

病理学検査結果速報

試験番号： XXXXXXXXXX

試験表題：BK1、BK2 及び PA：ラットを用いた 7 日間反復経口投与毒性試験

BK1、BK2 及び BK より抽出した PA の毒性を検討するため、0 mg/kg/日 (媒体、0.5 w/v% メチルセルロース溶液)、1200mg/kg/日の BK1、360 及び 1200mg/kg/日の BK2 並びに 8.52 mg/kg/日の PA を雌雄の SD ラットに 7 日間反復経口投与し、腎臓の病理組織学検査を実施いたしました。以下にその概要をご報告いたしますので、別紙「GROUP INCIDENCE」及び「INDIVIDUAL ANIMAL DATA」と共にご検討いただきますよう、お願いいたします。

剖検では、BK2 の 1200mg/kg 群の雄に腎臓の大型化、雌に腎臓の大型化及び退色、胸腺の小型化、PA 投与群の雌に腎臓の大型化及び退色がみられ、いずれも BK2 及び PA 投与に起因した変化と考えられました。BK2 の 1200mg/kg 群では、雌に肺の暗赤色巣がみられましたが、1 例にみられた限局性の変化であり、偶発性変化と考えられました。

病理組織学検査では、BK2 の 1200mg/kg 群及び PA 群の雌に、近位尿細管の変性、壊死、再生及び巨大核の出現、間質の細胞浸潤及び硝子円柱がみられ、さらに BK2 の 1200mg/kg 群では近位尿細管の拡張がみられました。巨大核の出現、間質の細胞浸潤及び硝子円柱は BK2 の 1200mg/kg 群と PA 群の間に差はみられませんでした。変性、壊死及び再生は、BK2 の 1200mg/kg 群で病変程度が強くみられました。

一方、雄では、BK2 の 1200mg/kg 群に近位尿細管の変性、壊死、再生及び巨大核の出現、間質の細胞浸潤、PA 群に近位尿細管の変性及び壊死がみられました。変性及び壊死は、雌同様、PA 群よりも BK2 の 1200mg/kg 群で強くみられました。

これらの BK2 及び PA 群の変化は雄に比べて雌で強くみられ、BK2 の 360mg/kg 群においても、雌では近位尿細管の変性及び壊死がみられましたが、雄ではいずれの変化もみられませんでした。

BK1 群では雌雄共に特記すべき変化はみられませんでした。

Study number: [REDACTED]

Date: 22 April 2024

GROUP INCIDENCE: NECROPSY - ALL DATA

Kill type: End of dosing period

Tissue	Group:	1	2	3	4	5
	Sex:	M	M	M	M	M
	mg/kg:	0.00	1200.00	360.00	1200.00	8.52
Observation	Number:	4	5	5	5	5
Kidney						
Large		0	0	0	1	0

Study number: [REDACTED]

Date: 22 April 2024

GROUP INCIDENCE: NECROPSY - ALL DATA

Kill type: End of dosing period

Tissue	Group: Sex: mg/kg: Number:	1 F 0,00 4	2 F 1200,00 5	3 F 360,00 5	4 F 1200,00 5	5 F 8,52 5
Observation						
Kidney						
Discoloration, pale		0	0	0	5	5
Large		0	0	0	4	5
Lung (bronchus)						
Focus, dark red		0	0	0	1	0
Thymus						
Small		0	0	0	3	0

Study number: XXXXXXXXXX

Date: 22 April 2024

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: End of dosing period

Tissue	Group:	1	2	3	4	5
	Sex:	M	M	M	M	M
	mg/kg:	0.00	1200.00	360.00	1200.00	8.52
Observation	Number:	4	5	5	5	5
Kidney						
Number examined		4	5	5	5	5
Not remarkable		4	5	5	0	1
Degeneration, tubule, proximal		0	0	0	5	4
minimal		0	0	0	3	4
mild		0	0	0	2	0
Necrosis, tubule, proximal		0	0	0	5	1
minimal		0	0	0	5	1
Regeneration, tubule, proximal		0	0	0	2	0
mild		0	0	0	2	0
Infiltrate, interstitium		0	0	0	1	0
minimal		0	0	0	1	0
Karyomegaly, tubule, proximal		0	0	0	1	0
minimal		0	0	0	1	0

Study number:

Date: 22 April 2024

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: End of dosing period

Tissue	Group:	1	2	3	4	5
	Sex:	F	F	F	F	F
	mg/kg:	0.00	1200.00	360.00	1200.00	8.52
Observation	Number:	4	5	5	5	5
Kidney						
Number examined		4	5	5	5	5
Not remarkable		4	5	0	0	0
Dilatation, tubule, proximal		0	0	0	4	0
minimal		0	0	0	2	0
mild		0	0	0	2	0
Degeneration, tubule, proximal		0	0	5	5	5
minimal		0	0	5	0	0
mild		0	0	0	0	2
moderate		0	0	0	1	2
severe		0	0	0	4	1
Necrosis, tubule, proximal		0	0	2	5	5
minimal		0	0	2	0	1
mild		0	0	0	1	3
moderate		0	0	0	4	1
Regeneration, tubule, proximal		0	0	0	5	5
mild		0	0	0	1	5
moderate		0	0	0	4	0
Cast, hyaline		0	0	0	4	3
minimal		0	0	0	4	3
Infiltrate, interstitium		0	0	0	5	5
minimal		0	0	0	5	5
Karyomegaly, tubule, proximal		0	0	0	5	5
minimal		0	0	0	1	2
mild		0	0	0	4	3

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 1001 Group 1M 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 1002 Group 1M 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 1003 Group 1M 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 1004 Group 1M 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2001 Group 2M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2002 Group 2M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 2003 Group 2M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2004 Group 2M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2005 Group 2M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 3001 Group 3M 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 3002 Group 3M 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 3003 Group 3M 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 3004 Group 3M 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 3005 Group 3M 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 4001 Group 4M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: minimal, bilateral Necrosis,tubule,proximal: minimal, bilateral
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Animal No. 4002 Group 4M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: minimal, bilateral Necrosis,tubule,proximal: minimal, bilateral
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Animal No. 4003 Group 4M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: mild, bilateral Necrosis,tubule,proximal: minimal, bilateral Regeneration,tubule,proximal: mild, bilateral
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Animal No. 4004 Group 4M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

Kidney	Large: mild, bilateral
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Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 4004 Group 4M 1200.00 mg/kg Day 8 End of dosing period

Histopathology:

Kidney	Degeneration,tubule,proximal: mild, bilateral Necrosis,tubule,proximal: minimal, bilateral Regeneration,tubule,proximal: mild, bilateral Infiltrate,interstitium: minimal, bilateral, mononuclear Karyomegaly,tubule,proximal: minimal, bilateral
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Animal No. 4005 Group 4M 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: minimal, bilateral Necrosis,tubule,proximal: minimal, bilateral
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Animal No. 5001 Group 5M 8.52 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: minimal, bilateral
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Animal No. 5002 Group 5M 8.52 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: minimal, bilateral
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Animal No. 5003 Group 5M 8.52 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney	Degeneration,tubule,proximal: minimal, bilateral
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Animal No. 5004 Group 5M 8.52 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

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INDIVIDUAL ANIMAL DATA

Animal No. 5004 Group 5M 8.52 mg/kg Day 8 End of dosing period

Histopathology:

No significant findings.

Animal No. 5005 Group 5M 8.52 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney

Degeneration,tubule,proximal: minimal, bilateral
Necrosis,tubule,proximal: minimal, bilateral

Animal No. 1101 Group 1F 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 1102 Group 1F 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 1103 Group 1F 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 1104 Group 1F 0.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 2101 Group 2F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2102 Group 2F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2103 Group 2F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2104 Group 2F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 2105 Group 2F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

No significant findings.

Animal No. 3101 Group 3F 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney

Degeneration,tubule,proximal: minimal, bilateral
Necrosis,tubule,proximal: minimal, bilateral

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 3102 Group 3F 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney Degeneration,tubule,proximal: minimal, bilateral

Animal No. 3103 Group 3F 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney Degeneration,tubule,proximal: minimal, bilateral

Animal No. 3104 Group 3F 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney Degeneration,tubule,proximal: minimal, bilateral

Animal No. 3105 Group 3F 360.00 mg/kg Day 8 End of dosing period

Necropsy:

No significant findings.

