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EJP-CONCERT

European Joint Programme for the Integration of Radiation Protection Research

H2020 – 662287

D 9.51 - Detailed work plan for irradiations (Gantt)

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Reviewer(s): CONCERT coordination team

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Abstract

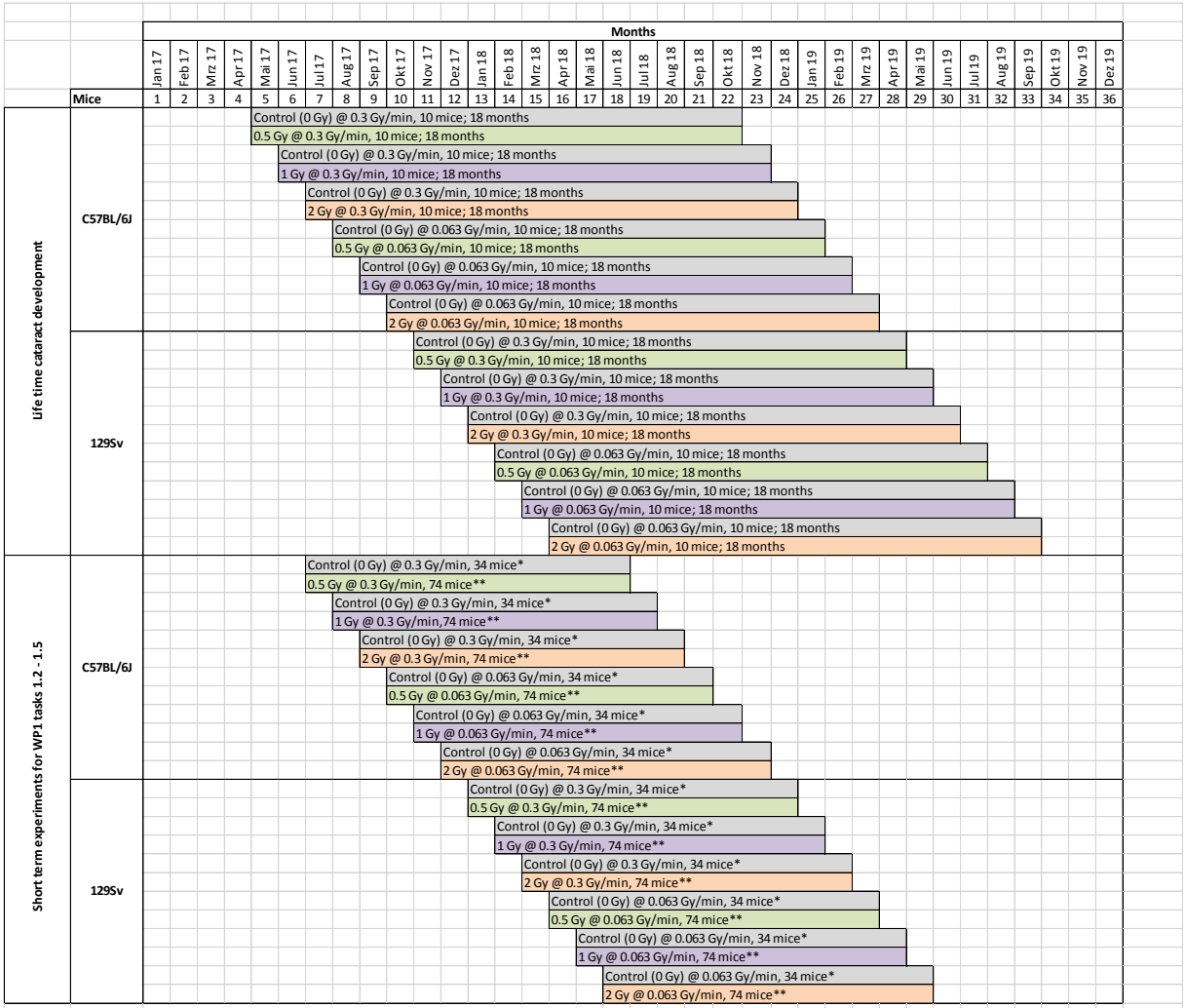
The lens of the eye is known to be more radiosensitive than previously thought but, despite a substantial reduction in occupational dose limits based on recent epidemiological information and reanalyses, the mechanisms of low dose radiation cataract induction are still unclear. This is an important current public health issue, for instance for medical radiation workers, many of whom will need to amend their working practices despite a clear understanding of the effects of chronic, low dose, ionising radiation exposure.

