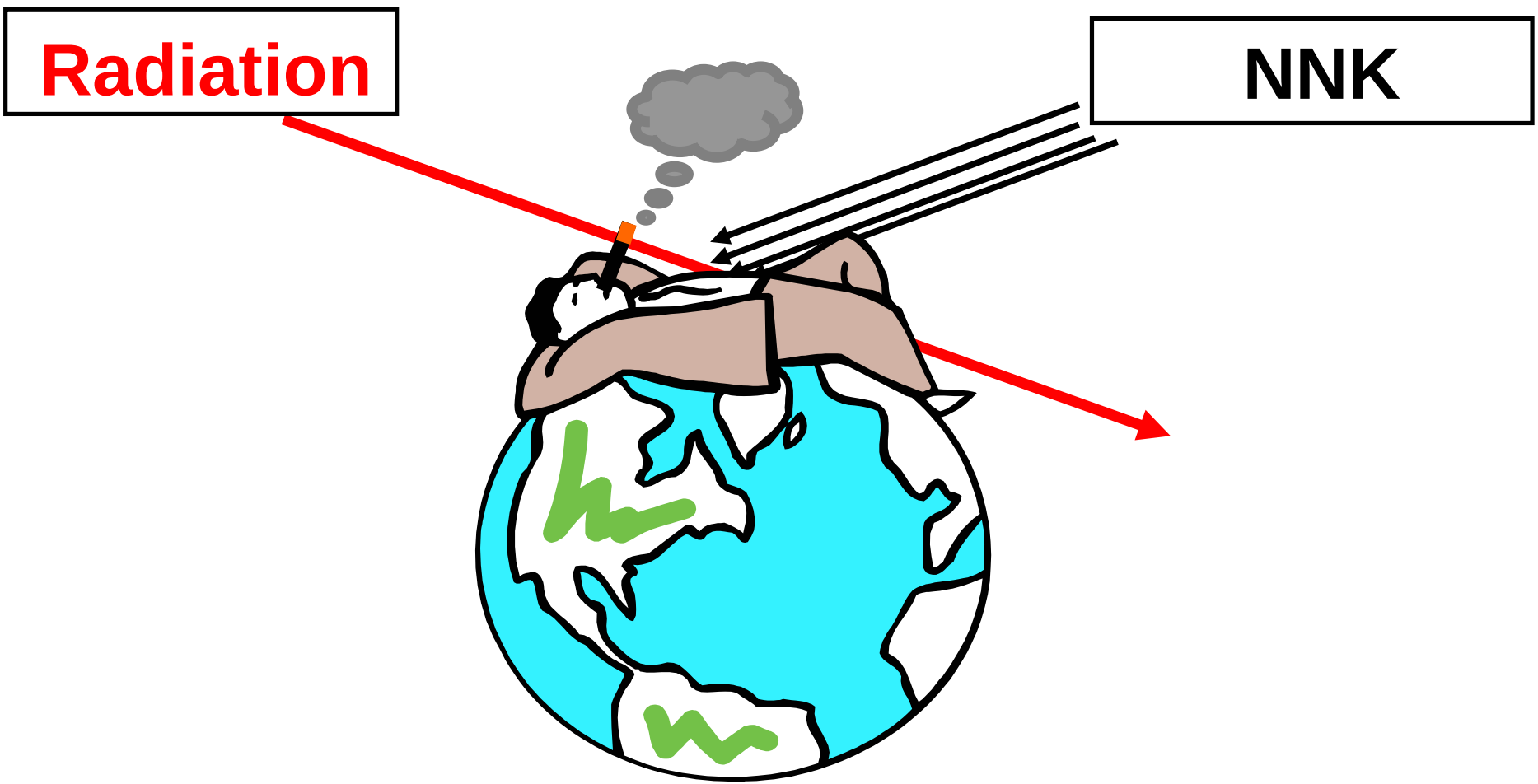
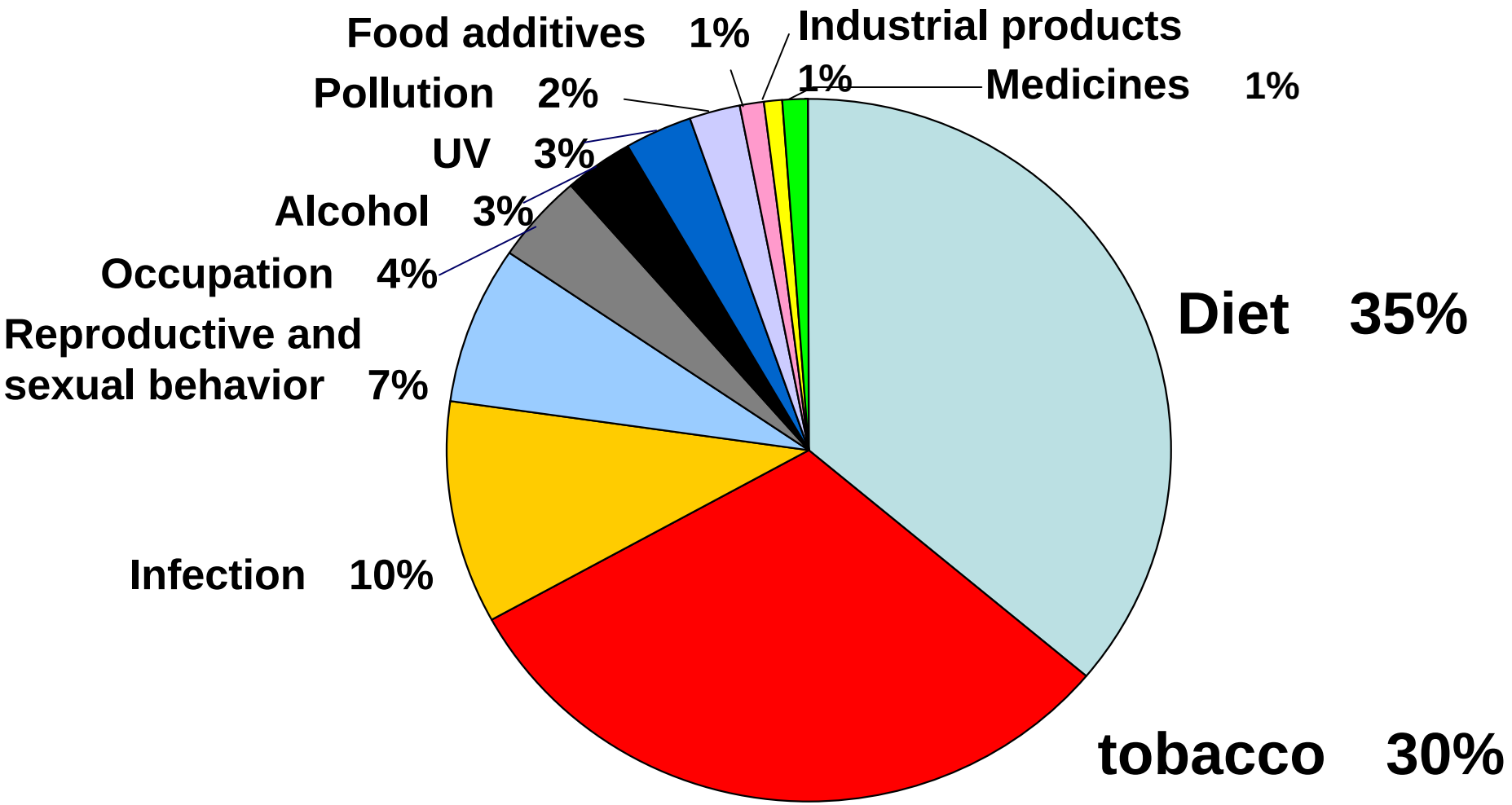
Combined genotoxicity of low-dose-rate radiation and tobacco-specific nitrosamine NNK

