreening can reveal subtle defects.

Ocular prescreening is a very effective way to identify ocular defects, and affected animals can then be excluded from a study.
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 assessment. This paper serves to elucidate the ways in which spontaneous ocular lesions are formed and the ways in which researchers may preemptively avoid rabbits with these confounding lesions.

**Problem Statement**
A wide array of spontaneous ocular lens defects in rabbits may occur due to infectious, environmental, or genetic causes. Pathologies of the lens may result from a lens-induced uveitis due to Encephalitozoon cuniculi, an obligate intracellular parasite. Cage and facility maintenance can help decrease the presence of these eukaryotic organisms. Also, cataracts have been described as idiopathic findings in older rabbits and due to incidental or familial causes (consistent with an autosomal recessive mode of inheritance) in young animals. Genetic defects within succeeding generations of rabbits may be avoided when affected animals are removed from the breeding process. Furthermore, various environmental factors can also contribute to lens defects. Research has shown that differences among sources of supplies such as nesting materials and shipping containers may lead to different rates of lesions, especially when sex is also taken into account. However, the rates of lesions cannot necessarily be determined for every supplier/sex/breed combination because not every sex and breed can be obtained from a given supplier. Rabbits acquired from suppliers with a high incidence of spontaneous lesions among their animals are costly both in terms of resources—affected rabbits must be housed but cannot be placed on an ocular study—and time—studies are delayed due to inadequate numbers of rabbits free of ocular lesions. Thus, it is vitally important that researchers take into account the breed of rabbit being used in a study as well as the facility from which they came.

<table>
<thead>
<tr>
<th>Incidence of Rabbits with Affected Ocular Structure</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>All Rabbits</td>
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<tr>
<td>Dutch Belted</td>
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<tr>
<td>New Zealand White</td>
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<td>New Zealand Red</td>
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<td>Supplier A</td>
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**Proposed Solution**
Spontaneous ocular lesions within laboratory rabbits have proven to have a perpetual negative effect on ocular research; however, there are multiple solutions available for limiting the ways in which these lesions may disrupt studies. One way a company or research facility may alleviate issues arising from having rabbits with spontaneous ocular lesions is by still including rabbits with lesions but using the lesioned eye as the untreated control in the study. In addition, rabbits excluded from ocular research protocols can still be used in non-ocular studies, but not every facility may have this option. Overall, 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 and by taking the necessary precautions. Corneal lesions are common in rabbits because of their environment, diet, lid abnormalities, and heritability; but if identified, they can be easily dealt with. Nesting material and fighting between rabbits in different cages largely contributes to the traumatic corneal lesions that occur prior to arrival (before or during shipment). This is a trivial problem that can be resolved if rabbits are single-housed and selected nesting material has no history of irritation.

A first step in eliminating ocular lesions within rabbits starts when the breeders only ship rabbits that pass ocular prescreening. In this way, fewer rabbits have to be rejected after arriving at the testing facility. In addition, facilities that eliminate rabbits with ocular lesions from their breeding program can decrease the incidence of spontaneous ocular lesions, because many defects are congenital. Lesions may still develop during shipment, from trauma or aging, as previously stated, necessitating a second examination at the testing facility. This second examination is pivotal if a researcher does not want any defect within the animals before the start of a study. Regular ocular screenings of rabbit breeding colonies also allow vendors to remove affected animals from the breeding program, given that defects like corneal dystrophy are heritable.

**Conclusion**

Investigators should always consider facility, breed, and sex when choosing rabbits for use in ophthalmic studies. As previously shown, 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. Overall, eliminating affected rabbits from breeding colonies, performing various prescreening exams, and examining the breeding facility before purchasing the laboratory animals are all ways these lesions may be controlled and their impact reduced.

**Appendix- References**

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