The LDLensRad project aims to bring together experts from across Europe to answer a number of key research questions on this topic, including: how does low dose radiation cause cataracts; is there a dose rate effect, and how does genetic background influence cataract development after radiation exposure. CONCERT Deliverable 9.51, 5.1.1 of the project, describes the detailed work plan and timing for irradiations of mice for long term and short term models of cataract initiation and development.

The experiments will be carried out in 6 different mouse strains, as described in the Gantt charts, to test the impact of genetic background and further inform the mechanistic understanding. Mice will be exposed to doses of 0 to 2 Gy at an acute, high dose rate (0.3 Gy/min) or at a more protracted, low dose rate (0.063 Gy/min), to assess the effect of dose protraction on the dose response for radiation cataractogenesis. Mice will be irradiated at 10 weeks (when they have fully developed lenses) at PHE and HMGU. At ENEA, mice will be irradiated at neonatal age (postnatal day 2), the age of peak susceptibility to radiation lens injury, and at 10 weeks, a non-responsive age, specifically in order to investigate the ageing effect in this particularly age-sensitive strain. The mice will then be followed for up to 18 mth post exposure, with Scheimpflug imaging taking place at 1 mth intervals to track the appearance and development of cataracts. Behavioural testing will be carried out concurrently and, at the end of the long term study, the lenses of surviving mice will be analysed for histological and morphological changes and further pathological analysis of organs will be carried out, to test the hypothesis that lens effects can be used as an indicator of global radiation effects.

In addition, for each strain, dose and dose rate, lenses extracted from groups of mice will be assessed for: initial DNA damage at 0, 4 and 24 hrs following exposure; intracellular communication, cell cycle effects, biochemical analyses and genetic pathway analyses at 0, 4 and 24 hrs, 4 and 12 mth; proliferative and morphological effects at 24 hrs, 4 and 12 mth; miRNA content using Next Generation Sequencing (NGS) at 4 hrs and qRT-PCR at 24 hrs, 4 and 12 mth. The results and associated analysis of these studies will be made available as further Deliverables as the project progresses.