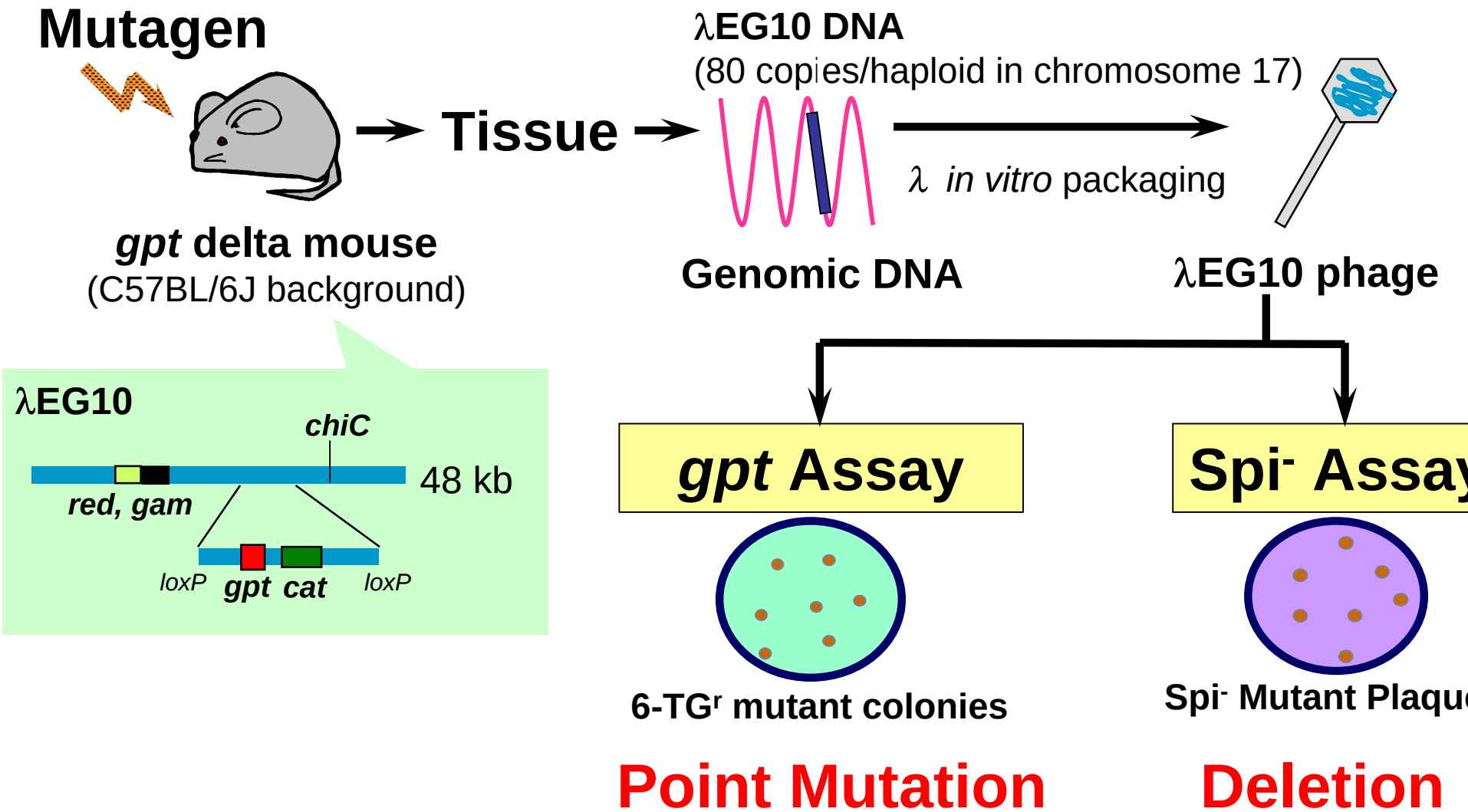


The causes of cancer



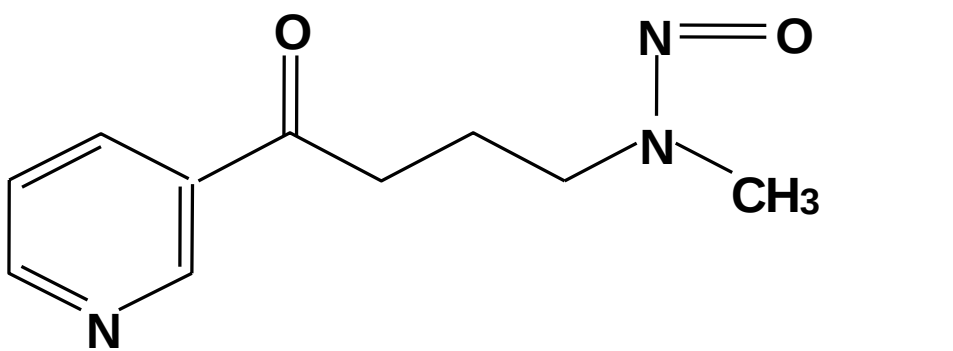
Doll, R. and R. Peto, The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today, J. Natl. Cancer Inst. 66, 1192 (1981)

gpt delta Transgenic mouse



NNK is a tobacco-specific nitrosamine that is carcinogenic in the lung of experimental animals

NNK= nicotine-derived nitrosamino ketone



4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

IARC : Group 2B
(possible human carcinogen)