Histopathology:

Kidney Degeneration,tubule,proximal: minimal, bilateral
Necrosis,tubule,proximal: minimal, bilateral

Animal No. 4101 Group 4F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

Kidney Discoloration,pale: bilateral
Large: mild, bilateral

Lung (bronchus) Focus,dark red: 1 present
5x4mm

Histopathology:

Kidney Dilatation,tubule,proximal: mild, bilateral
Degeneration,tubule,proximal: severe, bilateral
Necrosis,tubule,proximal: moderate, bilateral
Regeneration,tubule,proximal: moderate, bilateral
Cast,hyaline: minimal, bilateral
Infiltrate,interstitium: minimal, bilateral, mononuclear
Karyomegaly,tubule,proximal: mild, bilateral

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 4102 Group 4F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

Kidney Discoloration,pale: bilateral

Thymus Small: mild

Histopathology:

Kidney Dilatation,tubule,proximal: minimal, bilateral
Degeneration,tubule,proximal: severe, bilateral
Necrosis,tubule,proximal: moderate, bilateral
Regeneration,tubule,proximal: moderate, bilateral
Cast,hyaline: minimal, bilateral
Infiltrate,interstitium: minimal, bilateral, mononuclear
Karyomegaly,tubule,proximal: mild, bilateral

Animal No. 4103 Group 4F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

Kidney Discoloration,pale: bilateral
Large: mild, bilateral

Thymus Small: mild

Histopathology:

Kidney Dilatation,tubule,proximal: minimal, bilateral
Degeneration,tubule,proximal: severe, bilateral
Necrosis,tubule,proximal: moderate, bilateral
Regeneration,tubule,proximal: moderate, bilateral
Cast,hyaline: minimal, right
Infiltrate,interstitium: minimal, bilateral, mononuclear
Karyomegaly,tubule,proximal: mild, bilateral

Animal No. 4104 Group 4F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

Kidney Discoloration,pale: bilateral
Large: mild, bilateral

Histopathology:

Kidney Dilatation,tubule,proximal: mild, bilateral
Degeneration,tubule,proximal: severe, bilateral
Necrosis,tubule,proximal: moderate, bilateral
Regeneration,tubule,proximal: moderate, bilateral
Cast,hyaline: minimal, bilateral
Infiltrate,interstitium: minimal, bilateral, mononuclear
Karyomegaly,tubule,proximal: mild, bilateral

Animal No. 4105 Group 4F 1200.00 mg/kg Day 8 End of dosing period

Necropsy:

Kidney Discoloration,pale: bilateral
Large: mild, bilateral

Thymus Small: mild

Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 4105 Group 4F 1200.00 mg/kg Day 8 End of dosing period

Histopathology:

Kidney	Degeneration,tubule,proximal: moderate, bilateral Necrosis,tubule,proximal: mild, bilateral Regeneration,tubule,proximal: mild, bilateral Infiltrate,interstitium: minimal, bilateral, mononuclear Karyomegaly,tubule,proximal: minimal, bilateral
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Animal No. 5101 Group 5F 8.52 mg/kg Day 8 End of dosing period

Necropsy:

Kidney	Discoloration,pale: bilateral Large: mild, bilateral
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Histopathology:

Kidney	Degeneration,tubule,proximal: moderate, bilateral Necrosis,tubule,proximal: mild, bilateral Regeneration,tubule,proximal: mild, bilateral Cast,hyaline: minimal, bilateral Infiltrate,interstitium: minimal, bilateral, mononuclear Karyomegaly,tubule,proximal: mild, bilateral
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Animal No. 5102 Group 5F 8.52 mg/kg Day 8 End of dosing period

Necropsy:

Kidney	Discoloration,pale: bilateral Large: mild, bilateral
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Histopathology:

Kidney	Degeneration,tubule,proximal: severe, bilateral Necrosis,tubule,proximal: moderate, bilateral Regeneration,tubule,proximal: mild, bilateral Cast,hyaline: minimal, bilateral Infiltrate,interstitium: minimal, bilateral, mononuclear Karyomegaly,tubule,proximal: mild, bilateral
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Animal No. 5103 Group 5F 8.52 mg/kg Day 8 End of dosing period

Necropsy:

Kidney	Discoloration,pale: bilateral Large: mild, bilateral
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Histopathology:

Kidney	Degeneration,tubule,proximal: mild, bilateral Necrosis,tubule,proximal: mild, bilateral Regeneration,tubule,proximal: mild, bilateral Infiltrate,interstitium: minimal, bilateral, mononuclear Karyomegaly,tubule,proximal: minimal, bilateral
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Animal No. 5104 Group 5F 8.52 mg/kg Day 8 End of dosing period

Necropsy:

Kidney	Discoloration,pale: bilateral Large: mild, bilateral
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Study number: [REDACTED]

Date: 22 April 2024

INDIVIDUAL ANIMAL DATA

Animal No. 5104 Group 5F 8.52 mg/kg Day 8 End of dosing period

Histopathology:

Kidney	Degeneration,tubule,proximal: mild, bilateral Necrosis,tubule,proximal: minimal, bilateral Regeneration,tubule,proximal: mild, bilateral Infiltrate,interstitium: minimal, right, mononuclear Karyomegaly,tubule,proximal: minimal, bilateral
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Animal No. 5105 Group 5F 8.52 mg/kg Day 8 End of dosing period

Necropsy:

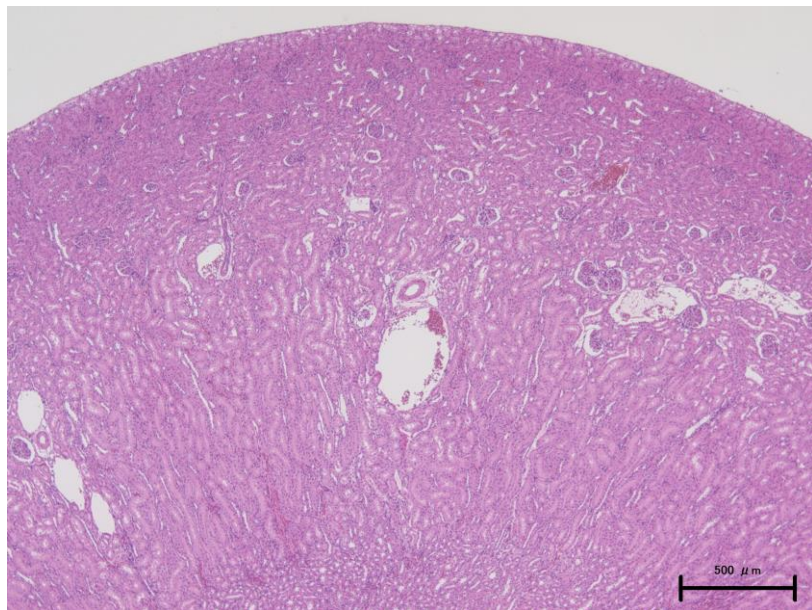
Kidney	Discoloration,pale: bilateral Large: mild, bilateral
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Histopathology:

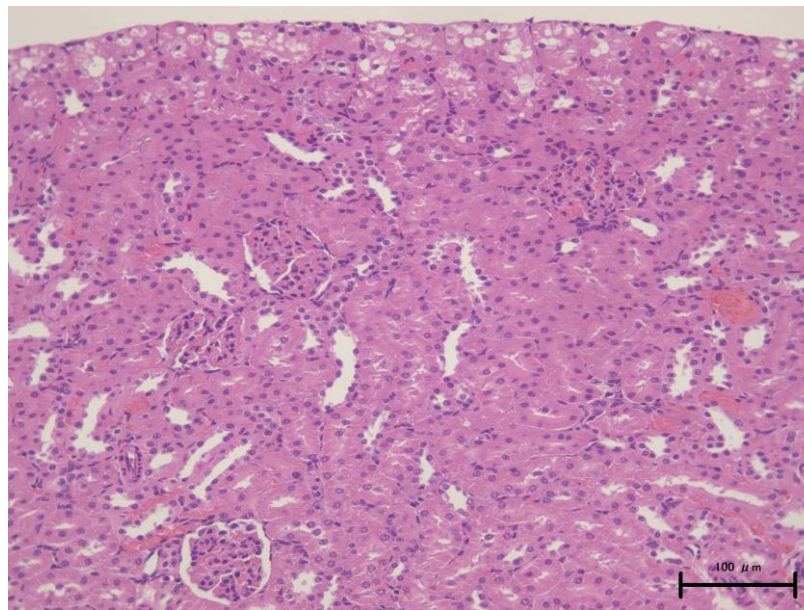
Kidney	Degeneration,tubule,proximal: moderate, bilateral Necrosis,tubule,proximal: mild, bilateral Regeneration,tubule,proximal: mild, bilateral Cast,hyaline: minimal, bilateral Infiltrate,interstitium: minimal, bilateral, mononuclear Karyomegaly,tubule,proximal: mild, bilateral
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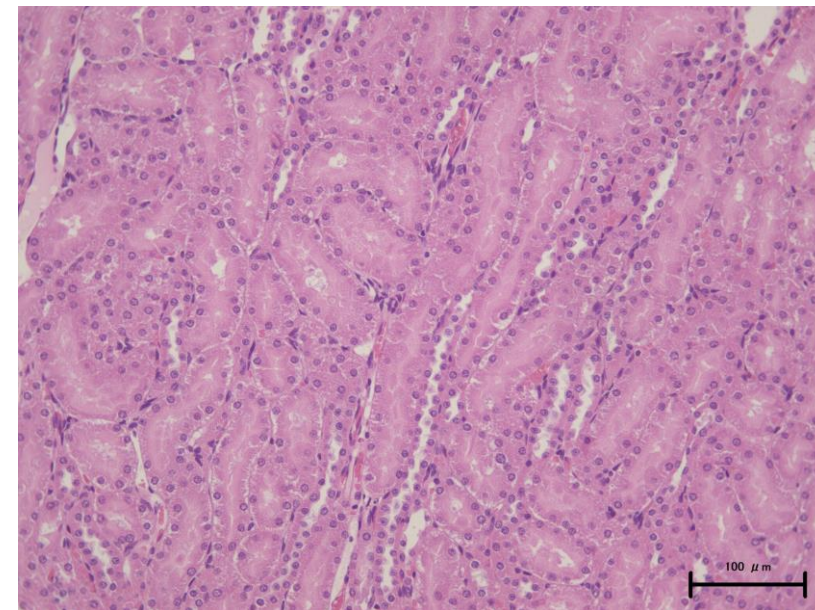
Kidney



