Non-Neoplastic Ocular Histologic Background Findings in Sprague-Dawley Rats at MPI Research

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ABSTRACT

Introduction: Discernment of test article-related lesions requires accurate recognition of spontaneous background lesions. Sprague-Dawley (SD) rats are among the most commonly used rodents for toxicology studies, and documentation of background findings is important in providing context for interpretation of potential toxicity. This study reviews non-neoplastic ocular background lesions in control SD rats from a nonclinical CRO over a 5-year period.

Methods: Histopathology data were tabulated for 7,392 SD control rats (3,656 males and 3,736 females) enrolled in toxicity studies ranging in duration from 2 weeks to 2 years. Comparisons of ocular lesion incidence were made across study duration and gender.

Results: The most prevalent findings were cataracts (1.23%), retinal atrophy (1.81%), and inflammation (1.14%) in the 2-year study population. Cataracts and inflammation were nearly four times more prevalent in males than in females. Retinal folds and rosettes were most prevalent in 4-week (1.64%) and 13-week (1.11%) study populations, with equal prevalence between genders. Overall, cataracts, retinal atrophy, inflammation, and retinal folds and rosettes occurred in greater than 0.5% of the total population across all study durations.

Conclusion: SD rats develop a range of spontaneous ophthalmology lesions, which may affect analysis of test article-related effects. The prevalence of lesions varied with study duration.

Impact Statement: This study provides a review of the incidence of ocular background lesions in Sprague-Dawley rats at a large preclinical CRO, allowing improved assessment of ocular toxicity and potential shifts in ocular background finding incidence over time in this strain.

INTRODUCTION

Sprague-Dawley (SD) rats are among the most commonly used model in toxicology studies. Pre-study ocular examinations are used to remove rats with congenital abnormalities that could interfere with accurate study interpretation. Common congenital abnormalities documented in laboratory mice and rats include microphthalmia, lens opacity, hyaloid artery remnants, retinal folding and atrophy, and colobomas.[1] Spontaneous lesions also develop in aging rats. SD rats between 4 and 6 weeks of age have been reported to develop corneal crystals, nuclear cataract, and vitreal hemorrhage.[3] SD rats ranging from 5 to 110 weeks of age can develop keratitis, lens opacity, lens vacuoles, and capsular cataracts with incidence increasing dramatically with age.[5] As SD rats approach 2 years of age, increased incidence of focal linear retinopathy, senile retinal atrophy, and colobomas is reported.[2] For these reasons, background data for each colony are important to document so that spontaneous lesions may be differentiated from toxic adverse effects, and provide a basis for determination of potential test article exacerbation of known spontaneous lesions.

METHODOLOGY

A retrospective study was performed using historical eye lesion records for control Sprague-Dawley rats in studies carried out between 2009 and 2013. Data were analyzed from oral gavage, subcutaneous, intravenous, dermal, and diet studies ranging from 2 weeks to 2 years in duration, with rats entering studies at 7 to 8 weeks of age. A total of 7,392 historical control animals, consisting of 3,656 males and 3,736 females, were included in the data. Lesions were ordered by diminishing prevalence and comparisons of incidence were made between the different study durations.

RESULTS

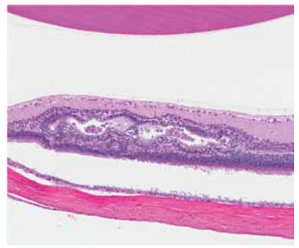

Image 1. Retinal fold/rosette. (H&E 80x)

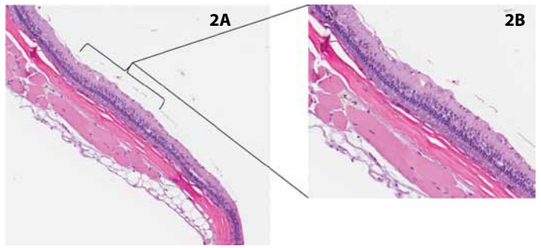

Image 2. Retinal atrophy/degeneration **A**: H&E 80x. **B**: H&E 200x

Background Microscopic Ocular Findings in Sprague-Dawley Rats in Acute, Chronic, and Carcinogenicity Studies