Cytochrome P450
CYP2A

DNA Adducts → **Point Mutations** → **Cancer**

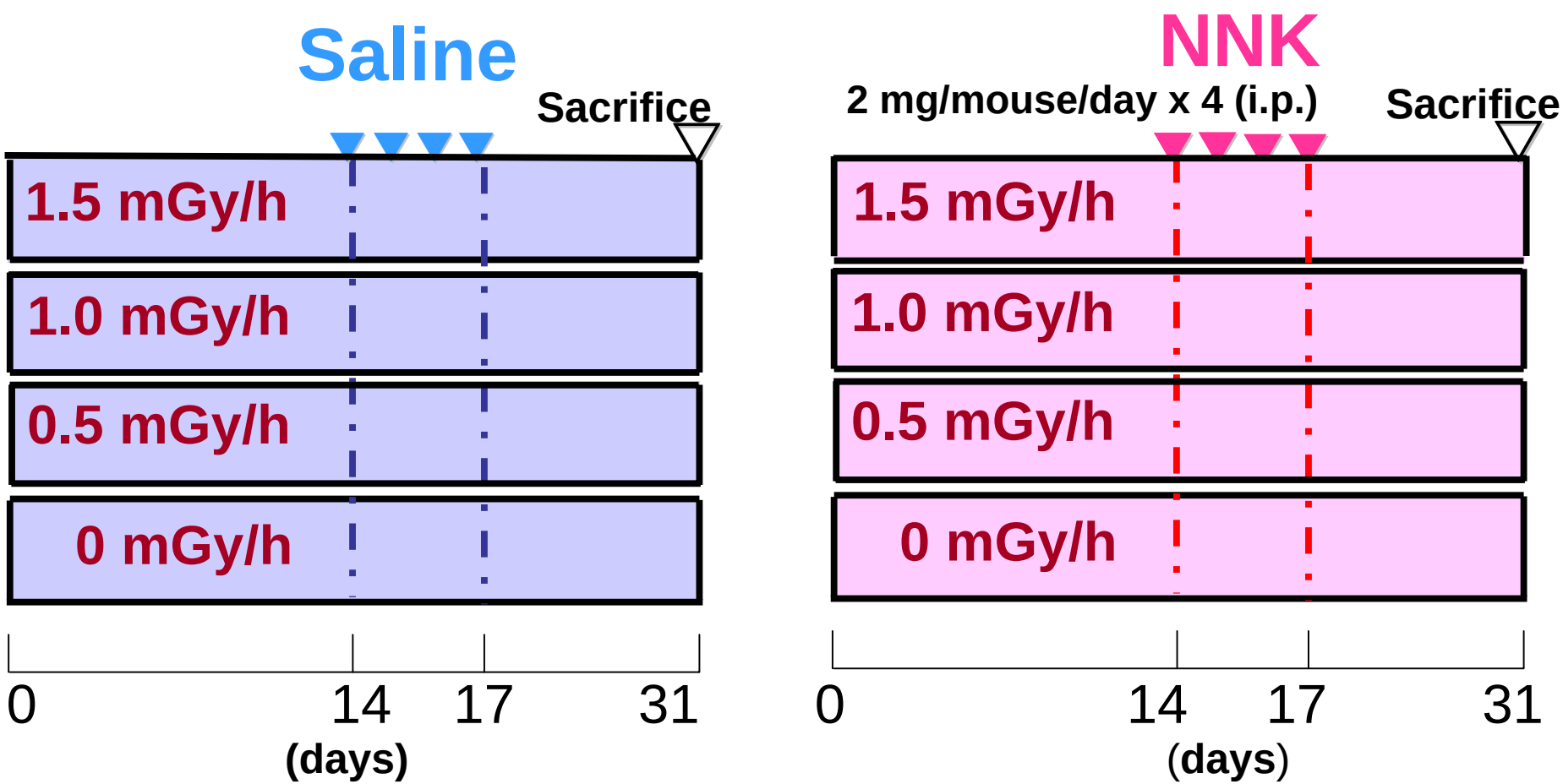
***O*^{6}-methylguanine**