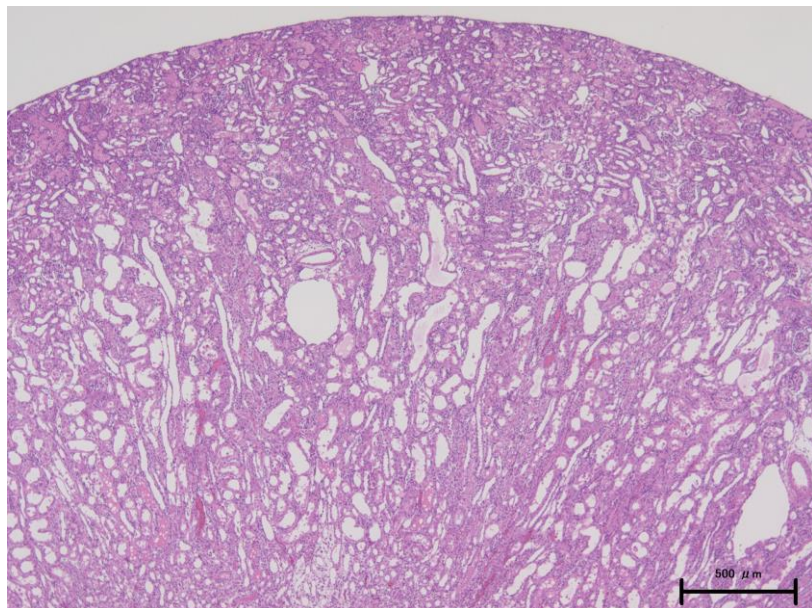
01. Animal No.1101 Vehicle control, 0 mg/kg



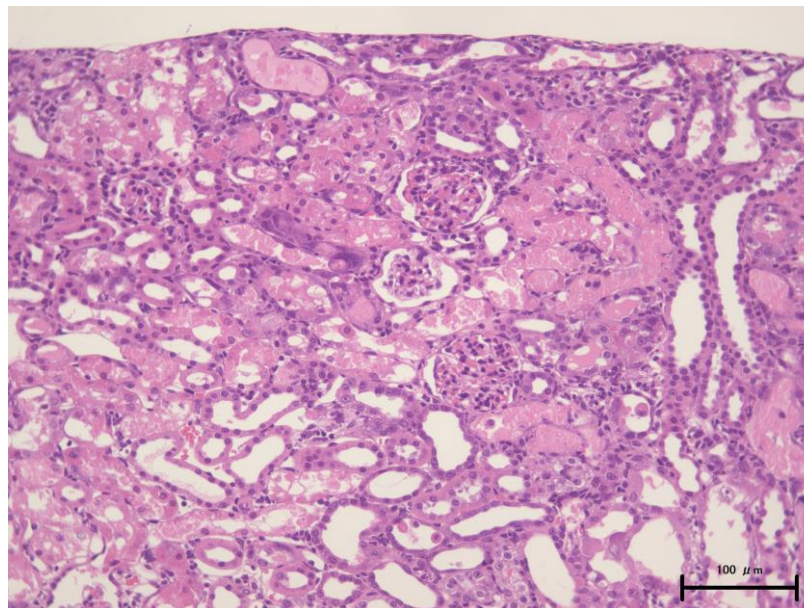
02. Animal No.1101 Not remarkable



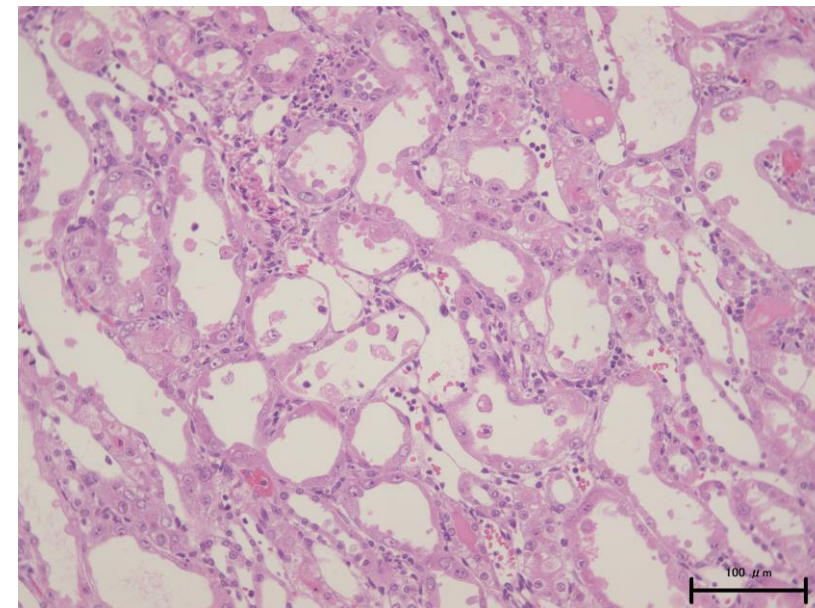
03. Animal No.1101 Not remarkable



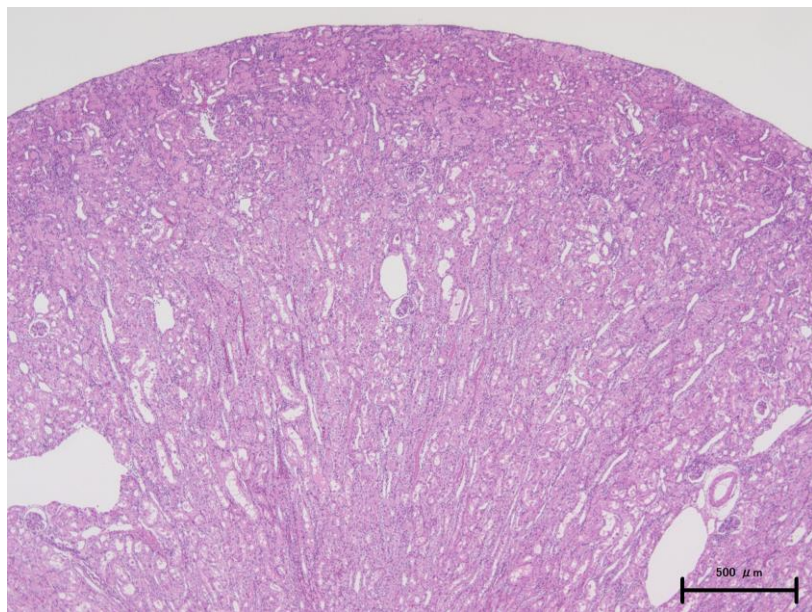
04. Animal No.4104 BK2 group, 1200 mg/kg