1. DH-PHE


Months
Jan 17 Feb 17 Mrz 17 Apr 17 Mai 17 Jun 17 Jul 17 Aug 17 Sep 17 Okt 17 Nov 17 Dez 17 Jan 18 Feb 18 Mrz 18 Apr 18 Mai 18 Jun 18 Jul 18 Aug 18 Sep 18 Okt 18 Nov 18 Dez 18 Jan 19 Feb 19 Mrz 19 Apr 19 Mai 19 Jun 19 Jul 19 Aug 19 Sep 19 Okt 19 Nov 19 Dez 19
Mice
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
Life time cataract development
C57BL/6J
Control (0 Gy) @ 0.3 Gy/min, 10 mice; 18 months
0.5 Gy @ 0.3 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 10 mice; 18 months
1 Gy @ 0.3 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 10 mice; 18 months
2 Gy @ 0.3 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 10 mice; 18 months
0.5 Gy @ 0.063 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 10 mice; 18 months
1 Gy @ 0.063 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 10 mice; 18 months
2 Gy @ 0.063 Gy/min, 10 mice; 18 months
129Sv
Control (0 Gy) @ 0.3 Gy/min, 10 mice; 18 months
0.5 Gy @ 0.3 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 10 mice; 18 months
1 Gy @ 0.3 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 10 mice; 18 months
2 Gy @ 0.3 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 10 mice; 18 months
0.5 Gy @ 0.063 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 10 mice; 18 months
1 Gy @ 0.063 Gy/min, 10 mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 10 mice; 18 months