***O*^{4}-methylthymine**

Lung

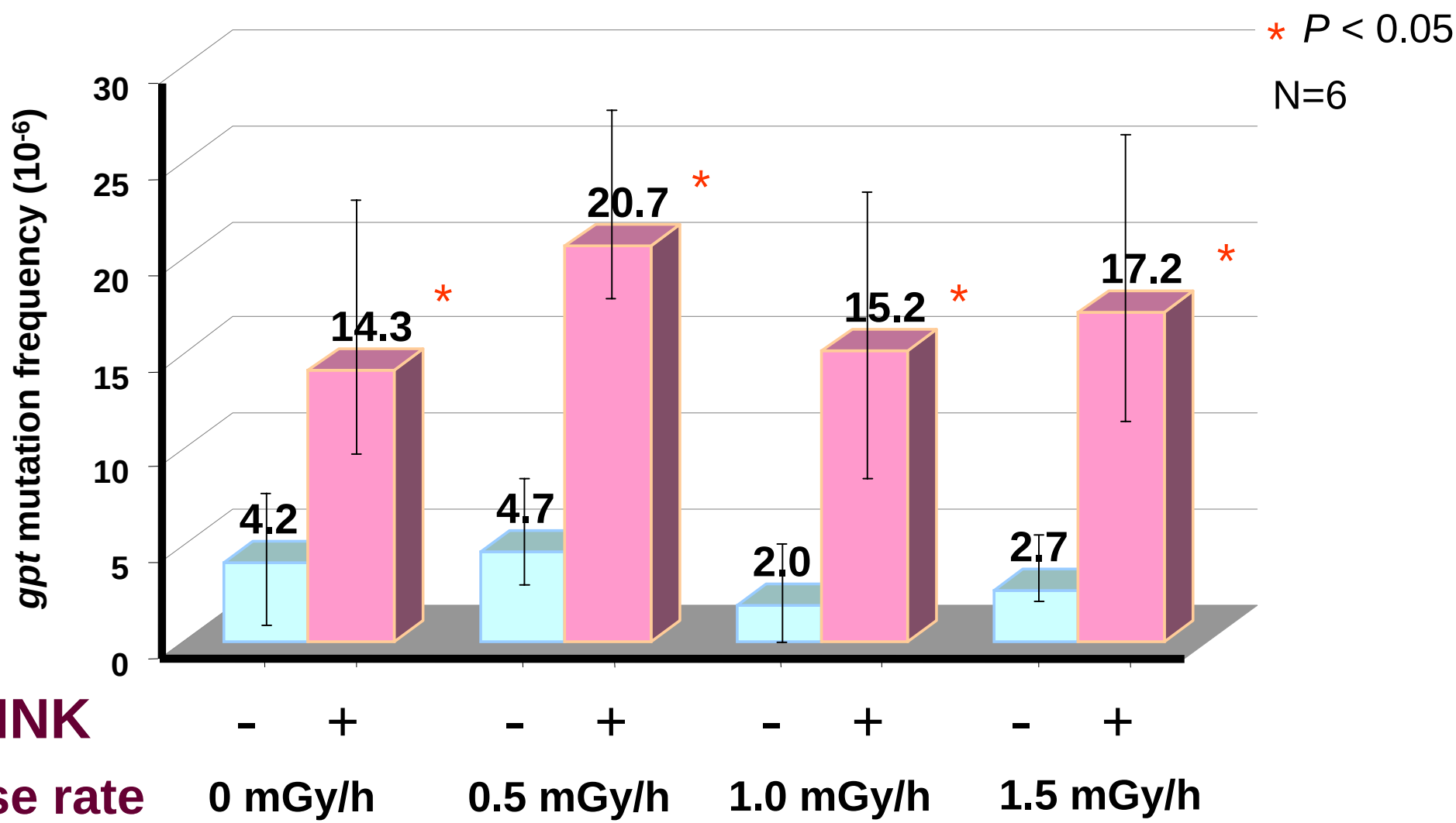
Combined treatments of *gpt* delta mice with NNK and γ-ray radiation