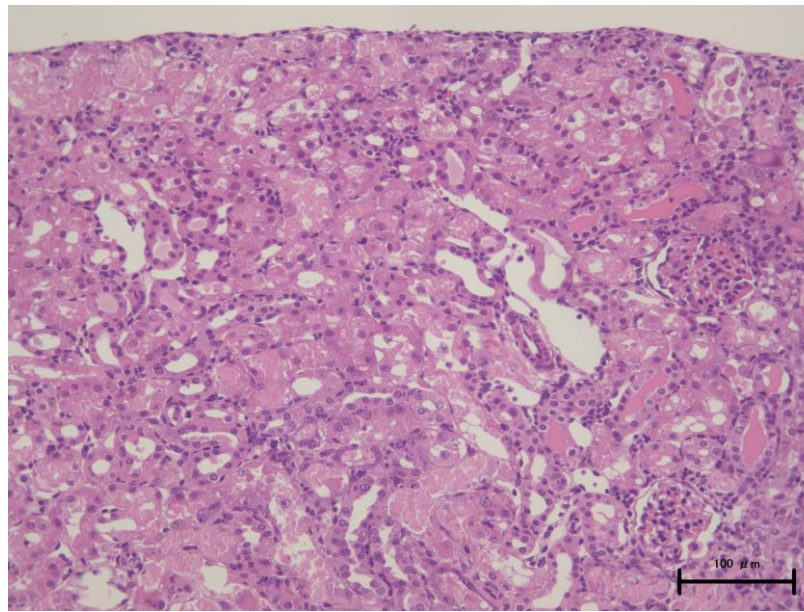
05. Animal No.4104 Necrosis and regeneration of proximal tubule



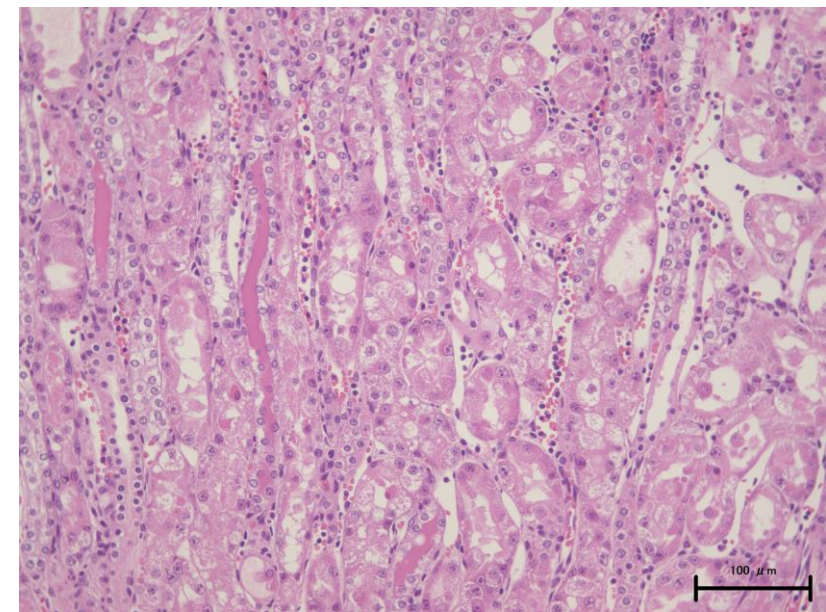
06. Animal No.4104 Degeneration, dilatation and Karyomegaly of proximal tubule, hyaline cast and mononuclear cell infiltration in interstitium



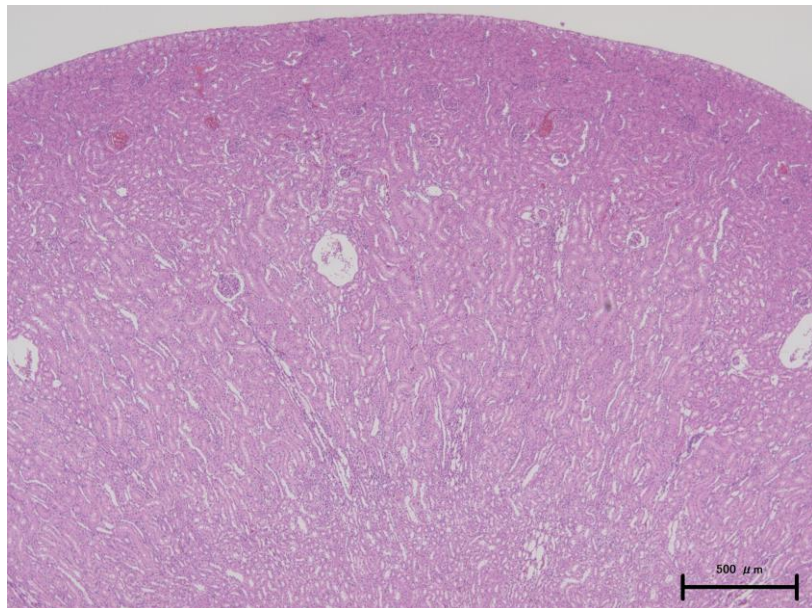
07. Animal No.5102 PA group, 8.52 mg/kg



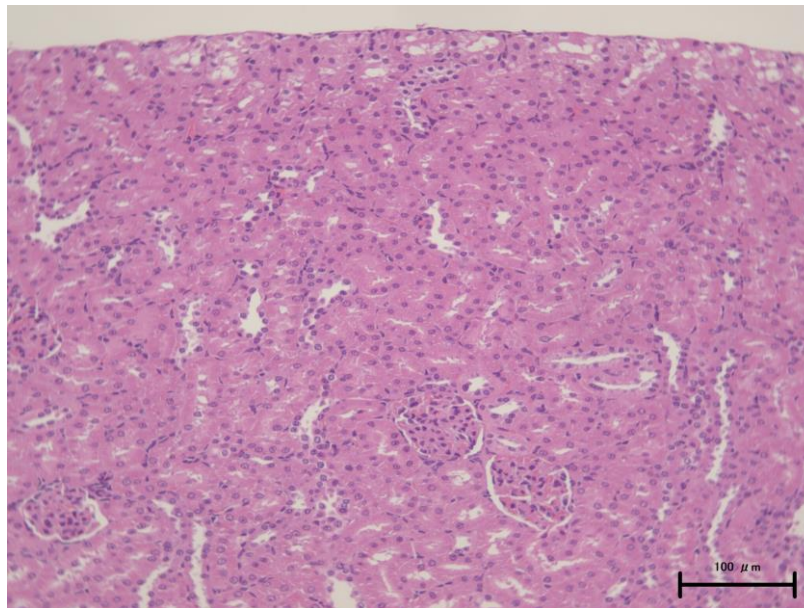
08. Animal No.5102 Necrosis and regeneration of proximal tubule



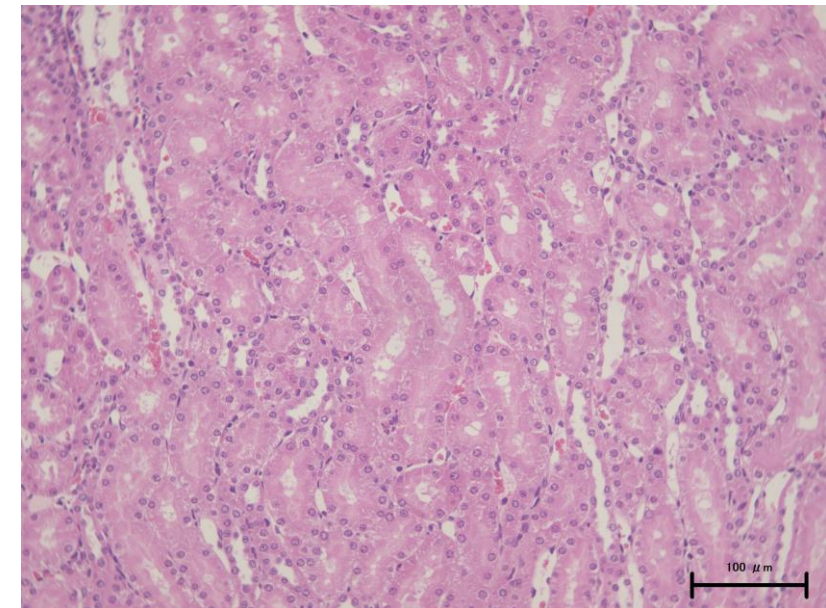
09. Animal No.5102 Degeneration and karyomegaly of proximal tubule, hyaline cast and mononuclear cell infiltration in interstitium