2 Gy @ 0.063 Gy/min, 10 mice; 18 months
Short term experiments for WP1 tasks 1.2 - 1.5
C57BL/6J
Control (0 Gy) @ 0.3 Gy/min, 34 mice*
0.5 Gy @ 0.3 Gy/min, 74 mice**
Control (0 Gy) @ 0.3 Gy/min, 34 mice*
1 Gy @ 0.3 Gy/min,74 mice**
Control (0 Gy) @ 0.3 Gy/min, 34 mice*
2 Gy @ 0.3 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 34 mice*
0.5 Gy @ 0.063 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 34 mice*
1 Gy @ 0.063 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 34 mice*
2 Gy @ 0.063 Gy/min, 74 mice**
129Sv
Control (0 Gy) @ 0.3 Gy/min, 34 mice*
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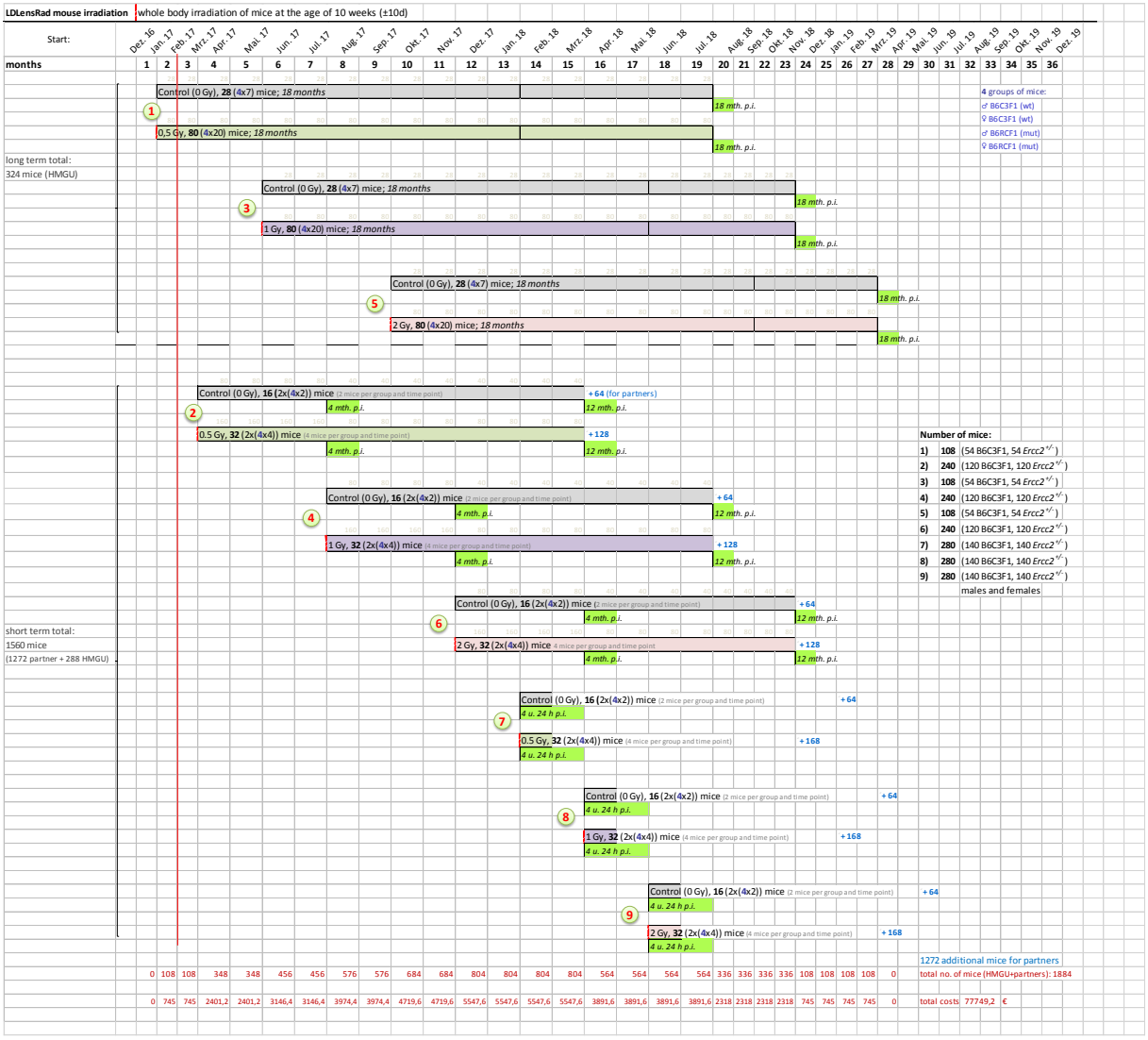
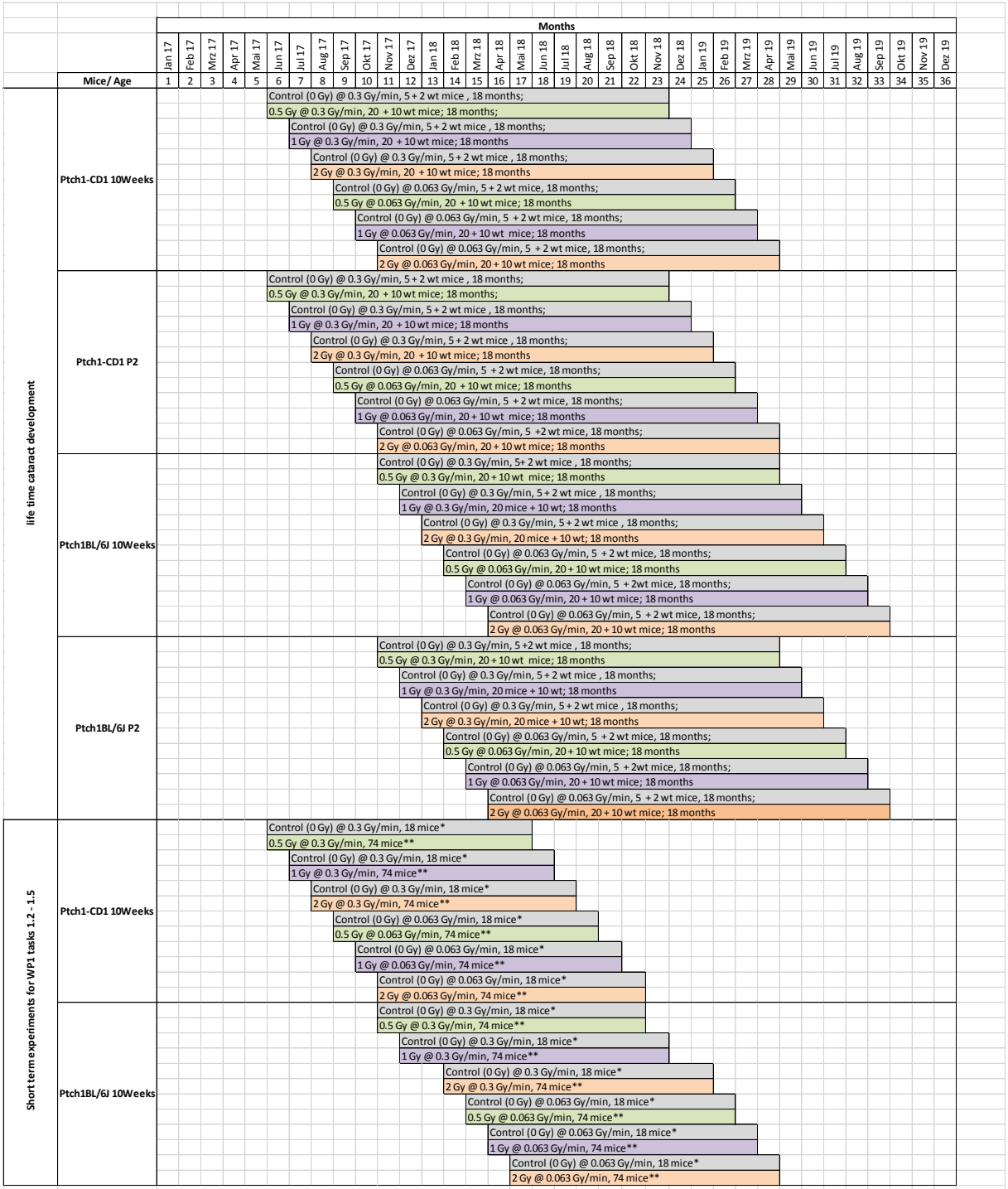
Control (0 Gy) @ 0.3 Gy/min, 34 mice*
1 Gy @ 0.3 Gy/min, 74 mice**
Control (0 Gy) @ 0.3 Gy/min, 34 mice*
2 Gy @ 0.3 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 34 mice*
0.5 Gy @ 0.063 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 34 mice*
1 Gy @ 0.063 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 34 mice*
2 Gy @ 0.063 Gy/min, 74 mice**
*34 mice: 8 mice -> 4 hrs; 10 mice -> 24 hrs; 8 mice -> 4 mth; 8 mice -> 12 mth
**74 mice: 22 mice -> 4 hrs; 20 mice -> 24 hrs; 16 mice -> 4 mth; 16 mice -> 12 mth
Total mice: 1536 (Life time study 240; Short term studies 1296)