Animal : *gpt* delta mouse, 8 mice (♀), 7 weeks old

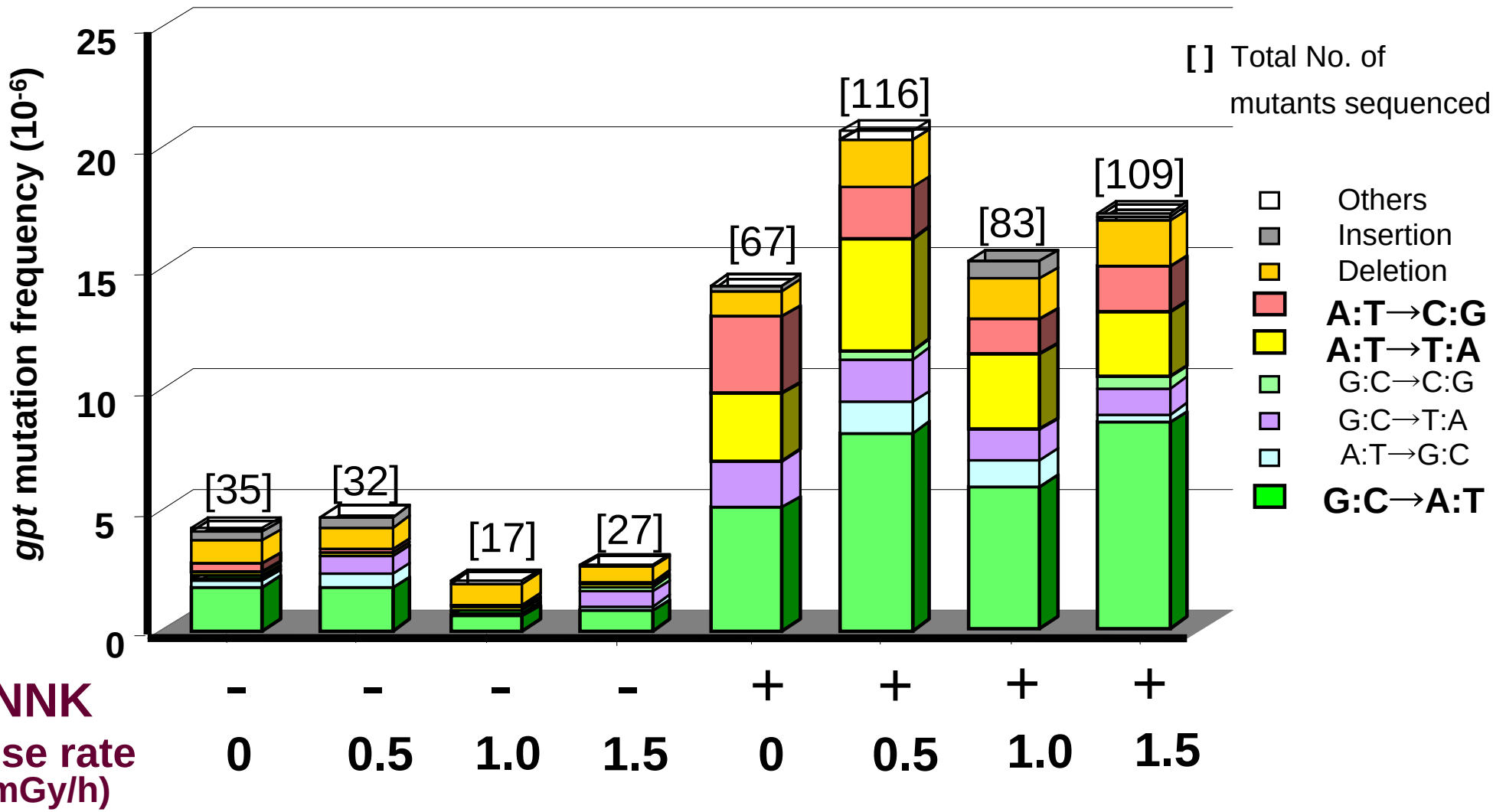


A. Sakai et al., Int. J. Low Radiation, 1, 142-146 (2003)

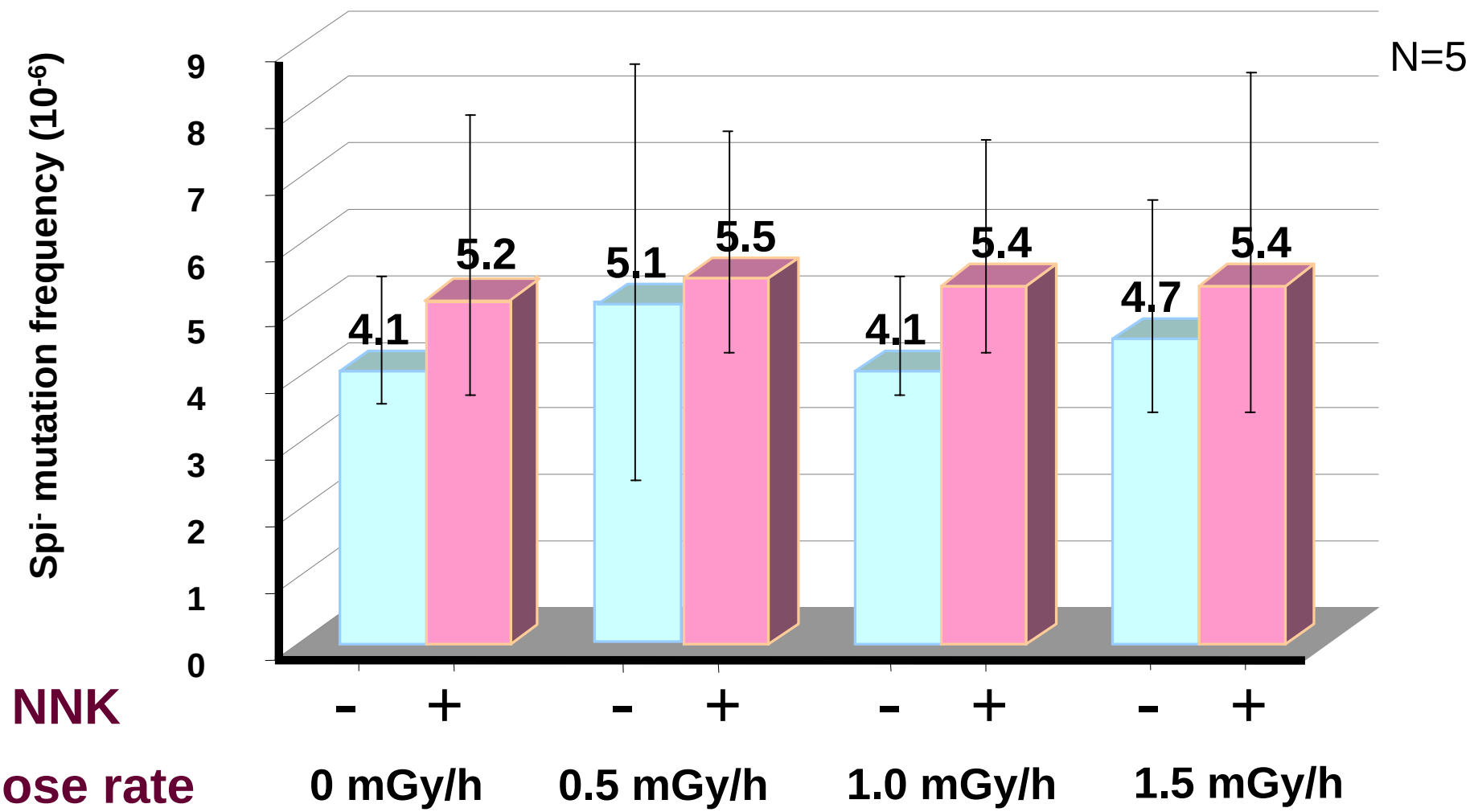
NNK treatments significantly enhanced *gpt* mutation frequencies in the lung of mice