10. Animal No.2103 BK1 group, 1200 mg/kg



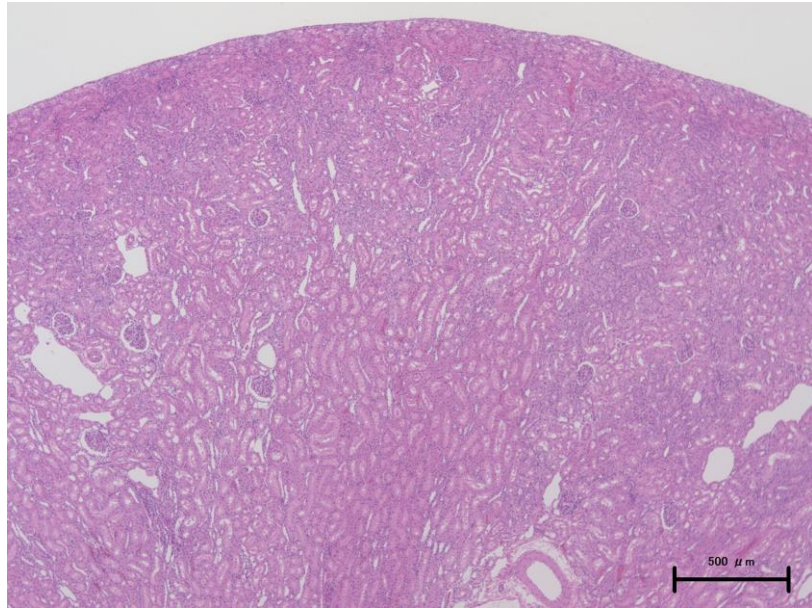
11. Animal No.2103 Not remarkable



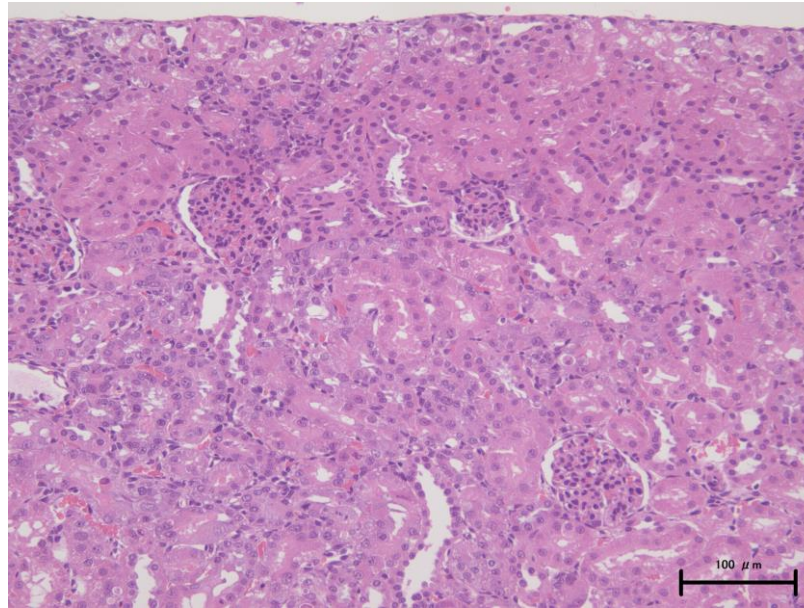
12. Animal No.2103 Not remarkable



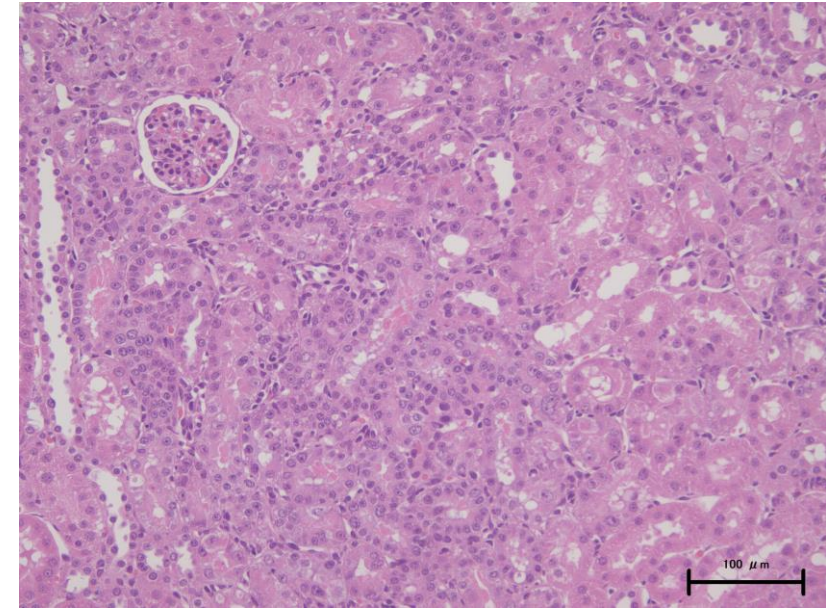
Kidney



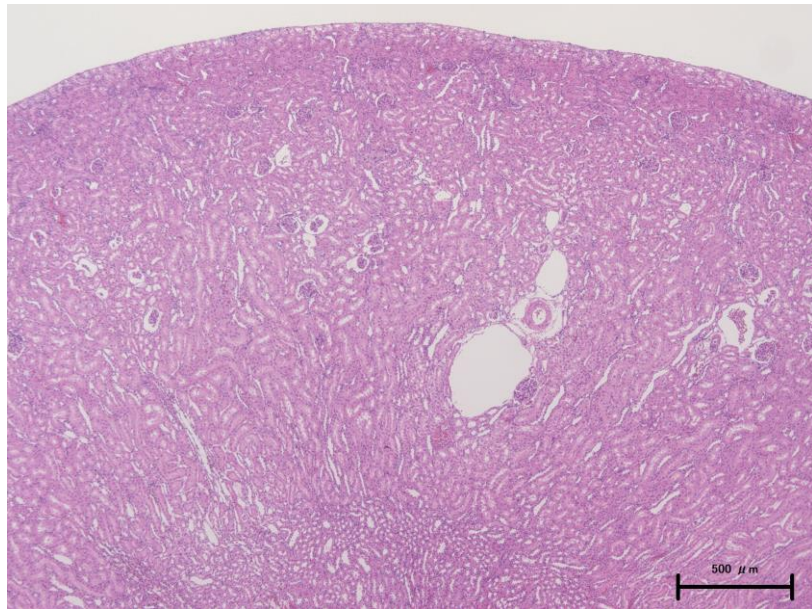
01. Animal No.4004 BK2 group, 1200 mg/kg



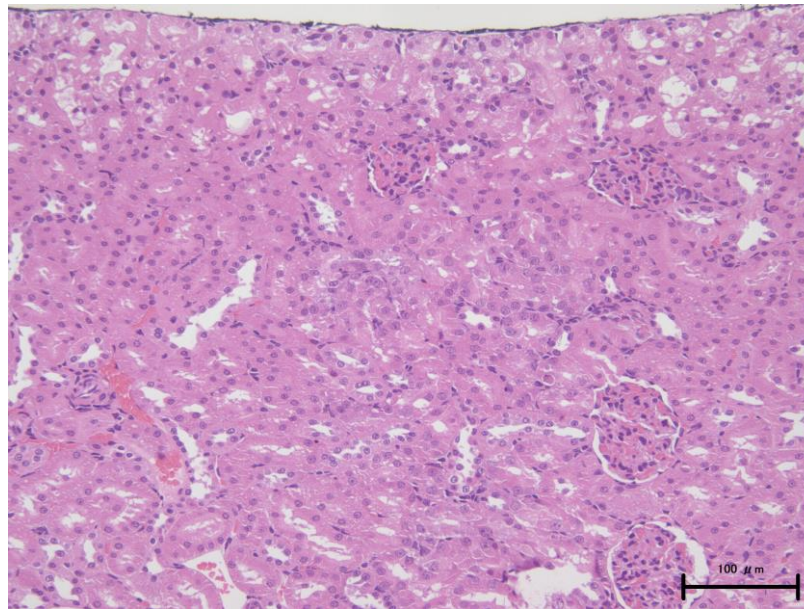
02. Animal No.4004 Necrosis and regeneration of proximal tubule



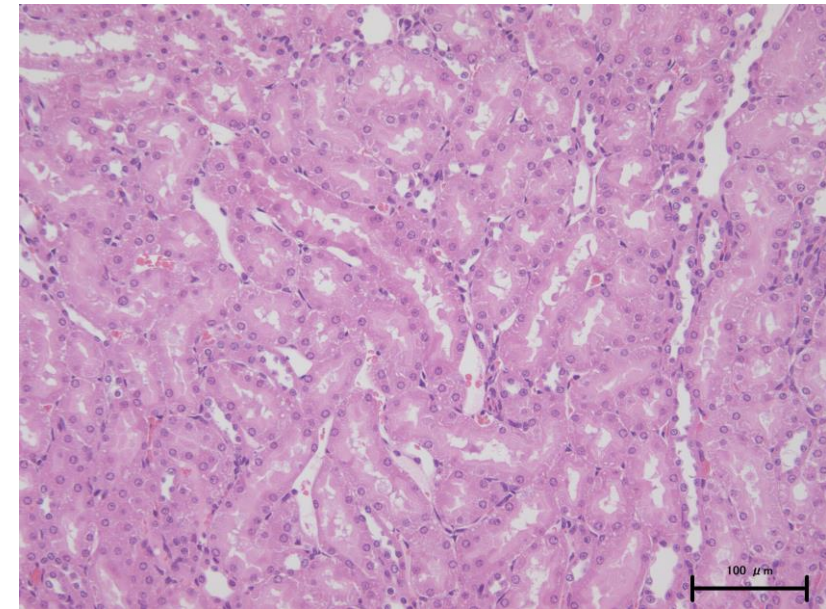
03. Animal No.4004 Degeneration, regeneration and karyomegaly of proximal tubule, and mononuclear cell infiltration in interstitium