Study Duration	2-4 Week		13 Week		6 Month		2 Year		Total	
Number of Animals Examined	1521		1347		1105		3419		7392	
Findings:	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Retinal Degeneration and Atrophy	6	0.39	2	0.15	8	**0.72**	62	**1.81**	78	**1.06**
Retinal Folds and Rosettes	25	**1.64**	15	**1.11**	10	**0.90**	6	0.18	56	**0.76**
Inflammation	6	0.39	3	0.22	3	0.27	39	**1.14**	51	**0.69**
Cataract	-	-	1	0.07	1	0.09	42	**1.23**	44	**0.60**
Pthisis Bulbi	-	-	1	0.07	1	0.09	10	0.29	12	0.16
Corneal Erosion and Ulcer	-	-	1	0.07	-	-	9	0.26	10	0.14
Optic Nerve Degeneration	1	0.07	-	-	1	0.09	5	0.15	7	0.09
Corneal Neovascularization	-	-	-	-	-	-	7	0.20	7	0.09
Optic Nerve Spongiosis	-	-	-	-	-	-	7	0.20	7	0.09
Focal Chorioretinal Hypoplasia	2	0.13	4	0.30	-	-	-	-	6	0.08
Squamous Metaplasia	-	-	-	-	-	-	6	0.18	6	0.08
Optic Nerve Gliosis	-	-	-	-	-	-	5	0.15	5	0.07
Hemorrhage	2	0.13	-	-	2	0.18	1	0.03	5	0.07
Keratitis	1	0.07	-	-	-	-	4	0.12	5	0.07
Keratopathy	-	-	1	0.07	-	-	3	0.09	4	0.05

Findings are listed in descending order of total prevalence at all ages combined. Those with percent incidence over 0.5% are in bold.

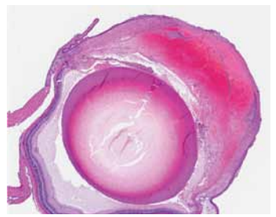

Image 3. Inflammation, ulceration, hemorrhage. (H&E 15x)

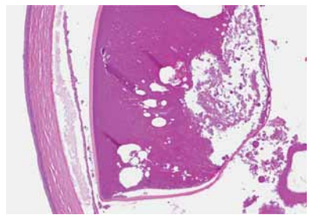

Image 4. Cataract and lens rupture. (H&E 50x)

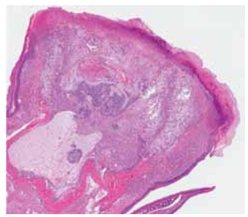

Image 5. Pthisis bulbi. (H&E 15x)

CONCLUSIONS

- Retinal degeneration and atrophy, retinal folds and rosettes, cataracts, and inflammation were the most prevalent findings in the total population (greater than 0.5% incidence).
- Incidence of retinal degeneration and atrophy, cataracts, and inflammation increased with age and study duration, and had highest incidences in the 2-year study population (1.81%, 1.23%, and 1.14% respectively). Retinal degeneration and atrophy identified here may represent a broad range of findings and causality; including hereditary atrophy, nutritional atrophy, phototoxic retinopathy, and senile atrophy, among others.
- Retinal folds and rosettes were more prevalent in acute studies, with decreasing incidence from the 6-month to two-year study population (0.90% to 0.18% respectively). Decreased incidence of retinal folds and rosettes with age has been documented elsewhere, and may be due to recovery over time.[2]
- Several similar studies have documented high incidence of colobomas, persistent pupillary membranes, linear focal retinopathy, and corneal opacities.2,4 These were not seen in significant numbers in this study, presumably because ophthalmoscopic pre-study examinations remove affected animals from the study population at MPI Research.
- Evaluation of this large number of variably-aged animals from a single site allows assessment and comparison of the historical incidence of ocular findings across multiple age cohorts and provides a clear historical basis for assessment of background findings in Sprague-Dawley rats.

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