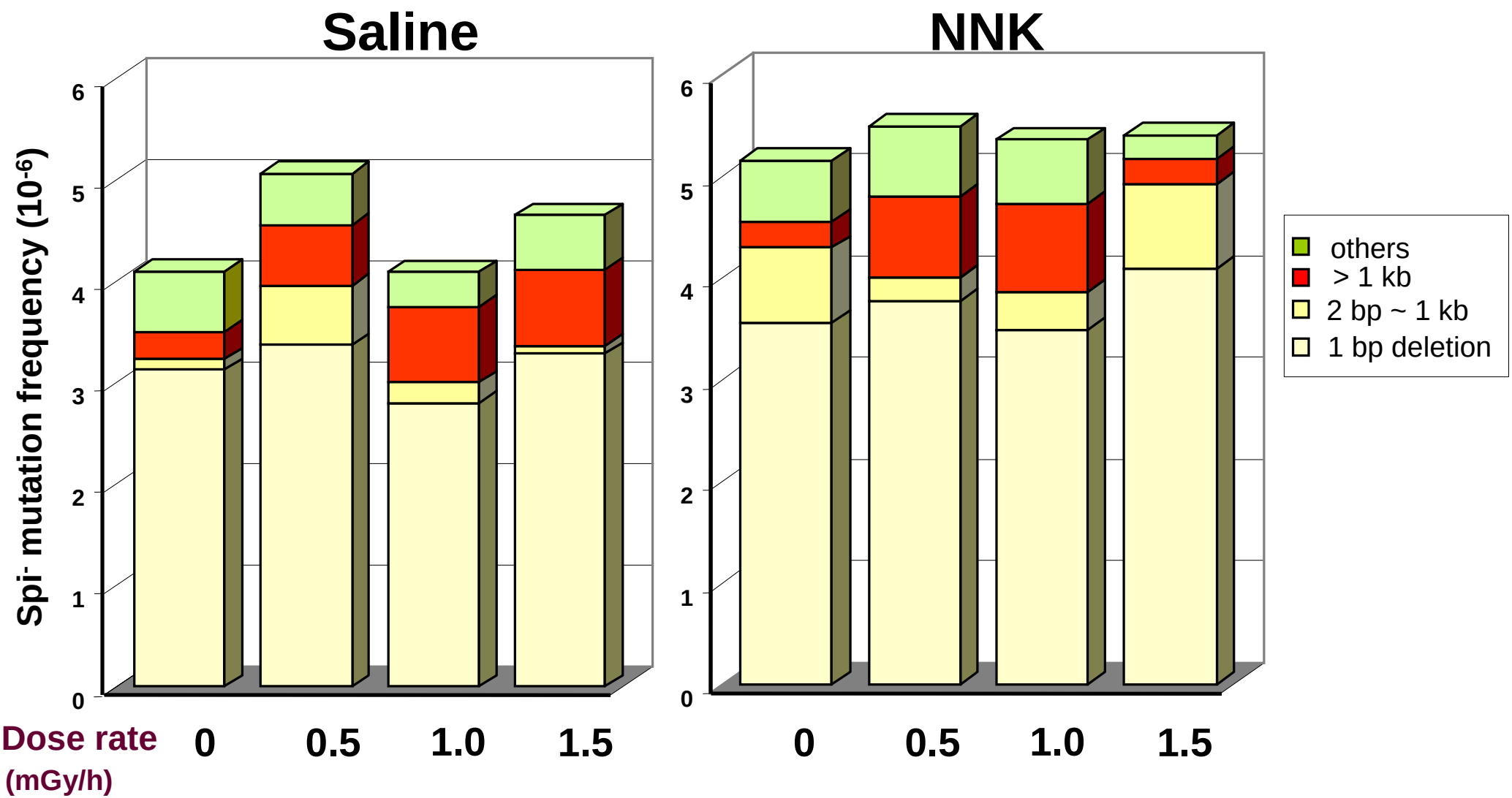
NNK-treatment mainly induced G:C to A:T, A:T to T:A and A:T to C:G mutations