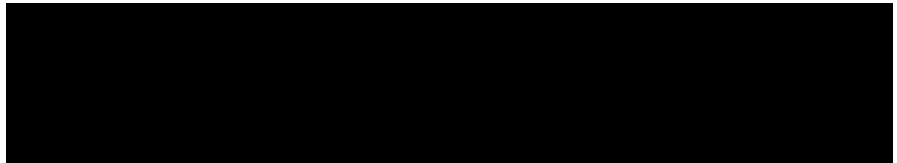
04. Animal No.3101 BK2 group, 360 mg/kg



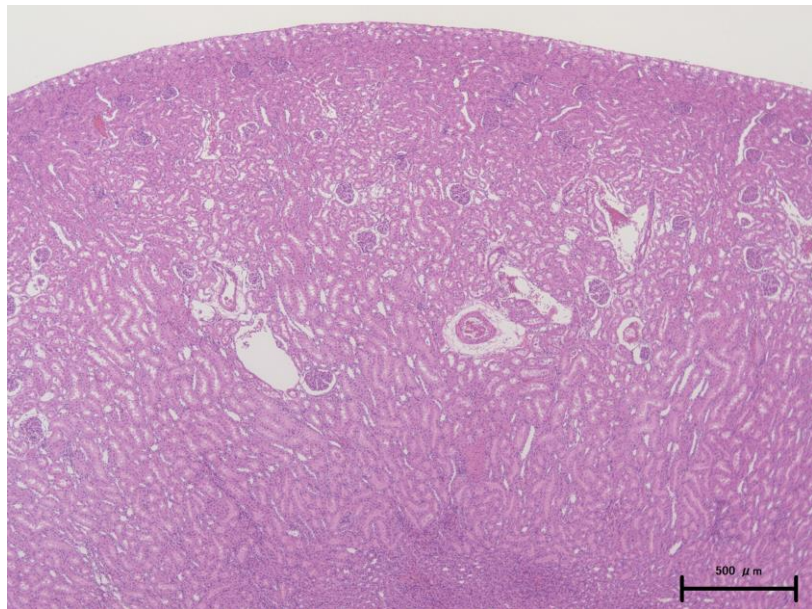
05. Animal No.3101 Necrosis and regeneration of proximal tubule



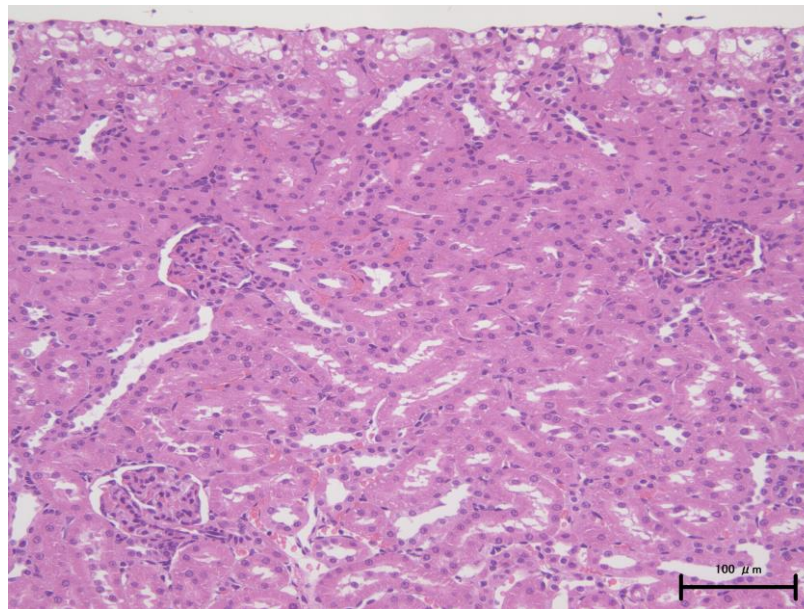
06. Animal No.3101 Not remarkable



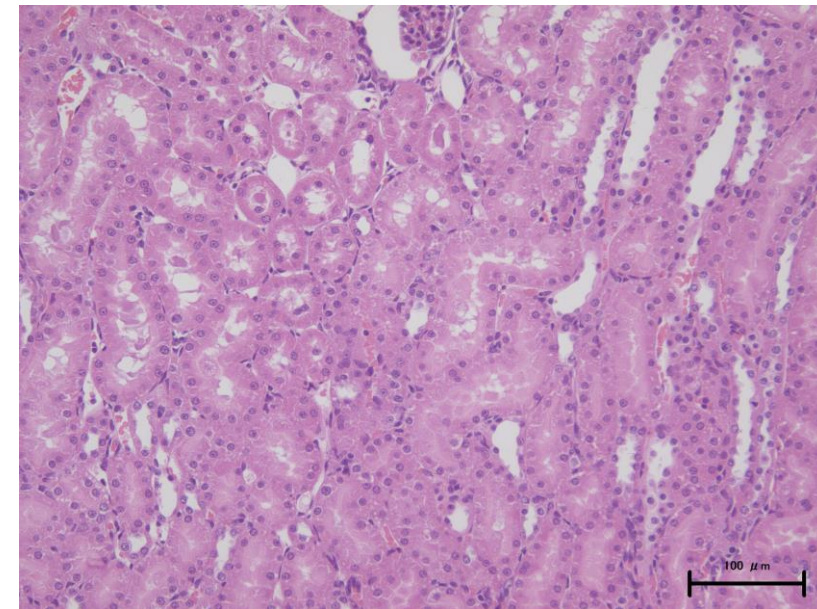
Kidney



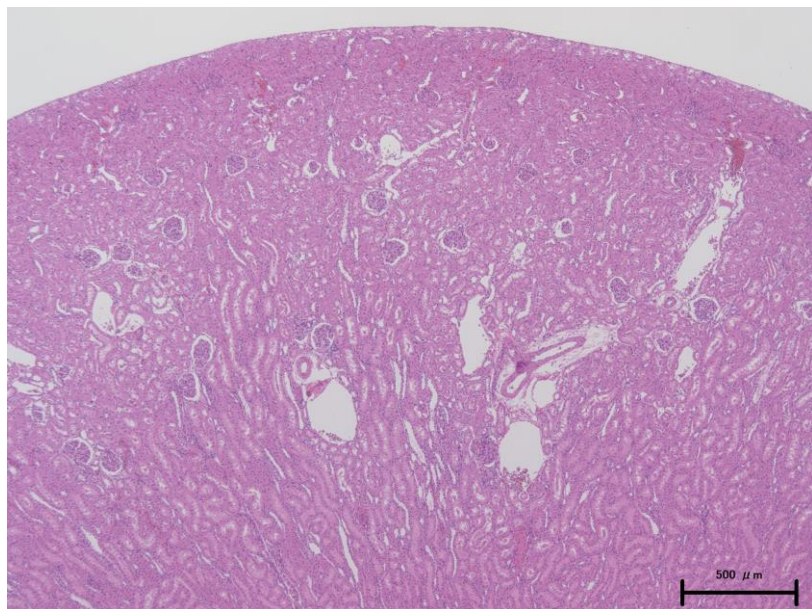
01. Animal No.1001 Vehicle control, 0 mg/kg