2. HMGU


LDLensRad mouse irradiation
whole body irradiation of mice at the age of 10 weeks (±10d)
Start:
months
Control (0 Gy), 28 (4x7) mice; 18 months
0,5 Gy, 80 (4x20) mice; 18 months
18 mth. p.i.
4 groups of mice:
♂ B6C3F1 (wt)
♀ B6C3F1 (wt)
♂ B6RCF1 (mut)
♀ B6RCF1 (mut)
long term total:
324 mice (HMGU)
Control (0 Gy), 28 (4x7) mice; 18 months
1 Gy, 80 (4x20) mice; 18 months
Control (0 Gy), 28 (4x7) mice; 18 months
2 Gy, 80 (4x20) mice; 18 months
Control (0 Gy), 16 (2x(4x2)) mice (2 mice per group and time point)
+64 (for partners)
4 mth. p.i.
12 mth. p.i.
0.5 Gy, 32 (2x(4x4)) mice (4 mice per group and time point)
+128
Control (0 Gy), 16 (2x(4x2)) mice (2 mice per group and time point)
+64
1 Gy, 32 (2x(4x4)) mice (4 mice per group and time point)
+128
Number of mice:
1) 108 (54 B6C3F1, 54 Ercc2+/-)
2) 240 (120 B6C3F1, 120 Ercc2+/-)
3) 108 (54 B6C3F1, 54 Ercc2+/-)
4) 240 (120 B6C3F1, 120 Ercc2+/-)
5) 108 (54 B6C3F1, 54 Ercc2+/-)
6) 240 (120 B6C3F1, 120 Ercc2+/-)
7) 280 (140 B6C3F1, 140 Ercc2+/-)
8) 280 (140 B6C3F1, 140 Ercc2+/-)
9) 280 (140 B6C3F1, 140 Ercc2+/-)
males and females
short term total:
1560 mice
(1272 partner + 288 HMGU)
2 Gy, 32 (2x(4x4)) mice (4 mice per group and time point)
Control (0 Gy), 16 (2x(4x2)) mice (2 mice per group and time point)
+64
4 u. 24 h p.i.
0.5 Gy, 32 (2x(4x4)) mice (4 mice per group and time point)
+168
1 Gy, 32 (2x(4x4)) mice (4 mice per group and time point)
2 Gy, 32 (2x(4x4)) mice (4 mice per group and time point)
1272 additional mice for partners
total no. of mice (HMGU+partners): 1884
total costs 77749,2 €

3. ENEA


Months
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Mice/ Age
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
life time cataract development
Ptch1-CD1 10Weeks
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
0.5 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months;
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
1 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
2 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
0.5 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
1 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
2 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Ptch1-CD1 P2
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
0.5 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months;
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
1 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
2 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
0.5 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
1 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 +2 wt mice, 18 months;
2 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Ptch1BL/6J 10Weeks
Control (0 Gy) @ 0.3 Gy/min, 5+ 2 wt mice , 18 months;
0.5 Gy @ 0.3 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
1 Gy @ 0.3 Gy/min, 20 mice + 10 wt; 18 months
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
2 Gy @ 0.3 Gy/min, 20 mice + 10 wt; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
0.5 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2wt mice, 18 months;
1 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
2 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
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Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
1 Gy @ 0.3 Gy/min, 20 mice + 10 wt; 18 months
Control (0 Gy) @ 0.3 Gy/min, 5 + 2 wt mice , 18 months;
2 Gy @ 0.3 Gy/min, 20 mice + 10 wt; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
0.5 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2wt mice, 18 months;
1 Gy @ 0.063 Gy/min, 20 + 10 wt mice; 18 months
Control (0 Gy) @ 0.063 Gy/min, 5 + 2 wt mice, 18 months;
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Control (0 Gy) @ 0.063 Gy/min, 18 mice*
1 Gy @ 0.063 Gy/min, 74 mice**
Control (0 Gy) @ 0.063 Gy/min, 18 mice*
2 Gy @ 0.063 Gy/min, 74 mice**
*18 mice: 6 mice -> 4 hrs; 6 mice -> 24 hrs; 3 mice -> 4 mth; 3 mice -> 12 mth
**74 mice: 22 mice -> 4 hrs; 20 mice -> 24 hrs; 16 mice -> 4 mth; 16 mice -> 12 mth
Total mice: 1992 (Life time study 888; Short term studies 1104)