Spi⁻ mutation frequencies in the lung of mice

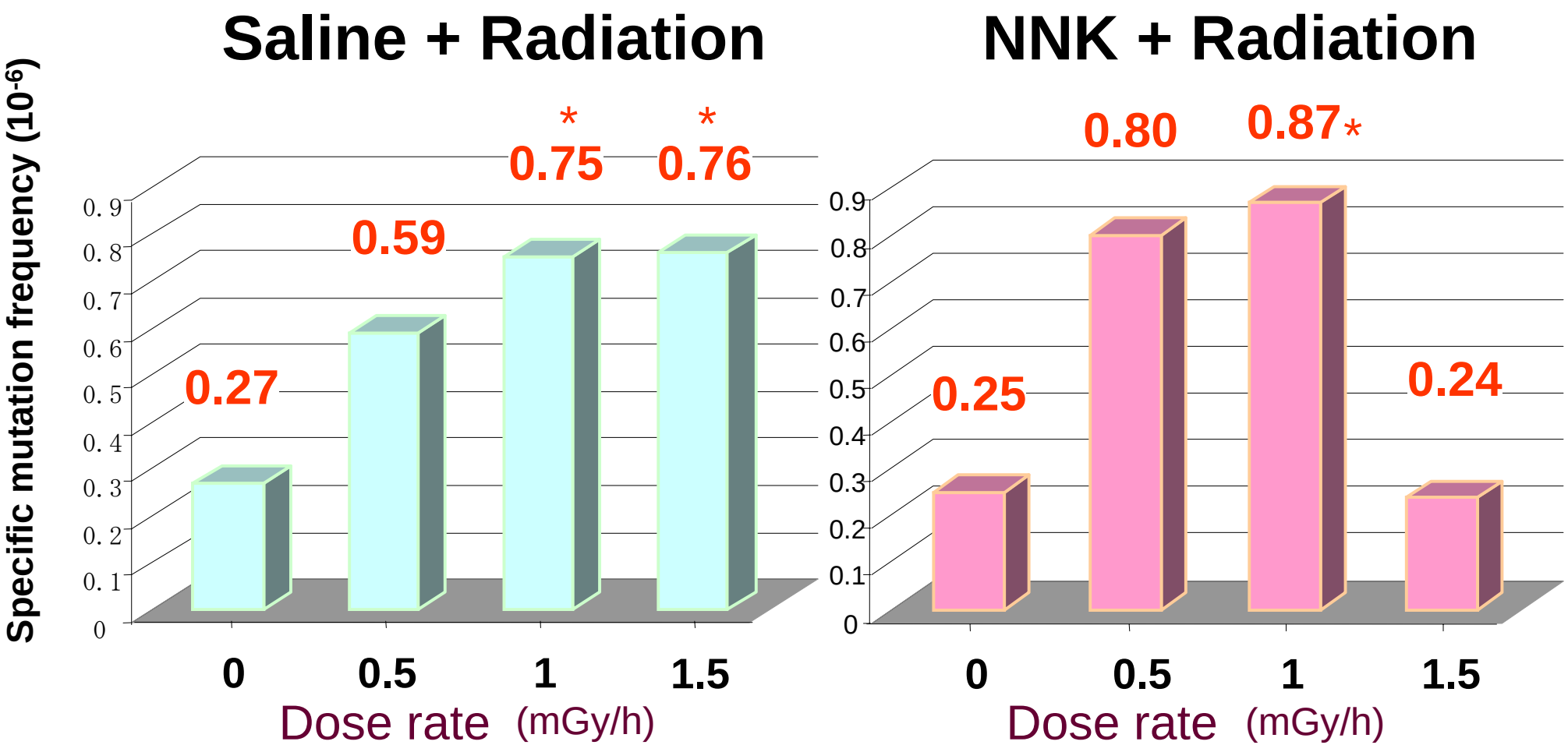


Mutation Spectra of Spi$^-$ mutants

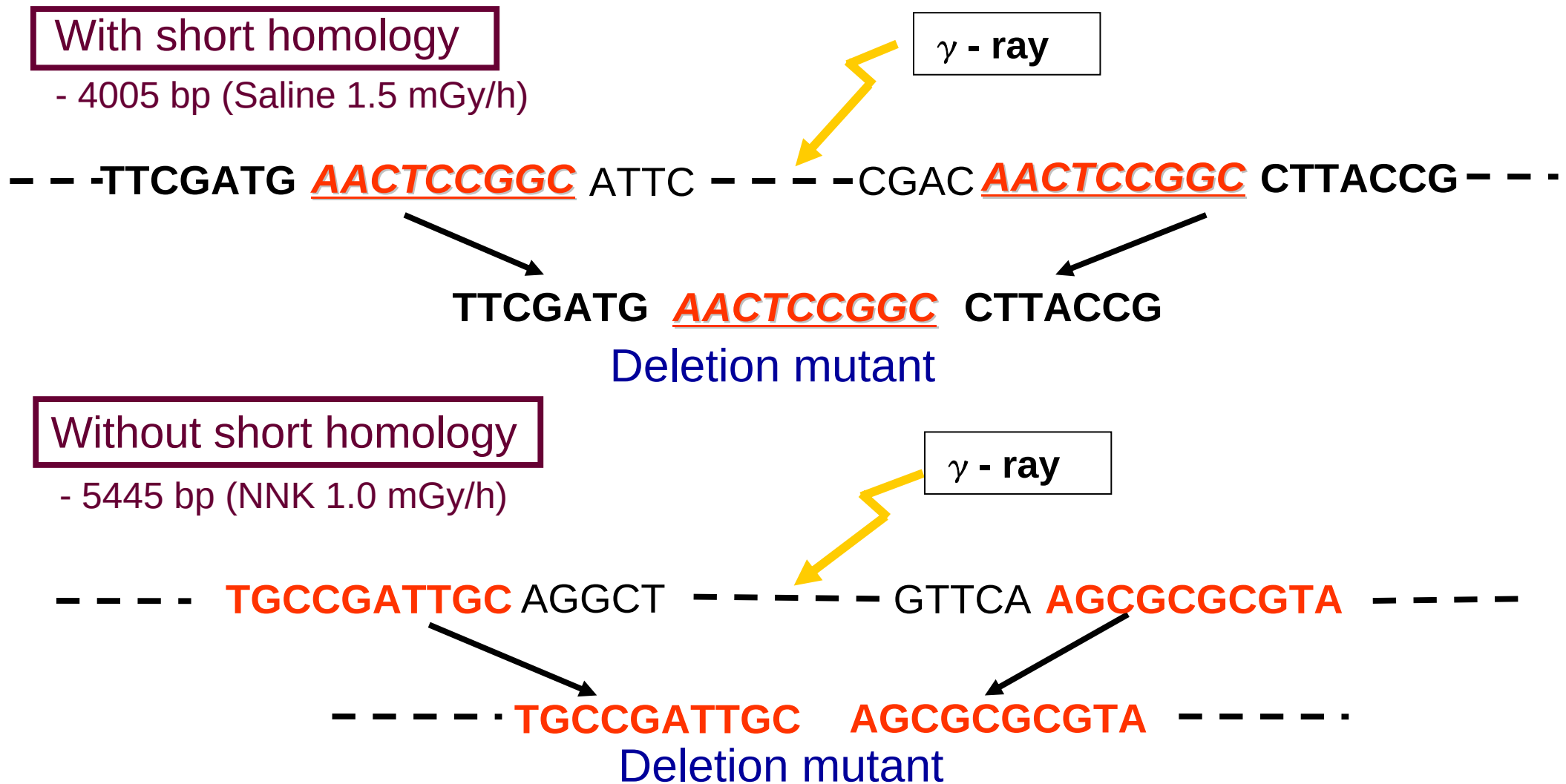


Suppression of large deletions in the mice treated with NNK + γ-radiation at 1.5 mGy/h

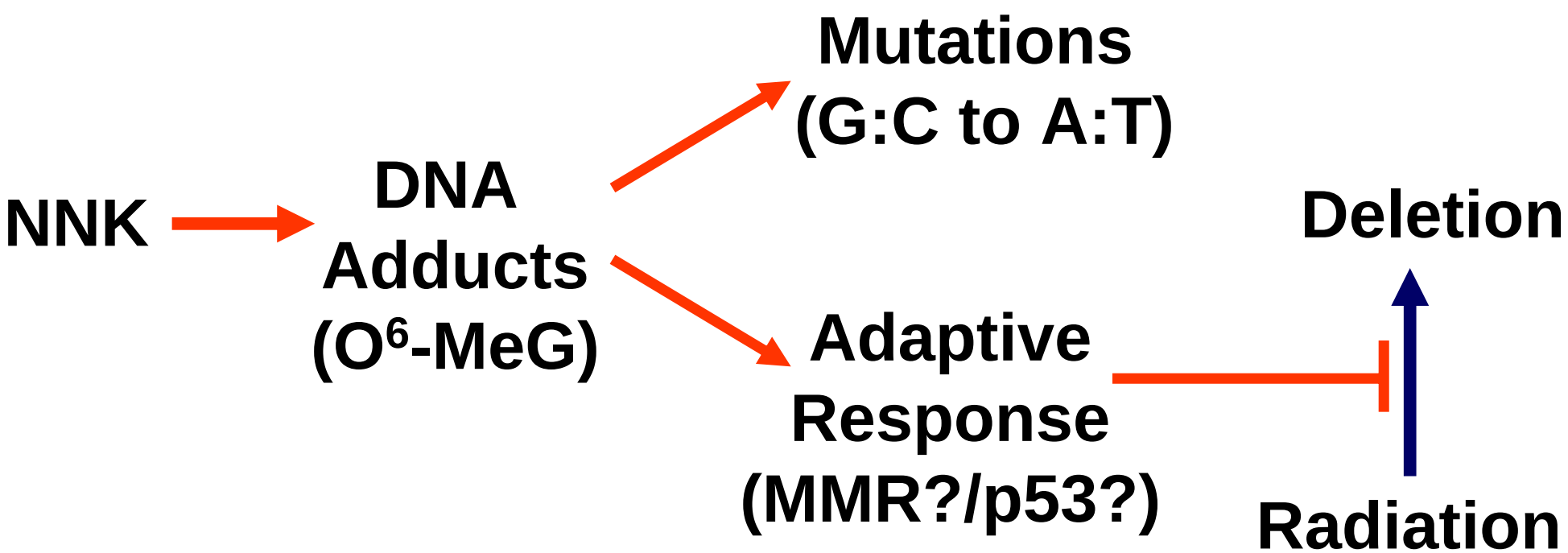
* $P < 0.05$



Large deletions are formed by non-homologous end-joining (NHEJ) of double-strand breaks in DNA (DSB)



NNK treatments induce mutations but suppress radiation-induced large deletions *in vivo*



Summary

- **To examine the combined effects of low dose rate radiation and chemical exposure, *gpt* delta mice were exposed to NNK and γ-irradiation, i.e., 0.5, 1.0 and 1.5 mGy per hour for 31 days. The total calculated doses were 0.34, 0.68 and 1.02 Gy, respectively.**
- **NNK treatments significantly induced base substitutions, i.e., G:C to A:T, A:T to T:A or A:T to C:G, in the lung of mice.**
- **The induction of base substitutions was not substantially modulated by the low dose rate γ-irradiation.**
- **The γ-irradiation induced large deletions with more than 1 kb in size in the lung of mice.**
- **The induction of large deletions at a dose rate of 1.5 mGy per hr was apparently suppressed by NNK treatments.**
- **NNK treatments may induce protective mechanisms by which large deletions induced by γ-irradiation are suppressed.**
- **Mechanistic approach is needed to fully understand the combined effects of low dose rate radiation and chemical exposure.**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NNK treatments apparently suppressed large deletion (> 1 kb) in the Lung of Mice exposed to γ-radiation at a dose rate of 1.5 mGy per hour for 31 days