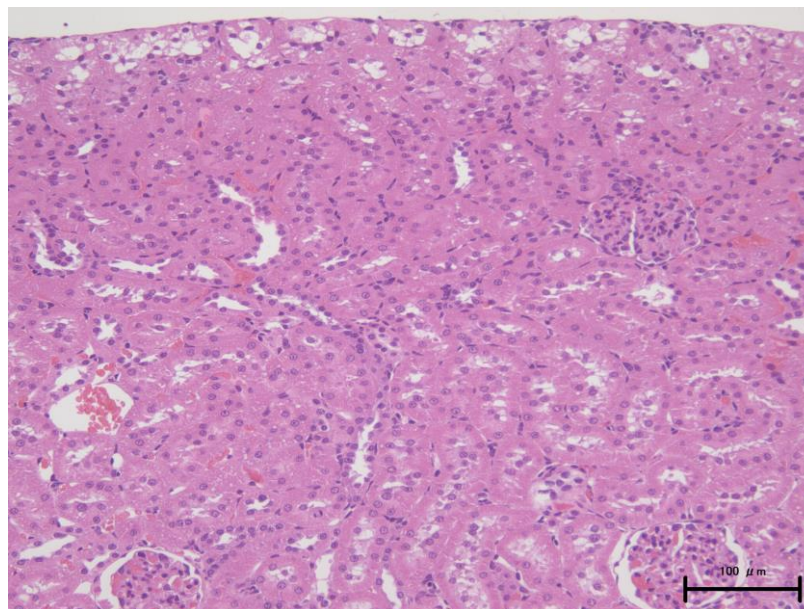
02. Animal No.1001 Not remarkable



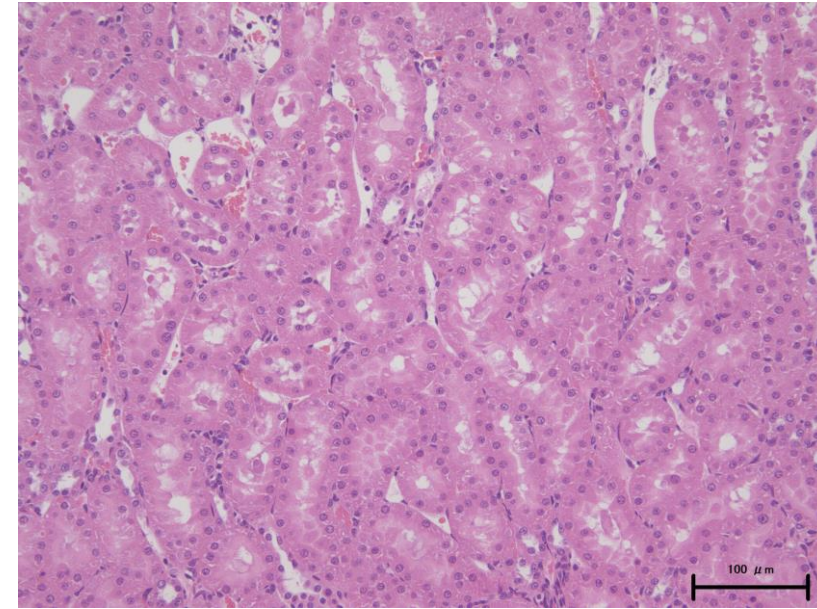
03. Animal No.1001 Not remarkable



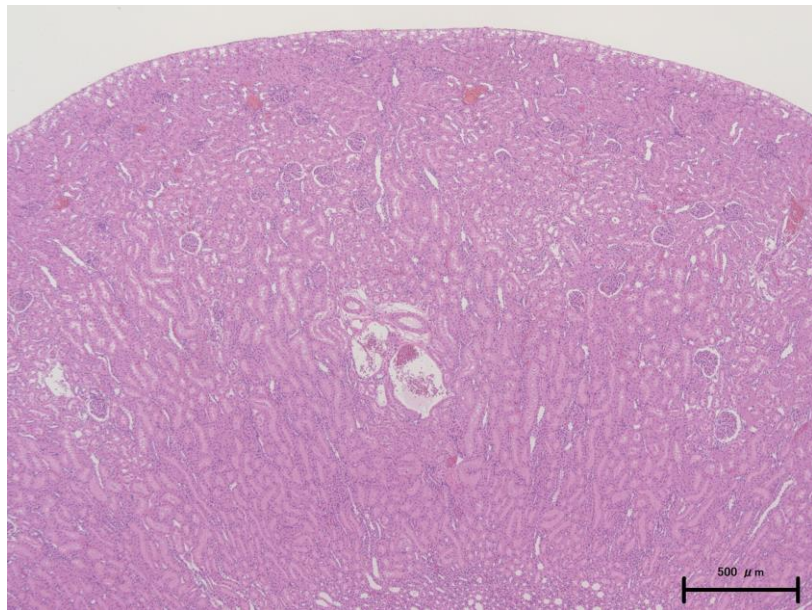
04. Animal No.2001 BK1 group, 1200 mg/kg



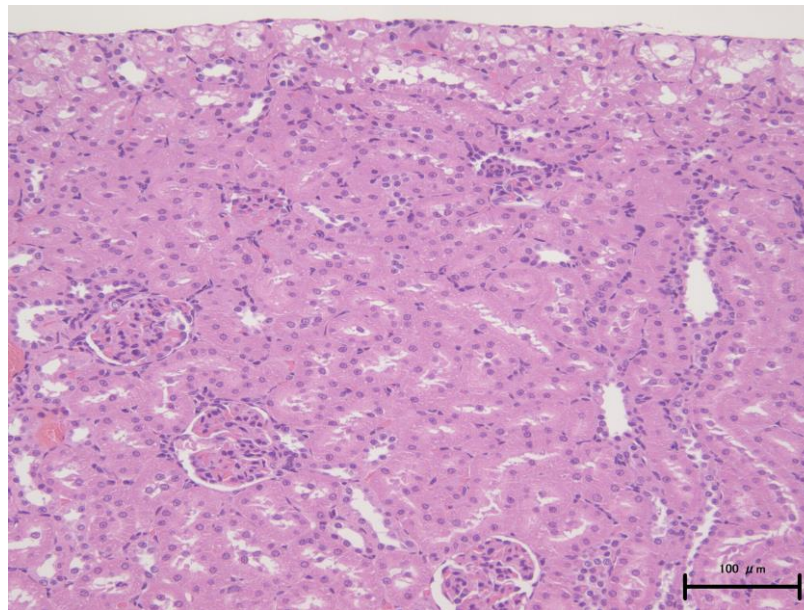
05. Animal No.2001 Not remarkable



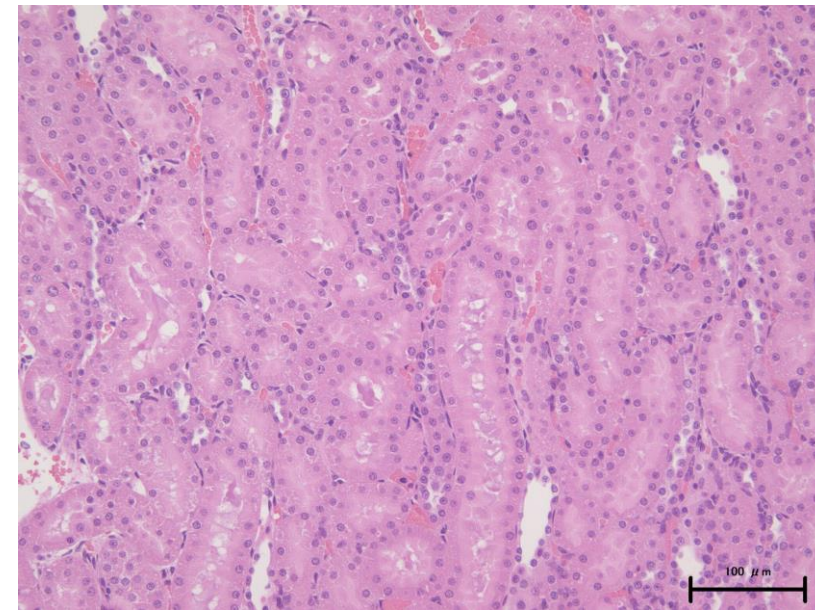
06. Animal No.2001 Not remarkable



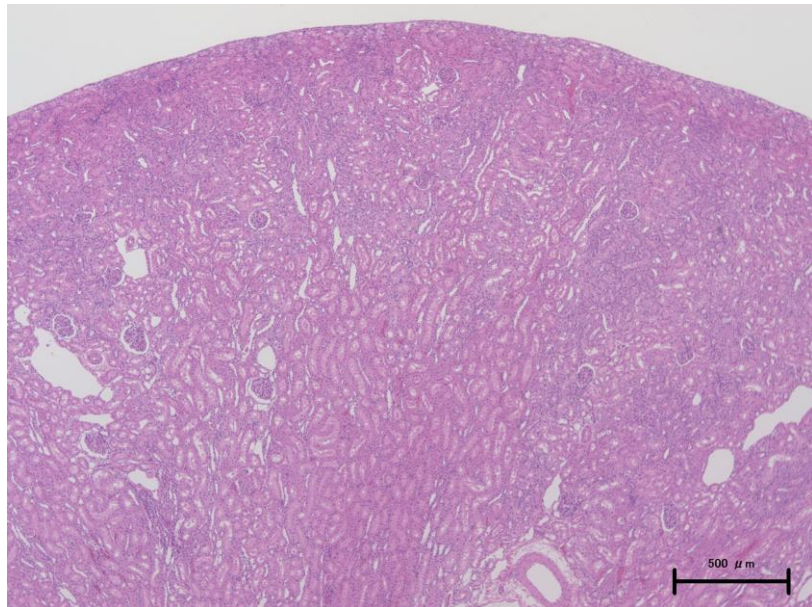
07. Animal No.3002 BK2 group, 360 mg/kg



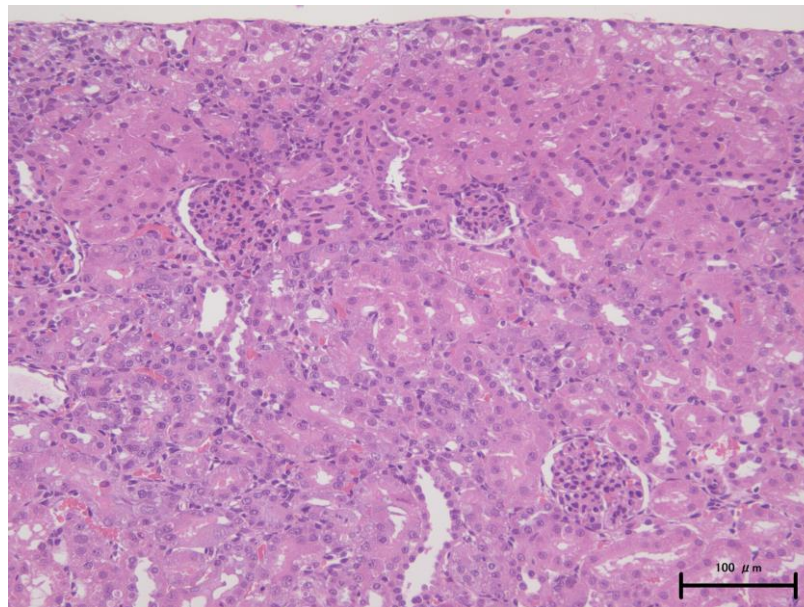
08. Animal No.3002 Not remarkable



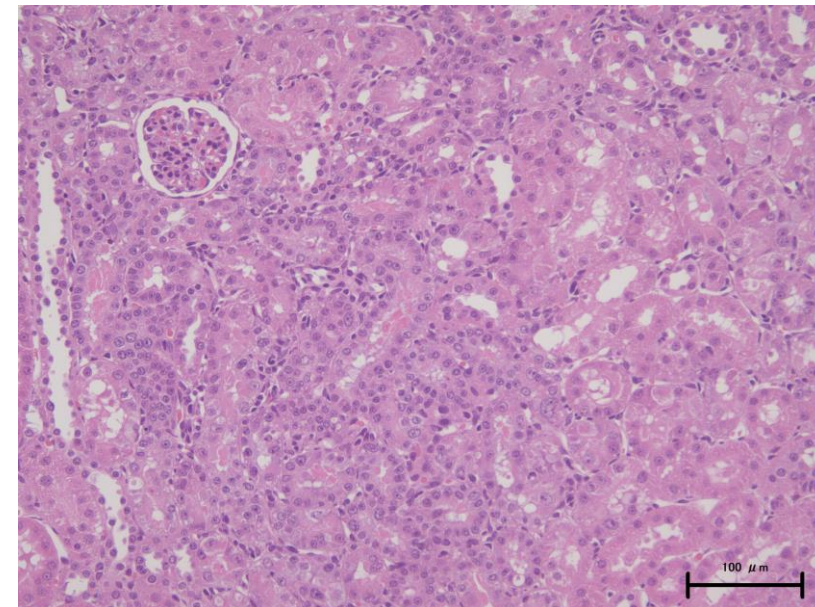
09. Animal No.3002 Not remarkable



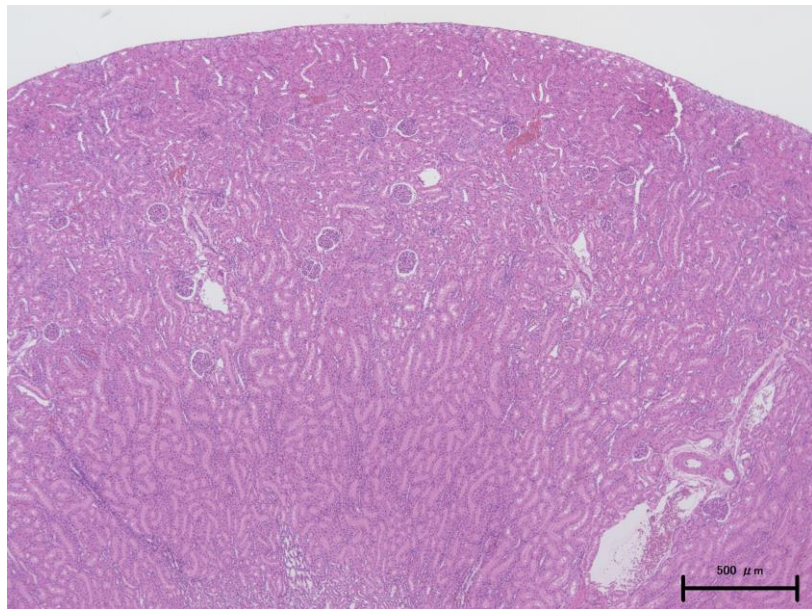
10. Animal No.4004 BK2 group, 1200 mg/kg



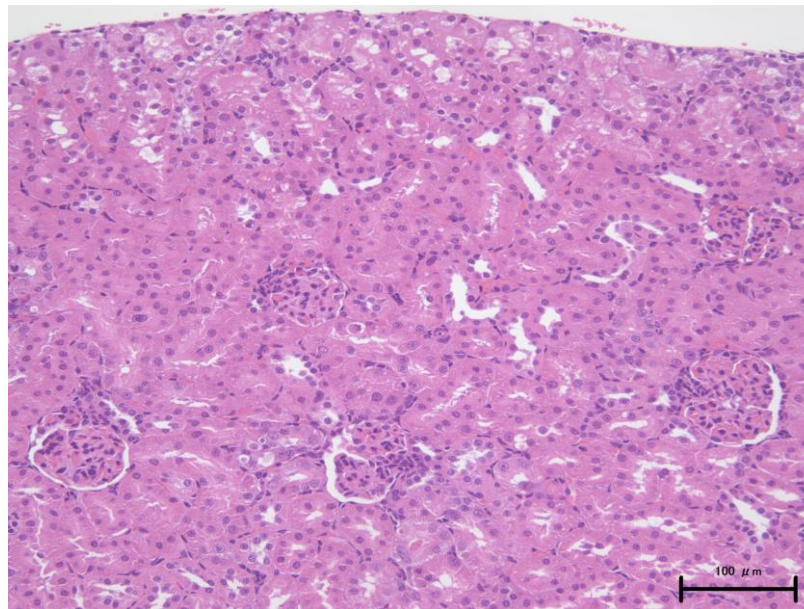
11. Animal No.4004 Necrosis and regeneration of proximal tubule



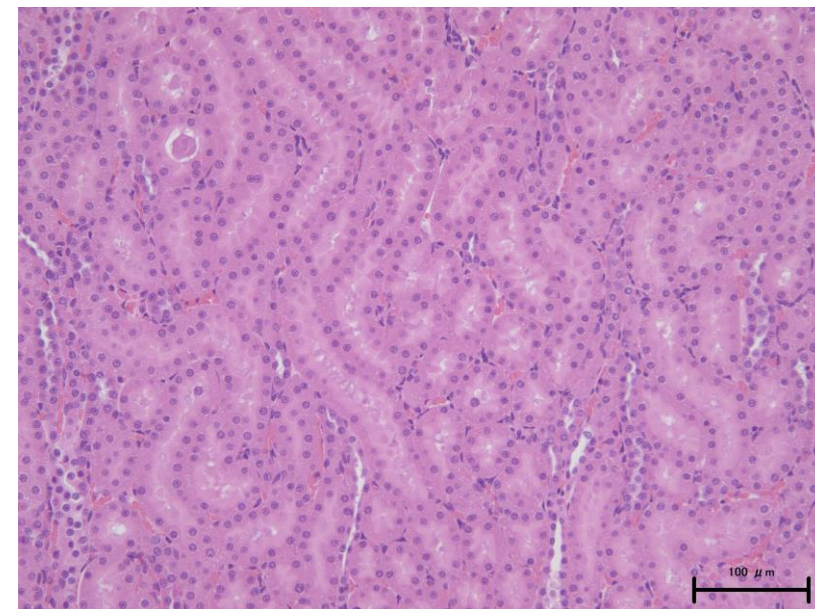
12. Animal No.4004 Degeneration, regeneration and karyomegaly of proximal tubule, and mononuclear cell infiltration in interstitium



13. Animal No.5005 PA group, 8.52 mg/kg



14. Animal No.5005 Degeneration and necrosis of proximal tubule



15. Animal No.5005 Not remarkable